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General Physiologic Processes

CELL STRUCTURE AND FUNCTION

Three structural features of human cells (Figure 1–1) identify them as **eukaryotic cells**. They are

1. a distinct membrane surrounding a central nucleus,
2. several membrane-lined intracellular structures and organelles, and
3. a number of well-defined subcellular domains in which different microenvironments are maintained so that several chemical reactions can occur simultaneously and optimally because the properties of the membranes defining these domains permit precise regulation of regional milieus.

Cytosolic Membrane Systems, Organelles, and Inclusions

Nucleus

The nucleus is the site where that portion of the human genome that represents “meaningful” deoxyribonucleic acid (DNA) is transcribed into ribonucleic acid (RNA) by a process of regulated polymerization. Of the transcribed RNA, the majority is **heterogeneous nuclear RNA** that is either destroyed or further modified by capping, polyadenylation, or splicing. A small portion is **messenger RNA** (mRNA), which leaves the nucleus in that form and reaches the cytosol and ribosomes to be translated into proteins.

The nucleus is the largest intracellular organelle. It is surrounded by the **nuclear membrane** and contains **chromatin** (densely packed DNA) and one or two **nucleoli**.

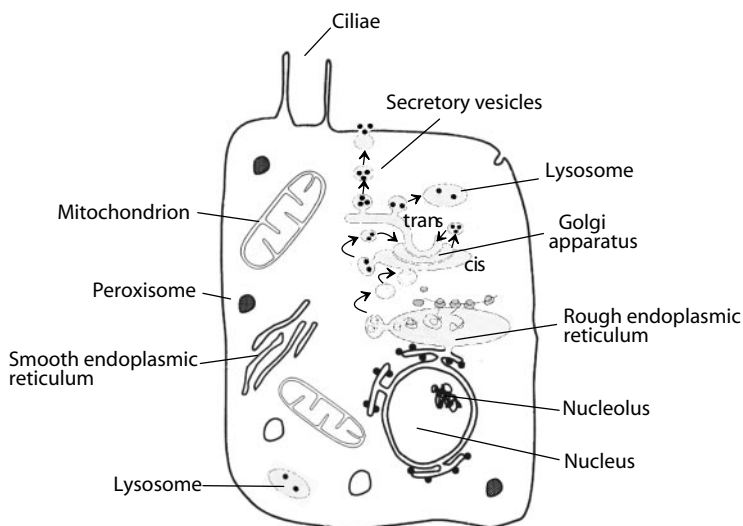


Figure 1–1 Elements of a typical human cell. Also shown is the pathway of protein synthesis from rough endoplasmic reticulum to cis-Golgi, to medial Golgi, to trans-Golgi and from there to its final destination, which can be a lysosome, the plasma membrane, or an exocytotic vesicle. These transfers occur by successive formation, delivery, and reception of transport vesicles.

Nuclear membrane. This is a double layer of phospholipids. The space between the layers is contiguous with the **rough endoplasmic reticulum** (see Figure 1–1), and the inner and outer membranes fuse together at various points and form **nuclear pores**, whose diameter (30 to 100 nm) permits unhindered exchange of ions, mRNA, ribosomes, and small proteins (up to 5 kilodaltons [kDa]).

Nucleolus. The nucleoli, more than one of which may be present within a nucleus, consist of ribosomal RNA and are the loci of RNA processing and ribosome synthesis. They are not surrounded by a membrane.

Chromatin. This is a specific arrangement of DNA and the protein family called **histones** in approximately equal proportions. Its physical arrangement is in repeating units of one DNA molecule and eight histone molecules. It exists, for much of the cell cycle, as long, loosely coiled strands but condenses at cyclic intervals into well-defined **chromosomes**. These are the functional subunits of chromatin.

Endoplasmic Reticulum

Endoplasmic reticulum (ER) is an interconnected system of parallel membranes that forms a fluid-filled network of interconnected chambers. Two distinct regions are recognized: rough and smooth ER.

Rough endoplasmic reticulum. This area of the ER is named “rough” because the outside of its membrane is studded with **ribosomes**. Protein synthesis usually begins with the N-terminal and with the ribosome unattached to the ER. The N-terminal sequence and ribosome are then bound by a specific ER membrane receptor; as amino acids are assembled on each ribosome, the growing polypeptide chain is fed into the interior of the ER for further processing. Export of synthesized proteins from the ER occurs by transport vesicles that form when a portion of the ER membrane encloses a localized volume, pinches off, and moves toward the Golgi apparatus.

Ribosomes. Genetic information is stored in the nucleus, but proteins are synthesized in the cytoplasm with the help of ribosomes. Ribosomes measure approximately 20×30 nm. They are 65% ribosomal RNA and 35% protein and consist of two subunits (40S and 60S). They are the sites of protein assembly (**translation**) in accordance with the blueprint carried from nuclear DNA by mRNA (Figure 1–2). Ribosomes can be attached to the cytosolic side of the rough endoplasmic reticulum, or they can be free in the cytosol. Attached ribosomes synthesize proteins that are eventually secreted from the cell, lysosomal proteins, and cell membrane proteins. Free ribosomes synthesize mitochondrial, peroxisomal, or cytoplasmic proteins (e.g., hemoglobin). When a protein molecule has been assembled, the two subunits of the ribosome dissociate.

Smooth endoplasmic reticulum. Smooth ER synthesizes membrane lipids. The amount of smooth ER varies greatly among the cells of different organs, depending on the special ER tasks required in those organs. For example, the smooth ER synthesizes steroid hormones in some cells, participates in fat metabolism in cells of the gastrointestinal (GI) tract, synthesizes and stores glycogen in cells of liver and skeletal muscles, detoxifies drugs in the cells of the liver and kidneys, and stores and releases ionized calcium (Ca^{++}) in cells of striated muscle.

The longitudinal sarcoplasmic reticulum of striated muscle is smooth ER.

Golgi Apparatus

The Golgi apparatus is the next station for the modification of proteins and polypeptides that were synthesized in the rough ER. It is near but not attached to the nuclear membrane and consists of a system of membrane-

lined cisternae. It is a polarized structure, with a **cis** side close to the rough ER (see Figure 1–1) and a **trans** side at the distal end from the rough ER. The sacs lying between the cis and trans sacs are termed **medial** Golgi. The cis-Golgi receives transport vesicles from the rough ER, and the trans-Golgi releases other vesicles to their final destination (see Figure 1–1).

The Golgi apparatus is a major site of membrane formation. It is here that proteins are modified, sorted, and accumulated in distinct vesicles whose ultimate destination is the plasma membrane, lysosomes, or exocytotic storage granules.

Lysosomes

Lysosomes are membrane lined and assume a variety of shapes. Primary lysosomes have just budded off from the Golgi apparatus and tend to be spherical. They are filled with enzymes that are capable of digesting proteins, carbohydrates, lipids, nucleic acids, and other biologic material. Their digestive function follows fusion with vesicles that have enclosed the target.

Peroxisomes

Peroxisomes resemble lysosomes in structure (single phospholipid bilayer membrane) but differ in their point of origin (they bud off the smooth ER), and they contain mostly the peroxidases and hydrolases that are required for metabolism of free oxygen radicals or the oxidation of lipids, amino acids, ethanol, and so on.

Mitochondria

These are elongated structures, surrounded by two phospholipid bilayers that generally do not touch (Figure 1–3). Their number in a cell is closely corre-

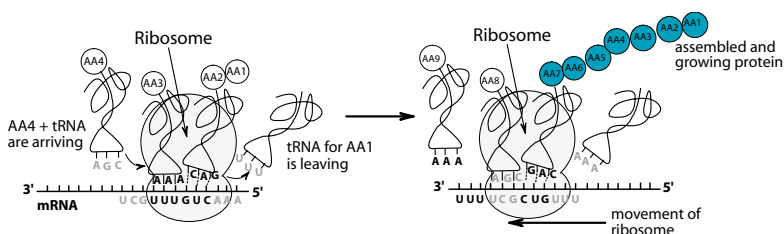


Figure 1–2 Ribosomes are the sites of protein assembly (translation) in accordance with the blueprint carried from nuclear DNA by mRNA. Amino acid constituents of the protein are selected by the appropriateness of the base coding carried by the attached transfer RNA (tRNA). After each amino acid is joined to the preceding one the ribosome advances one codon toward the 3' end of the mRNA. When a protein molecule has been assembled, the two subunits of the ribosome dissociate.

lated with metabolic activity and rate of adenosine triphosphate (ATP) production. The two mitochondrial membranes differ greatly in their properties:

1. The inner bilayer has a much larger surface area because it forms **cristae** that project into the mitochondrial **matrix**.
 - It contains the carnitine shuttle transporter for free fatty acids that can be beta oxidized to form acetyl-coenzyme A (Co-A) as substrate for the Krebs cycle.
 - It contains the transporters that function in association with the electron transport chain to pump hydrogen ions (H^+) from the mitochondrial matrix into the space between the inner and outer mitochondrial membranes, thereby creating gradients for H^+ , charge (matrix = -150 mV), and free energy. The H^+ gradient is used, in part, for inner membrane co-transport of pyruvate and phosphate with H^+ into the matrix. The charge gradient is used, in part, for the accumulation of Ca^{++} into the matrix.
2. The outer bilayer is more leaky to ions and small molecules than is the inner layer.

In addition to synthesizing ATP, mitochondria also synthesize urea and heme.

Mitochondria contain their own DNA but also the DNA codes for a limited number of proteins. Other proteins must be imported by active transport from the cytosol of the cell. This requires close interaction between the inner and outer membranes.

Cytosol

The cytosol is an aqueous solution of ions and proteins. It is contained by the **plasma membrane** and is stabilized by the **cytoskeleton**. In spite of very short intracellular diffusion distances, the activities of at least some ions

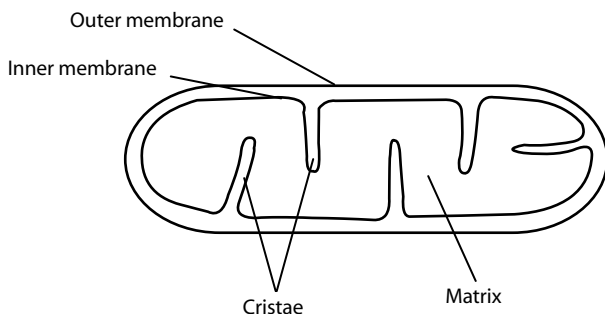


Figure 1–3 Structure of a mitochondrion.

may not be homogeneous throughout the cytosol, and the importance of this for normal function is not yet fully evident.

Cytoskeleton

The cytoskeleton, an arrangement of intracellular structural elements, (1) helps maintain cell shape, (2) permits motion of one part of a cell relative to other parts, and (3) provides the machinery for the locomotion of the whole cell. The primary skeletal elements are, in descending order of size, **microtubules**, **intermediate filaments**, and **actin** (or **microfilaments**).

Microtubules, centrioles, and ciliae. Microtubules are hollow, cylindrical arrangements of the proteins α - and β -tubulin, 20 to 30 nm in diameter and 10 to 25 μ m in length. They grow from one end (the **plus end**) by polymerization of tubulin, whereas the minus end tends to disintegrate by hydrolysis unless it is stabilized. Microtubules are present in almost all mammalian cells and have three main functions: (1) control of the mitotic process, (2) movements of ciliae and flagellae, and (3) guided intracellular transport of proteins or vesicles.

Control of the mitotic process. In most cells, with the notable exception of nerve cells, the negative end of most microtubules is anchored and stabilized in the **centrosome**.^{*} The plus ends, as long as they are free, grow from the pericentriolar material of the centrosome along an arbitrary path. During the S phase of the cell replication cycle, when DNA replicates, the centrosome duplicates and divides into two equal parts, each containing a centriole pair. When mitosis begins, the two centrosomes move to opposite sides of the nucleus and form the two poles of the **mitotic spindle**, an array of microtubules that aligns chromosomes and holds them in place for the subsequent steps of cell division. These aspects are described more fully below (see The Cell Cycle).

In the long phase preceding mitosis, the configuration of microtubules attached to a centrosome changes continually as new microtubules grow by tubulin polymerization at the plus end and old ones disintegrate by tubulin hydrolysis at the minus end. A variety of chemical agents can inhibit microtubule formation and, with that, inhibit cell division. Examples of such chemical agents, all of which bind α - and β -tubulin, are colchicin, vinblastine, and vincristine.

^{*}A region that lies near the nucleus. The centrosome contains amorphous pericentriolar material and two centrioles (see Figure 1-4), each a pair of cylindrical bodies, positioned at right angles to each other.

Movements of ciliae and flagellae. Ciliae and flagellae are hair-like cell surface projections. Their walls are formed by nine arrays of paired tubular structures, much in the same way as centrioles are formed by nine arrays of triplets (Figure 1–4). They grow from and are anchored to structures called **basal bodies**, whose structure resembles that of each member of a centriole pair. A motor protein, dynein, causes the bending and sweeping motion of these projections. The heads of this molecule project from one tubular structure of a pair to the other fiber, bind there, hydrolyze ATP, and use the liberated energy to “walk” along the fiber, thereby causing local bending.

Intracellular transport. Microtubules serve as binding sites for motor proteins that are able to hydrolyze ATP and use the liberated energy to cause motion and perform mechanical work.

- The **kinesins** move and can carry cargo toward the positive end of the microtubule.
- The **dyneins** move and carry cargo in the opposite direction, toward the negative end of the microtubule.

Intermediate filaments. These elements of the cytoskeleton are 12 to 15 nm in diameter and include a variety of polymerized, mechanically stiff polypeptides, such as keratin, desmin, vimentin, lamin, and others. The relative abundance of different filamentous proteins varies among different cells:

- Keratin is found in epithelial cells, hair, and nails.
- Desmin filaments link together the myofibrils in striated muscle cells.
- Vimentin is found mostly in fibroblasts.
- The lamins are the major constituent of the intermediate filament mesh that lines the inner surface of the nuclear membrane (the nuclear lamina).

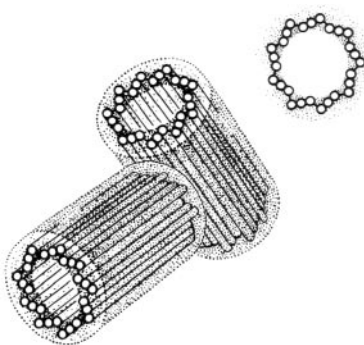


Figure 1–4 Schematic of a centriole. Nine groups of three microtubules run longitudinally in the walls of each centriole.

- Ankyrin and spectrin fix in place the $3\text{Na}^+/2\text{K}^+$ pump that is found in all cell membranes.

Intermediate filaments are thought to give structural strength to cells and help them withstand mechanical stress.

Actin filaments. Actin is an abundant cytosolic protein. It exists in F-actin, the polymerized, fibrous form, as a helical arrangement of monomeric G-actin chains. They are present throughout the cell and are concentrated in a narrow band just under the plasma membrane. A variety of proteins form anchoring links between this band and the elements of the plasma membrane. Actin has many additional functions in cells, including (1) aggregation into bundles so as to form microfilaments and (2) participation in movements of the cell surface, including phagocytosis.

Plasma Membrane

The plasma membrane defines the perimeter of the cell. Its special composition allows

1. export/import functions of substances that were synthesized or are to be metabolized within the cell,
2. control of intracellular composition,
3. recognition of other cells, and
4. interaction with neighboring cells.

Membrane Structure

The two major components are **lipids** and **proteins** in proportions that vary among different tissues. The lipids can both rotate and move laterally within their membrane leaf; the proteins are relatively fixed in position because of cytoskeletal anchoring (Table 1–1).

Lipids. More than half the lipid mass in plasma membranes is **phospholipids** and their physicochemical behavior imparts many of the characteristics that are associated with cell membranes. The plasma membrane also contains a high proportion of **cholesterol**. There are two classes of phospholipids: **glycero-phospholipids** and **sphingolipids**. Both contain a phosphorylated, charged head group and a pair of different, noncharged hydrocarbon tails (Figure 1–5).

In an aqueous medium, phospholipids arrange themselves in a double layer with the fatty acid tails facing one another so that the charged heads

face the watery medium. This arrangement results from the fact that water is a charged molecule.*

The compositions of the two halves of the bilayer forming the plasma membrane are different. For example, the outer half contains most of the glycolipids (lipids with sugar groups attached to them). These are particularly suited for membrane protection, cell-to-cell recognition, Ca^{++} binding, electrical insulation, and interactions with the extracellular matrix.

Glycero-phospholipids. In the glycero-phospholipids, the two hydrocarbon tails are fatty acids that are joined at one end by glycerol. This general structure is called **diacylglycerol (DAG)** (see Figure 1–5). A phosphate group links a charge-carrying head to the DAG.

One of the tails may be kinked or straight, depending on whether there is a *cis* double bond between one or more of the carbon pairs. Each *cis* double bond bestows a small kink. If the tails are straight, then the molecule assumes a conical shape; an aggregation of them will form a sphere, such as a lysosome. If, however, one tail is kinked, then the molecule is cylindrical in outline, and several of them will aggregate to form a flat layer. The plasma membrane contains a significant number of kinked-tail phospholipids.

*Both hydrogen (H) atoms in water (H_2O) carry a partial positive charge, whereas the oxygen atom carries a partial negative charge. As a result, water molecules interact with one another because the positively charged hydrogen atoms (H) on one molecule are attracted to the negatively charged oxygen (O) on the another.

Table 1–1

Components of the Plasma Membrane

Component	Classes	Subclasses	Function
LIPIDS	Phospholipids	Glycero-Phospholipids	Two fatty acid tails joined by a glycerol-containing head
		Sphingolipids	Head joins 1 fatty acid tail to sphingosine
	Cholesterol		Steroid ring contributes rigidity to membrane
PROTEINS	Peripheral Proteins		Enzymes or signal transducers
	Integral Proteins	Channel Proteins	Selective ion channels
		Carrier Proteins	Selective transporters
CARBO-HYDRATES			Extracellular coating (glycocalyx)

Sphingolipids. The sphingolipids, like the glycerophospholipids, have a charged, phosphorylated head group and two hydrocarbon tails. Only one of the tails is a fatty acid; the other one is formed by **sphingosine**. The most common sphingolipid is sphingomyelin, and it is abundant in the myelin sheath that surrounds many axons.

Membrane phospholipids are cleaved by specific **phospholipases** (see Figure 1–5). Thus, phospholipase A_2 yields arachidonic acid, and phospholipase C yields DAG plus the (head and phosphate) grouping (see Figure 1–5).

Cholesterol. The cholesterol molecule contains a steroid ring, which is a structure of physical rigidity. As a result, the presence of cholesterol at a fairly high concentration (20 g per 100 g of lipid) in the phospholipid bilayer of the plasma membrane reduces membrane fluidity and makes it more difficult for molecules to force their way through the membrane. The number of cholesterol molecules is equal in the two leaves of the bilayer.

Proteins. The plasma membrane of many cells contains a high fraction of proteins, and they are responsible for many biologic functions of the plasma membrane. The proteins either are attached to just one side of the bilayer (= peripheral proteins) or penetrate through the bilayer (= integral proteins). Integral proteins span the membrane only once or several times, each membrane-spanning domain being serially linked to its neighbor by a loop that may be intra- or extracellular. They function as channels, carriers, enzymes, or signal transducers, as detailed elsewhere.

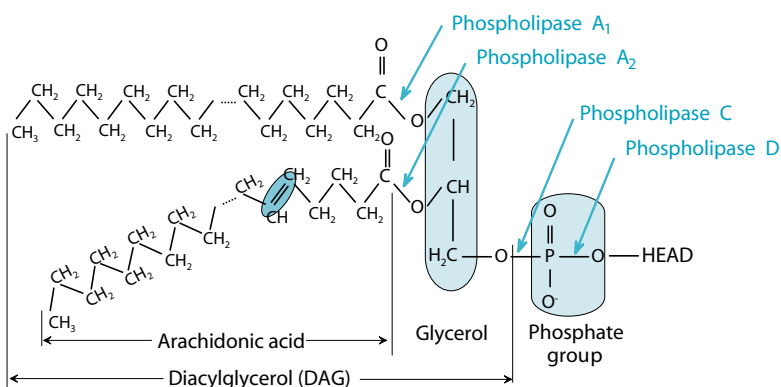


Figure 1–5 Specific sites of action of different phospholipases. Also shown is the kinking effect of a double bond in one of the fatty acid tails.

Membrane carbohydrates. Some plasma membrane proteins are heavily glycosylated, with carbohydrate chains as long as 100 units and facing only the extracellular region. Such protein–carbohydrate combinations are named **proteoglycans**, and they form a dense covering, the **glycocalyx**. This covering offers mechanical and chemical protection, participates in cell-to-cell recognition, and plays a role in cell-to-cell adhesion.

Membrane Function

Membrane transport mechanisms. The plasma membrane separates the cytosol from extracellular space and maintains the highly unequal ion concentrations of the two spaces. This is accomplished by four membrane transport strategies:

- Macromolecules, such as proteins, are transported in carrier vesicles either out of the cell (**exocytosis**) or into the cell (**endocytosis**).
- Gases and lipid-soluble molecules cross the membrane by **diffusion** through the lipid phase and are driven down their concentration gradients.
- Some ions and selected nonionic substances are transported by specific protein **carriers** by processes that are classified as **active** or **passive transport mechanisms**, depending on whether metabolic energy is directly and stoichiometrically applied to run the process (Table 1–2).
- Some ions move through protein **channels** that can be exquisitely selective in what ion(s) they will accept. The conductance of such channels can be varied so that they offer a mechanism of changing membrane permeability. The driving force for ion transport is the electrochemical gradient of the ion.

Active transport. Transport is active when it is tightly coupled to a source of metabolic energy, usually the stoichiometric hydrolysis of ATP.[†] It occurs in only one direction across the plasma membrane and generally transports substances against their electrochemical gradient and by means of a specific **carrier**.

- **Primary active transport** utilizes ATP directly.
- **Secondary active transport** has an absolute requirement for the simultaneous movement of an ion (generally Na⁺) down a concentration gradient that was created by primary transporters.

[†]For example, the Na⁺–K⁺ pump requires one ATP molecule to be hydrolyzed for every turn of the pump, moving 3Na⁺ out of the cell and 2K⁺ in.

Table 1–2

Membrane Transport Mechanisms

Class	Subclasses	Features
ACTIVE	Primary Active	Metabolic energy is applied directly and stoichiometrically to accomplish transport AGAINST an electrochemical gradient.
	Secondary Active	Energy for transport derives from simultaneous movement of an ion down its (actively maintained) electrochemical gradient.
PASSIVE	Simple Diffusion	<ul style="list-style-type: none"> • Transport is driven by and in the direction of the electrochemical gradient. • Membrane channels are often involved. • Transport rate varies linearly with the electrochemical gradient
	Facilitated Diffusion	<ul style="list-style-type: none"> • Transport is in the direction of the electrochemical gradient AND is mediated by a carrier protein. • Transport is specific. • Transport rate reaches a maximum when all carrier molecules are occupied.

Carrier-mediated transport: A carrier is a membrane-spanning transport protein that binds one or more species on one side of the membrane and then undergoes a transformational change, releases the species on the other side, and returns to the original state.

- Carriers that transfer a single solute across the membrane are called **uniports**.
- There are also carriers that transport two or more solute species such that the transfer of one depends on the coupled transfer of the others, either in the same direction (**symport**) or in the opposite direction (**antiport**).

Primary active transport: $\text{Na}^+ - \text{K}^+$ ATPase (the **sodium pump**) and $\text{Ca}^{++} - \text{ATPase}$ (the **calcium pump**) are two examples of primary active transporters. The calcium pump is more fully described in Chapter 6, “Cardiovascular Physiology.”

The sodium pump is present, to a varying extent, in nearly all animal cells. Up to 4,000 per μm^2 are found in the thick ascending limb of the loop of Henle, and as few as ≤ 1 per μm^2 are found in the erythrocytes. Its distribution over the plasma membrane can be highly nonuniform. For example, the epithelial cells, such as renal tubular cells, have all the pumps located on the basolateral side.

$\text{Na}^+ - \text{K}^+$ ATPase translocates, in a reciprocal manner, 3Na^+ outwardly and 2K^+ inwardly across the membrane and at the expense of one molecule of ATP.

This 3:2:1 stoichiometry remains constant over a wide range of membrane potentials as well as the cytosolic or extracellular concentrations of Na^+ , K^+ , and ATP.

The rate of $\text{Na}^+ - \text{K}^+$ pumping is slow (about 100 cycles. sec^{-1} , transporting about $50 \text{ pmol} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$), compared with the rate of Na^+ entry during an action potential ($\approx 1,000 \text{ pmol} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$), and is modulated by several factors. The pumping rate is

- increased by significant depolarization, insulin, β_2 -adrenergic agonists and aldosterone; and
- decreased by significant hyperpolarization, extracellular ouabain, and α -adrenergic agonists.

Secondary active transport: Unlike ATP-dependent ion pumps, secondarily active carriers do not require stoichiometric hydrolysis of ATP for solute transport, and they show saturation of transport as a function of ion concentration.

A common feature is that the driving force for these carriers must be created by primarily active transporters that establish the requisite concentration gradients.

- Many such carriers rely on the Na^+ gradient that is built up across cell membranes by $\text{Na}^+ - \text{K}^+ - \text{ATPase}$. Typical examples are the Na^+ -glucose co-transporter (SGLT1), the $\text{Na}^+ - \text{H}^+$ exchanger that is found in most cells, and the amino acid transporters that are found in the early portions of the proximal convoluted tubule in the kidney.
- Other carriers are not driven by the gradient for $[\text{Na}^+]$. Examples are (1) the $\text{K}^+ - \text{Cl}^-$ co-transporter that removes KCl and water from cells and (2) the band-3 protein (**capnophorin**) transporter that exchanges Cl^- for HCO_3^- across the erythrocyte membrane for the purpose of facilitating carbon dioxide (CO_2) transport away from metabolically active tissues. The phenomenon is often called the **chloride shift**.

Band 3 transports monovalent anions other than Cl^- and HCO_3^- but at a much slower rate. They include nitrate (NO_3^-), sulfate (HSO_4^-), phosphate (H_2PO_4^-), superoxide anion O_2^- , and hydroxyl ion (OH^-).

Passive transport. Substances are said to be transported passively across the plasma membrane when metabolic energy is not directly applied and when the driving force is one or more of (1) a difference in concentration, (2) a difference in electrical potential, or (3) a difference in osmolarity.

Membrane conductance: Only lipid-soluble (also called **hydrophobic** or **nonpolar**) compounds, gases, and water cross the plasma membrane with relative ease. Of these, water is believed to cross by specific water channels, whereas the other two cross by permeating the lipid bilayer. As expected, their rates of permeation vary directly with lipid solubility and inversely with molecular size. All gas transport occurs by simple diffusion down a concentration (partial pressure) gradient. The plasma membrane offers enough resistance to make its permeability to gas diffusion only about 1% of that found in water. Nevertheless, gases move across quickly because the membrane is only 3 to 5 nm thick.

The plasma membrane is very poorly conductive for water-soluble molecules and almost impermeable to charged molecules, even to such small monovalent ions as Na^+ and Cl^- . However, cells have developed techniques for the controlled modification of membrane conductance to Na^+ , K^+ , Ca^{++} , and Cl^- so that these ions can cross the plasma membrane by passive mechanisms under some circumstances. This selective and regulated conductance is bestowed by **channel proteins**, a class of membrane-spanning proteins that form **ion channels**. Ion channels are assembled so as to have three essential properties: (1) they form a central pore (Figure 1–6) through which ions flow down their electrochemical gradient; (2) they include a selectivity filter that controls which ions are permitted to flow through the pore; and (3) they incorporate a gating structure that switches the channel between the open and closed state. The gating structure may be sensitive to electrical (**voltage-gated channels**), chemical (**ligand-gated channels**), or mechanical forces.

The basic pore-forming structure of ion channels is called the α -subunit. It is formed, in many cases, by four monomeric assemblies (see Figure 1–6), each consisting of membrane-spanning domains that are linked serially by amino acid chains looping into the cytosol or into the extracellular space. Many voltage-gated channels comprise the pore-forming α -subunit plus other accessory subunits. For example, the voltage-gated Ca^{++} channel in most tissues consists of four subunits ($\alpha 1$, $\alpha 2$, δ , and β). In skeletal muscle, it contains an additional γ -subunit. Accessory subunits do not conduct ion flow, but they do modulate the function of the α -subunit with respect to its gating and current kinetics or sensitivity to extracellular and cytosolic factors.

Ion channels can be in one of three states: **closed**, **open**, or **inactivated**.

- When a channel is in the closed state, no ions flow through it, but the channel can be activated (i.e., “gated” to be in the “open” state).

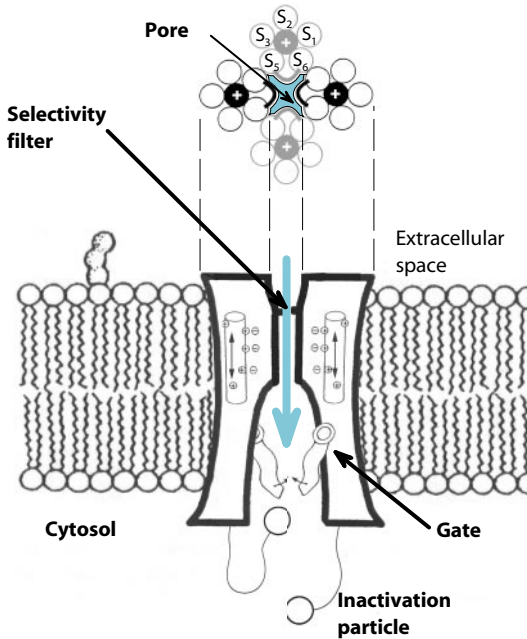


Figure 1-6 Schematic of a typical ion channel. The upper portion shows the tetrameric arrangement of the identical subunits around a central pore, each subunit consisting of six membrane-spanning domains, S1 to S6. A selectivity filter (about 0.3 nm in diameter) is formed by extracellular loops, each between S5 and S6 of the corresponding subunit. This “P loop” of about 20 amino acids folds and doubles back partway into the central pore region. A voltage-sensitive domain (S4) is indicated by the “+” sign in this view. The lower portion shows a cross-sectional view of two subunits so as to suggest the central pore and the selectivity filter. A gating mechanism, linked to the voltage-sensitive domain, is also indicated. This is sometimes called the “m-gate.” The cytoplasmic region of the channel includes a “ball-and-chain” mechanism for channel inactivation (“h-gate”), such as would be observed in voltage-gated channels for K^+ . In the Na^+ channels, the mechanism is formed by a smaller loop, attached at both ends, and is, therefore, called a “hinged lid.” Ca^{++} channels have inactivation mechanisms that depend on several regions.

(The degree of openness of the h-gates, even in fully repolarized cells, depends on membrane potential. For that reason, the rate and extent of depolarization in excitable cells are smaller if the resting membrane potential is less negative.)

- A channel that is in the open state allows current to flow.
- A channel is inactivated when it conducts no ion flow, even though its gating stimulus continues to be present. An inactivated channel must recover from inactivation and be brought to the closed state before it can be opened again. Inactivation is a process by which a cytoplasmic portion of the channel occludes the inner pore region (see Figure 1-6).

Ion channel selectivity is primarily bestowed by the presence of specific amino acid motifs in the region of the selectivity filter. For example, the motif

GYG (glycine, tyrosine, glycine) is found in all but one of the single-pore K^+ channels cloned to date; the motif DEKA (aspartate, glutamate, lysine, alanine) is found in Na^+ channels; and E (glutamate) is found in Ca^{++} channels.

Cell Environment

A large portion of tissue volume is occupied by the extracellular space. This is a complex arrangement of unconjugated proteins, glycoconjugated proteins, and glycosaminoglycans, all forming a structured network, named the **extracellular matrix**. Its physical composition is that two types of unconjugated proteins (**collagen** and **elastin**) are embedded in a hydrated polysaccharide gel, named **ground substance**. Collagen and elastin can be visualized as reinforcing rods that are embedded in the ground substance, much like structural steel rods are embedded in concrete.

Collagen

Collagen constitutes about 25% of the proteins in the human body, and this makes it the most common of proteins. It is a structural protein and consists of three left-handed helical polypeptide chains, individually named the pro- α -chains, wound around one another along the long axis in a right-handed superhelix. Each α -chain is encoded by a single gene and consists of about 1,000 amino acids. Twenty-five different α -chains have been identified, and they differ in their relative contents of amino acids versus the amino acid proline or its hydroxylated derivative hydroxyproline (Figure 1–7). Hydroxyproline and hydroxylysine are found only in collagen. They are formed from their respective parent by proline hydroxylase or lysine hydroxylase, both of which require vitamin C for their action. Lack of vitamin C brings on the complex of connective tissue disease known as **scurvy**.

The steric conformation of individual amino acids is of crucial importance to the helix conformation, and point mutations affecting only one amino acid can have profound consequences and result in hereditary disorders of connective tissue. Thus, if glycine, which occupies every third position in the amino acid sequence and has only a single H-atom side chain, is replaced by cysteine, whose side chain is a CH_2-SH , the outcome is **osteogenesis imperfecta**, a condition that is characterized by hearing loss and fragility of bone and blood vessels.

Collagens differ with respect to chain composition, and the 16 types that make up the family are grouped according to the shape of their aggregates.

Fibril-forming collagens. These include types I, II, III, V, and XI. Type I is the most abundant form of collagen and is found in skin, bone, tendons, ligaments, and the cornea. Types III and V are found in blood vessel walls.

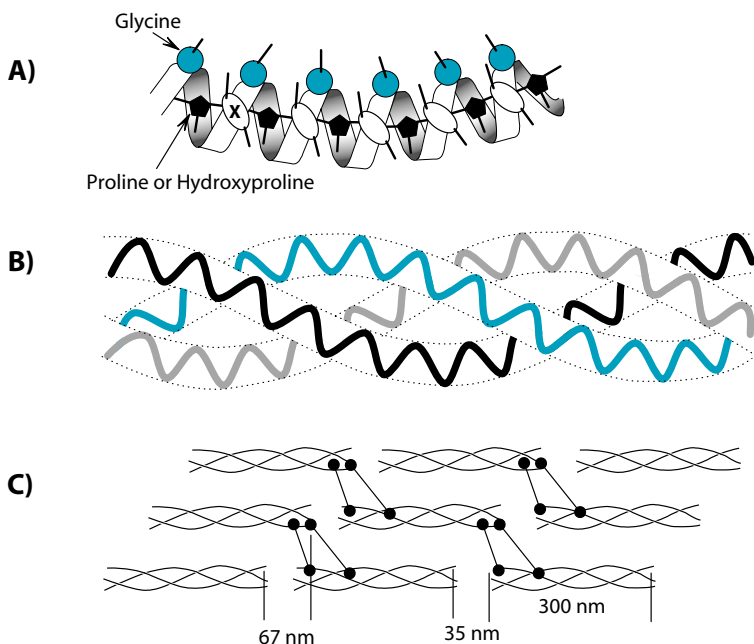


Figure 1-7 Structure of collagen. *A*, Section of one left-handed helical α -chain showing the typical glycine-proline/hydroxyproline-X motif. *B*, The assembled right-handed helix of 3 α -chains that constitute a single collagen molecule. The H side chain of glycine in each chain faces into the center of the triple-stranded helix. Each strand is 350 repeats of the glycine-proline-X motif. *C*, Type I collagen is characterized by fibrils composed of a staggered, linear arrangement of collagen molecules, the N terminal of one molecule being linked covalently to the C terminal of a neighbor. Other types of collagen show different molecular arrangements and linkages. X = any amino acid.

The others contribute to the interstitial supporting structures in cartilage, intervertebral discs, gut, and bone.

Fibril-associated collagens. These include types IX, XII, XIV, and XVI. A structural feature of this group is an interrupted triple helix. They are attached to the surface of the collagen fibrils and provide links between the fibrils and between the fibril and the extracellular matrix. They are found mostly in skin, tendon, and cartilage.

Mesh-forming collagens (nonfibrillar collagens). These include types IV, VI, VII, VIII, X, and XIII. They arrange themselves in multilayered networks of sheet-like meshes. Type IV dominates in basement membranes, type VIII is found in the vascular endothelium, type X in the calcifying cartilage, and type XIII in a variety of tissues.

Except for bone, in which collagen is very strongly cross-linked, the molecular chains of collagen are not generally so interconnected. However, with increasing age, such cross-connections appear, and the result is loss of pliability and a more “leathery” appearance of skin.

Elastin

Elastin is an elastic protein. It can be stretched without tearing, and when it is released from the stretched state, it will recoil quickly to its original state. It is found wherever elastic properties are required, but it also contains amino acid sequences that are chemotactic for fibroblasts and monocytes. Elastin exists as an amorphous, extensively cross-linked, coiled structure, and these covalent desmosine and isodesmosine cross-linkages bestow elastic behavior. When elastin molecules aggregate to form elastic fibers, then the amorphous elastin core of the fiber is surrounded by a sheath of fibrillin, a large glycoprotein that is secreted by fibroblasts and smooth muscle cells.

Ground Substance

Ground substance consists partly of structural elements (**glycoproteins**) and partly of hydrated gel that is formed by glycosaminoglycans and glycosaminoglycans covalently linked to a protein backbone (**proteoglycans**).

Glycoproteins. This group includes **fibronectin**, **laminin**, **vitronectin**, **tenascin**, **fibrillin**, **entactin**, and several more. Their main function is to provide scaffolding or adhesion. They do this by establishing contacts between the cellular or macromolecular components of the extracellular matrix or between the matrix and the outside of cells.

Cell surface receptors and adhesion molecules. Both classes of molecules are required for the interaction of cells with matrix elements as well as with other cells. Two important families of glycoproteins providing such functions are the **integrins** and the **cadherins**. Also involved are

- a variety of cellular adhesion molecules (CAM), such as NCAM (neural-), ICAM (intercellular-), VCAM (vascular-), and myelin-associated glycoprotein (MAG);
- CD44, the principal cell surface receptor for hyaluronic acid (hyaluronan); and
- laminin-binding protein.

Integrins: This large family of cell surface glycoproteins functions as (1) receptors for almost all glycoproteins of the extracellular matrix, (2) cell-to-cell adhesion molecules, and (3) transmembrane signal linkers. The lat-

ter function is possible because a typical integrin molecule will bind to fibronectin on the outside of the cell and to the actin cytoskeleton inside the cell.

Cadherins: These are cell-to-cell adhesion glycoproteins that function only in the presence of Ca^{++} . They consist of a large extracellular domain, a single transmembrane domain, and a short cytoplasmic domain. The cytoplasmic portion is closely associated with cytoskeletal elements by way of the **catenins** in a region that is histologically identified as a **desmosome** in anchoring junctions.

The cadherins are of particular importance during development but are expressed in adults in the epithelial cells, nervous tissue, and muscle. One of their roles in development is that cell types expressing specific cadherins collect in groups so that particular cells occupy particular locations.

Glycosaminoglycans. The glycosaminoglycans are unbranched polysaccharide chains consisting of disaccharide repeats. Each disaccharide is made up of two types of monosaccharides arranged in an alternating fashion. The glycosaminoglycans tend to exist as gels at body temperature. Their high density of negative charges binds clouds of ions whose osmotic activity attracts and holds water in the extracellular matrix.

Six glycosaminoglycans are found in human tissue (Figure 1–8): (1) hyaluronic acid (hyaluronan); (2) chondroitin 4-sulfate; (3) dermatan sulfate; (4) heparan sulfate; (5) heparin, and (6) keratan sulfate. Except for hyaluronic acid, they all attach themselves to a core protein to form proteoglycans.

Proteoglycans. The glycosaminoglycans other than hyaluronic acid arrange themselves around one of many core proteins. These include perlecan, lumican, fibroglycan, versican, and several more. The main functions of proteoglycans are

- mechanical support for cells;
- modulation of extracellular diffusion, enzyme activity, and growth factors; and
- modulation of cell adhesion, motility, and proliferation.

CELL NOURISHMENT AND GROWTH

Energy Metabolism

Maintenance of cell functions requires energy, and most human cells derive this energy by hydrolysis of ATP (**adenosine 5'-triphosphate**), which yields $\text{ADP} + \text{P} + 30.5 \text{ kJ}$ of energy per mole of ATP.

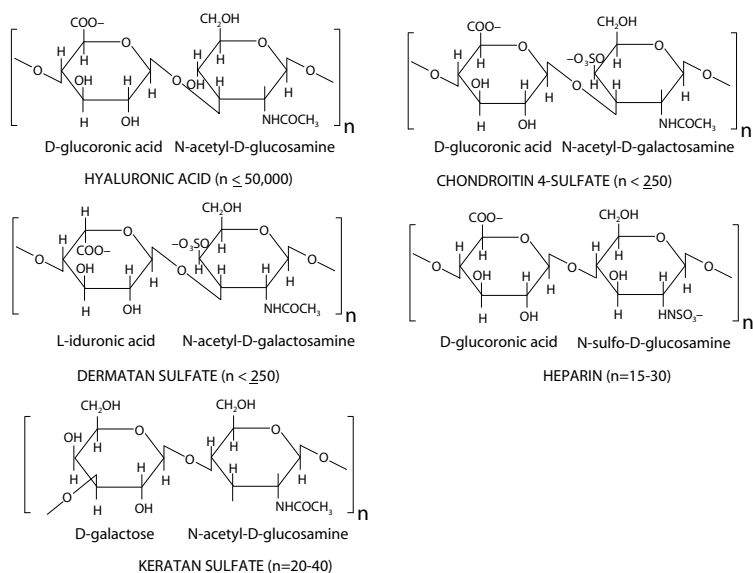


Figure 1-8 Each of the glycosaminoglycans is formed by polymerization of a particular disaccharide. The carboxyl and sulfate groups contribute to the highly charged polyanionic nature of glycosaminoglycans. Heparan sulfate is not shown. It resembles heparin in its disaccharide repeats but differs in the number of acetyl- and sulfate groups. n = the number of repeat units in each chain.

In many cases, ATP is used directly, but some reactions are powered by different nucleoside triphosphates:

- **Guanosine triphosphate (GTP)** is used in gluconeogenesis and protein synthesis.
- **Uridine triphosphate (UTP)** is used in glycogen synthesis.
- **Cytosine triphosphate (CTP)** is used in lipid synthesis.
- **Inosine triphosphate (ITP)** is used in several enzyme-catalyzed reactions.

A variety of enzymes promote transfer of the terminal energy-rich phosphate bond from ATP to these other triphosphates.

Energy Production

Energy production involves the formation of the terminal phosphate bond in the ATP molecule. This happens most abundantly in mitochondria by oxidative phosphorylation when NADH and FADH_2 are oxidized by electron

* NADH = reduced nicotinamide adenine dinucleotide; FADH_2 = reduced flavin adenine dinucleotide.

transport through the respiratory chain when oxygen is freely available. The substrates NADH and FADH₂ are produced in the Krebs cycle (citric acid cycle), and its substrate is acetyl Co-A. Acetyl Co-A can be formed by different pathways from the three dietary sources: carbohydrates, proteins, and fats.

- Carbohydrates are broken down to glucose and other simple sugars. Glucose is converted to two pyruvate molecules by the steps of **glycolysis**. Pyruvate is converted to acetyl Co-A by the enzyme pyruvate dehydrogenase.
- Proteins are broken down to their constituent amino acids. Amino acids are then degraded by the removal of the alpha-amino group in a process called **transamination**. The resulting carbon skeleton is converted into one of only seven metabolic intermediates. Of these seven, four are intermediates in the Krebs cycle, two are readily converted to acetyl Co-A (pyruvate and acetoacetyl Co-A), and the remaining one is acetyl Co-A itself.
- Dietary fats are mostly triglycerides, and they are broken down to glycerol (10% of the triglyceride molecule) and fatty acids (90%). Glycerol is rapidly converted to glucose, and the fatty acids are first transferred from the cytosol to the mitochondria and then broken down by beta-oxidation, two carbon atoms at a time, to acetyl Co-A.

Cell Cycle

Regulation of the Cell Cycle and Cell Growth

Cells that are not destined to replicate are in the G₀ state. Those that will replicate are in one of the phases of the cell cycle (Figure 1–9). This cycle consists of **interphase** (G₁ + S + G₂), during which a newly formed cell becomes a parent cell by doubling its content, and **mitosis** (M) (see Figure 1–9), during which a parent cell becomes two daughter cells, each with a complete set of chromosomes.

Regulation of the cell cycle is critically dependent on the **cyclin** family of proteins. Mitosis is initiated when cyclins combine with **p34^{cdc2}** to form **cdc2-kinase** that, in turn, phosphorylates relevant target proteins.

Cell growth is regulated by extracellular protein **growth factors** that initiate receptor-mediated intracellular cascades for gene transcription and cell cycle control systems.

CELL-TO-CELL COMMUNICATION

Gap Junctions

Gap junctions are regions where a uniform, narrow gap of 2 to 3 nm between the membranes of two neighboring cells is “bridged” by an assembly of six rods (2.5 nm in diameter, 7.5 nm in length). The rods are formed by a group

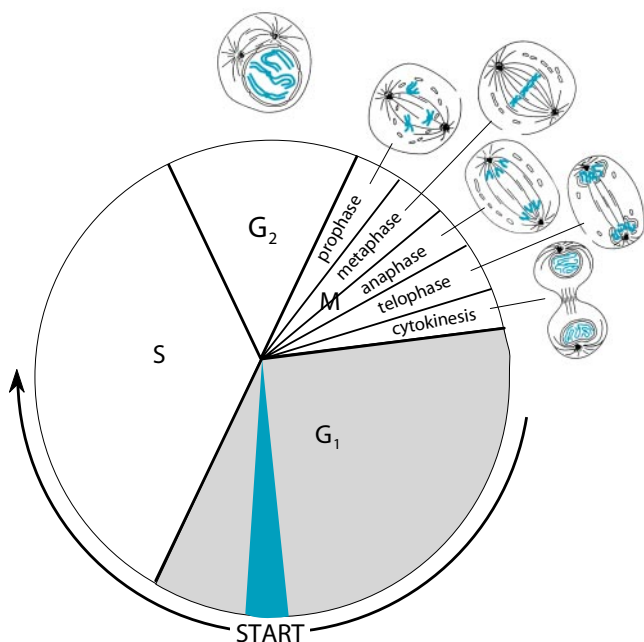


Figure 1–9 Schematic of the cell replication cycle. The life of the cell begins in G₁ and progresses in response to intra- and extracellular signals. G₁ = “Gap 1.” Cell growth occurs here. The brief interval labeled “START” represents a time at which certain components within the cell determine adequacy of cell size and quality of the extracellular environment; S = Replication of DNA within the nucleus; G₂ = “Gap 2.” A quiescent period during which a group of proteins, the cyclins, is synthesized; M = the period of mitosis. Mitosis is divided into prophase, metaphase, anaphase, telophase, and cytokinesis, each characterized by a particular arrangement and location of the genetic material as shown:

- Prophase:** Condensed chromosomes first become visible as paired chromatids that are attached to each other at the centromere with its associated kinetochore. Microtubules of each aster begin to capture randomly moving chromosomes, and the two centrosomes begin to move toward opposite sides of the nucleus. The nuclear envelope begins to disintegrate in late prophase, and such breakdown defines the beginning of prometaphase. Prometaphase lasts about 10 minutes and is followed by metaphase.
- Metaphase:** All of the chromosomes become attached at their centromere to the microtubules of the spindle and become aligned across the middle of the spindle, each pair of sister chromatids being held by oppositely directed microtubules. Metaphase lasts about 30 minutes.
- Anaphase:** Chromatids separate in unison and begin to move toward the spindle poles. They complete the migration to the poles within about 5 minutes.
- Telophase:** The chromosomal condensations at each pole fade and start reverting to chromatin, new nuclear membranes form, and the parent cell begins the processes of cytokinesis.
- Cytokinesis:** A constriction ring of actin filaments and myosin forms around the midbody of the elongated cell. The cytoplasm then cleaves. The chromosomes continue to disperse, and a nucleolus reappears in each daughter cell.

of proteins called the **connexins**. They are not continuous across the gap but align themselves at a slight angle so as to form a **connexon**, a formation that creates a 1- to 1.5-nm pore between the two cells (Figure 1–10). The angle of the tilt may be important for modulation of conductivity across the junction.

Gap junctions are regions of permeation for small molecules and ions less than 1,500 to 2,500 kDa in size. This includes all intracellular ions and second messengers. Neutral molecules move across more easily than do negatively charged species.

The total number of gap junctions between two cells is increased by cyclic adenosine monophosphate (cAMP). In addition, conductance of individual gap junctions is

- increased by (1) diminished $[H^+]_i$ and (2) elevated [cAMP] and its consequent protein kinase A–dependent connexin phosphorylation;[§] and
- decreased by (1) elevated protein kinase C–dependent connexin phosphorylation, (2) cell depolarization, (3) elevated $[H^+]_i$, (4) elevated tyrosine kinase–dependent phosphorylation, and (5) markedly elevated $[Ca^{++}]_i$.

Reduction of gap junction conductance leads to electrical and chemical uncoupling of neighboring cells.

Synapses

Synapses are specialized appositions between presynaptic and postsynaptic membranes for the purpose of information transfer between a nerve and another cell. The two synapsing cells do not touch physically but are separated

[§]This inhibitory effect of cAMP on gap junction conductance is seen in some cells. In others, elevated cAMP and protein kinase A–dependent connexin phosphorylation have the opposite effect.

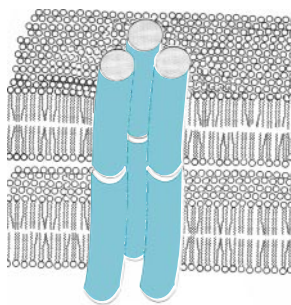


Figure 1–10 Schematic of half a gap junction between the adjoining plasma membranes of two cells. They are 2 to 3 nm apart and are bridged by the slightly tilted rods of connexins, a group of gap junction proteins. Only three rods are shown in each cell. Normally, groups of six arrange themselves in a rosette that forms a central pore.

by a narrow cleft. While electrical synapses (gap junctions) are known to occur in the nervous system, most synapses are regions of chemical information transfer. The presynaptic element synthesizes and releases a chemical substance named a **neurotransmitter** or a **neuropeptide**, and this acts mostly on the postsynaptic element by way of postsynaptic membrane **receptors**. In some cases, the released chemical may also act on membrane receptors in the presynaptic element as a strategy for modulating transmitter (or peptide) release.

Electrical Communication

Membrane Potentials

The concentration differences for several ion species distributed on the two sides of the plasma membrane cause healthy human cells to have an electrical life, the gross manifestation of which can be measured as a difference in voltage between the inside and outside of the cell. This voltage is called the **membrane potential**. **Excitable cells** display a **resting membrane potential** when they are at electrical rest and an **action potential** when they are excited.

Balance of forces across cell surface membranes. The presence of conducting ion channels and some leakage through the lipid bilayer make the plasma membrane a leaky barrier between two regions of generally large differences in ion concentrations. When an ion species moves across the plasma membrane down its concentration gradient, then an opposing transmembrane gradient in electrical potential is created. As a result, ion movement down a concentration gradient will not continue to the point where the concentration difference has been abolished. Instead, passive ion (net) transport across the plasma membrane stops when the force arising from the remaining concentration gradient is balanced by the opposing force arising from the gradient in electrical potential.

As a result, electrically resting cells exist in a steady state, in which each of the ion species is maintained at a concentration difference across the plasma membrane by an equal and opposite electrical force. It is possible to calculate for any ion species the electrical force that *would* be required to provide an exact counterbalance for its steady-state concentration gradient. That electrical force is named the **ion equilibrium potential** or the **Nernst potential** for that ion.

Ion equilibrium potential. Definition. The ion equilibrium potential (E_{ion}) or the Nernst potential of an ion species is the electrical driving force that *would* (1) be equal in magnitude but opposite in direction to the driving force represented by the concentration gradient and (2) prevent net passive transport of that ion species.

Any ion species would stop to move passively across the plasma membrane and down its concentration gradient once the potential difference across the membrane is equal to E_{ion} .

Determination. E_{ion} can be measured directly only when there is but one ion species present. Therefore, E_{ion} is normally calculated from the existing concentrations of the ion species of interest and the valence (z) of the ion:

$$E_{\text{ion}} = - \frac{61}{z} \log \frac{\text{intracellular concentration of the ion}}{\text{extracellular concentration of the ion}}$$

Significance. E_{ion} is a fictitious number in that it represents an electrical force that is not likely to be actually present. The electrical force that is present and measurable across the plasma membrane is the **membrane potential**.

- The magnitude and polarity of E_{ion} are equal to the electrical potential that would have to be applied to the inside of the cell if the existing concentration difference for that ion is to be maintained by an opposing electrical force alone.
- If E_{ion} for a given ion species is equal to the membrane potential of an electrically resting cell, it is likely that the steady-state distribution of the ion on both sides of the plasma membrane is determined by passive transport mechanisms only.
- If E_{ion} is different from the resting membrane potential of the cell, active transport mechanisms are involved in maintaining the distribution of the ion across the plasma membrane.

Resting membrane potential. Definition. E_{rest} is the voltage that can be measured across the plasma membrane of the electrically resting cell. It is *not* simply the algebraic sum of all ion equilibrium potentials because that sum does not account for voltage losses resulting from the flow of each ion through the resistance of the membrane.

Determination. The resting membrane potential of a cell is usually determined by direct voltage measurement. However, it can be calculated with the help of the **Goldman-Hodgkin-Katz equation**:

$$E_{\text{rest}} = 61 \log \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i + \dots}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o + \dots}$$

Where E_{rest} = resting membrane potential

P_X = membrane permeability coefficient for ion species X

K or K^+ = potassium ion

Na or Na^+ = sodium ion

Cl or Cl^- = chloride ion

o = extracellular concentration

i = intracellular concentration

Action potential. Definition. An action potential is a response in which the membrane potential changes transiently from E_{rest} to a peak value that is more positive than E_{rest} (Figure 1–11). It is initiated when a stimulus depolarizes the membrane to a certain voltage threshold. Levels of depolarization that fail to reach the threshold also fail to initiate an action potential.

Transmembrane currents. Action potentials in nerves arise mostly from conductance changes in Na^+ and K^+ channels. Both are activated at membrane potentials near -40 to -50 mV. The Na^+ channels are activated and inactivated rapidly. The K^+ channels are of the outwardly rectifying type and have a more complicated behavior.

- The large inward current creating the upstroke of the action potential in many, but not all, excitable cells is carried by Na^+ , after a sufficient stimulus has raised the membrane potential from E_{rest} to the gating voltage for i_{Na} . The resulting influx of Na^+ depolarizes the cell further and causes more Na^+ channels to open in a regenerative process that drives

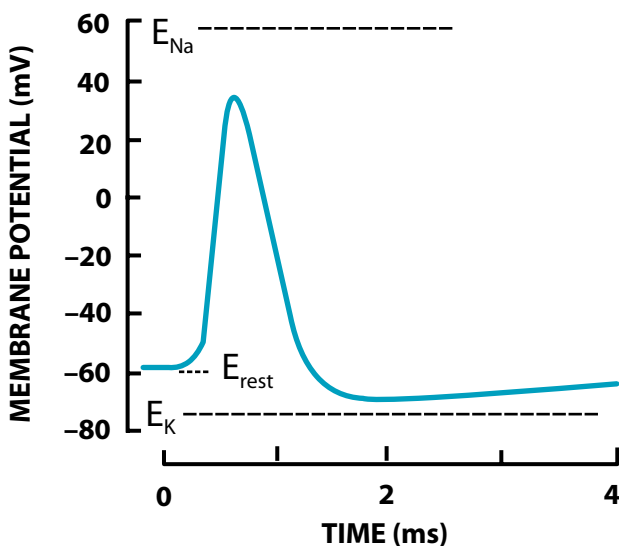


Figure 1–11 Changes in membrane voltage during a typical nerve action potential. A stimulus, applied at 0 ms, causes a gradual rise in membrane potential from E_{rest} to the gating voltage for Na^+ channels. When the gating voltage is reached, the membrane potential begins to rise sharply toward E_{Na} . K^+ efflux causes the subsequent fall in membrane potential. There is a slight hyperpolarization before a variety of small currents restore membrane voltage to E_{rest} . E_{rest} = resting membrane potential; E_{Na} , E_{K} = ion equilibrium potentials for Na^+ and K^+ , respectively.

the membrane potential toward the sodium equilibrium potential (E_{Na}). After <1 ms and before E_{Na} is reached, the inward current diminishes when the channels are inactivated by closure of the h-gate (see Figure 1–6). They cannot be activated again until some time after the cell has repolarized. Reactivation of the Na^+ channels is a much slower process than their activation, and this is responsible for the **refractory period** of excitable cells because a subsequent action potential can occur only when Na^+ channels can be opened again.

- Delayed rectifier-type outwardly rectifying K^+ channels activate more slowly than do the Na^+ channels and do not inactivate nearly as quickly. A sufficient number of them are open only by the time most of the fast-inactivating Na^+ channels are already closed and i_{Na} is declining. At that point, K^+ ions leave the cell rapidly, driven by the K^+ gradient, and continue to leave it through the open channels. This produces the downstroke of the action potential. The potassium current stops when the membrane potential reaches the potassium equilibrium potential (about -80 mv). This is slightly more negative than normal E_{rest} , and the difference is called **after-hyperpolarization**. When all net ion transport has stopped, the membrane potential settles again at the resting level.

During the period between action potentials the Na^+/K^+ pump restores to normal the slight ionic imbalances that are left after the action potential.^{||}

Chemical Communication

Some lipid-soluble chemicals, such as steroid hormones, thyroid hormone, or vitamin D, cross the plasma membrane of their target cells and cause biologic responses after binding to **receptors** that are located in the cytosol or on the nuclear envelope.

Many chemicals elicit responses in cells without actually crossing the plasma membrane. This requires interaction of the chemical (the first messenger) with a membrane receptor and consequent intracellular activation of a variety of **second messenger** systems. Some second messengers, such as Ca^{++} or cyclic guanosine monophosphate (cGMP), couple the signal directly, whereas others operate by way of kinases or calmodulin.

^{||}The inside of the cell has a slight excess of Na^+ and a slight deficit of K^+ . It should be noted that these imbalances are so small that several hundred thousand action potentials could be generated before the cell would run low on K^+ .

Membrane Receptors

These are membrane-spanning proteins that bind a specific signaling molecule (= **ligand**) and then initiate cascades that result in a biologic response of the target cell. They are grouped according to their transduction mechanisms into (1) **ion channel-linked**, (2) **enzyme-linked**, (3) **tyrosine kinase-linked**, or (4) **G protein-linked receptors**. Whereas any one receptor recognizes only one ligand that occurs naturally in the body, many ligands are recognized by more than one type of receptor.

Ion channel-linked receptors. These are receptors that are associated directly with an ion channel. When such a receptor is activated by its ligand, it modulates channel conductance.

Enzyme-linked receptors. These receptors are linked to or incorporate an enzyme within the intracellular domain of the membrane-spanning protein. Examples are atrial natriuretic peptide receptors linked to intrinsic (particulate) guanylate cyclase and platelet-derived growth factor receptors with intrinsic **tyrosine kinase** domains (Figure 1–12A).

Tyrosine phosphatases. Several membrane-spanning tyrosine phosphatases have been identified, but their physiologic importance remains unclear. Their extracellular domains have sequences that could act as receptors. Their biologic effects would, presumably, be dephosphorylation of proteins that were phosphorylated by tyrosine kinases.

Tyrosine kinase-linked receptors. These do not have tyrosine kinase domains in their cytosolic tail. However, they respond to ligand binding in the extracellular domain with formation of a dimerized complex whose intracellular domains bind and activate cytosolic protein-tyrosine kinase. The activated kinase then phosphorylates tyrosine residues in the receptor and leads to biologic activity (Figure 1–12B).

G protein-linked receptors. This large class of membrane receptors is characterized by being coupled with intracellular effector mechanisms through a **G protein**.[#] Each receptor consists of a single polypeptide chain that threads back and forth across the lipid bilayer and has an extracellular ligand-binding domain and an intracellular domain for G-protein binding.

G proteins. G proteins are couplers that link membrane receptors occasionally to an ion channel but most often to the intracellular enzyme that

[#]A class of plasma membrane-associated proteins that are capable of binding GDP and GTP.

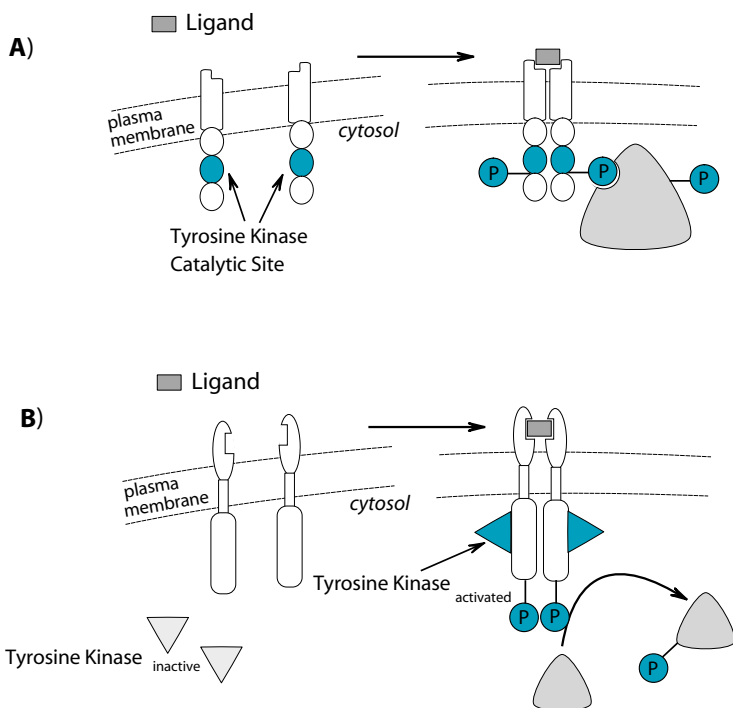


Figure 1-12 There is a difference between enzyme-linked receptors that incorporate a tyrosine kinase domain and tyrosine kinase-linked receptors. *A*, Some membrane receptors include a tyrosine kinase domain within their cytosolic tail. Ligand binding to such receptors activates the kinase, phosphorylates a tyrosine residue within the receptor tail, and can then phosphorylate and activate other cytosolic enzymes. *B*, Tyrosine kinase-linked receptors form dimers when extracellular ligand binds to them. The intracellular domains of the dimer bind and activate cytosolic tyrosine kinase. The activated kinase then phosphorylates tyrosine residues in the receptor and leads to biologic activity by way of phosphorylation cascades.

produces a second messenger. They consist of three subunits, α , β , and γ . In the resting state, a molecule of guanosine diphosphate (GDP) is bound to the α -subunit (Figure 1-13). Binding of a ligand to the G protein-associated receptor causes a conformational change, dissociation of GDP from the α -subunit and binding of guanosine triphosphate (GTP) in its stead. The combined β - and γ -subunits then dissociate; in most cases, the α -GTP-subunit performs the next action. This may be modulation of an ion channel or the activation of the catalytic subunit of one of the distal enzymes, **adenylate cyclase**, **phospholipase C**, or a **phosphodiesterase**. The dissociated β -/ γ -subunit can also activate a **phospholipase A** and

stimulate production of arachidonic acid from membrane phospholipids (see Figure 1–4).

Activated G proteins spontaneously return to their resting state.

Activated G proteins that are linked to intracellular enzymes will inhibit (in the case of G_i proteins) or promote (in the case of G_s or G_q proteins) the intracellular concentration of the second messengers, **cAMP**, **cGMP**, **diacylglycerol (DAG)**, **inositol triphosphate (IP_3)**, and Ca^{++} .

Second Messengers

These chemicals were named “second” messengers to make it clear that the ligand activating the receptor is the first messenger. The second messengers are intracellular transducers and function to produce cellular responses to extracellular signals.

The adenylate cyclase system. Formation of cAMP from ATP by the plasma membrane-bound enzyme **adenylate cyclase** is modulated by both stimulatory and inhibitory receptors (R_s and R_i) (see Figure 1–13) and G proteins (G_s and G_i) (see Figure 1–13). Cyclic adenosine monophosphate (cAMP) promotes the activation of protein kinase A (PKA). Protein kinase A exists as two subunits, one regulatory and the other catalytic. Binding of cAMP causes the two subunits to dissociate and the catalytic subunit to become activated so that it is capable of phosphorylating proteins, thereby altering their function and bringing about a biologic action.

The most prominent example of this second messenger system and the duality of effects that can be elicited by the same ligand are seen in the action of epinephrine (adrenaline). When it acts on α_2 -adrenoreceptors, it causes inhibition of cAMP formation; when it acts on β_1 -adrenoreceptors, it promotes cAMP formation.

The phospholipase C system. As shown in Figure 1–5, phospholipase C cleaves membrane phospholipids so as to yield DAG plus the head portion of the phospholipid. The two most relevant C-type phospholipases are phospholipase $C\beta$ (PLP- $C\beta$), which is attached to the cytosolic side of the plasma membrane, and phospholipase $C\gamma$ (PLP- $C\gamma$), which is a cytosolic enzyme. Phospholipase- $C\beta$ is activated by G_q proteins and, therefore, requires binding and hydrolysis of GTP (Figure 1–14). Phospholipase- $C\gamma$ is activated by tyrosine kinase-linked receptors and requires (1) ATP hydrolysis for activation and (2) translocation from the cytosol to an attachment point on the plasma membrane. **Phosphatidylinositol 4,5-bisphosphate (PIP_2)** is the membrane phospholipid that is most important for the phospholipase-C system. Phosphatidylinositol 4,5-bisphosphate₂ is

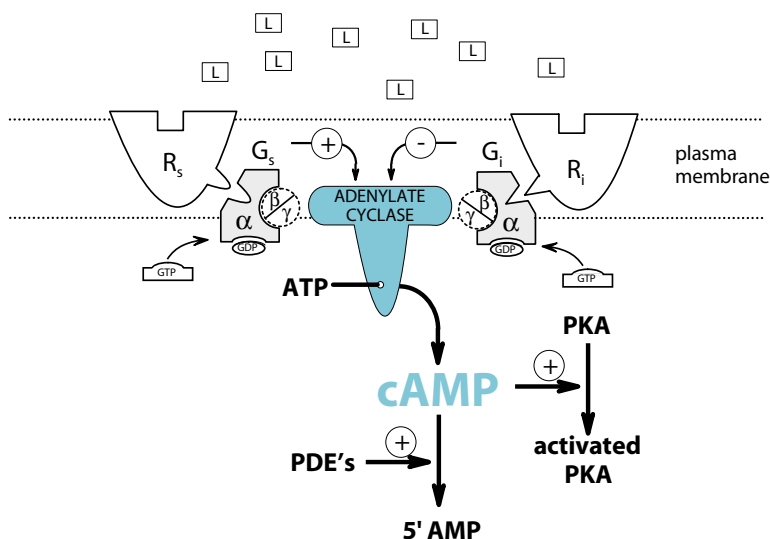


Figure 1-13 The adenylate cyclase system by which the second messenger cAMP is formed. Both stimulatory and inhibitory paths are shown. When a G protein is activated by receptor-ligand interaction, its α -subunit replaces the bound GDP molecule with a GTP and the β - γ moiety dissociates, allowing the GTP- α -subunit to act on the membrane enzyme adenylate cyclase. Before it is rapidly metabolized by phosphodiesterases, cAMP activates protein kinase A (PKA). Protein kinase A promotes phosphorylation of a variety of intracellular effectors. α , β , γ = subunits of G protein; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; 5' AMP = 5' adenosine monophosphate; G_i , G_s = inhibitory, stimulatory G protein; GDP = guanosine diphosphate; GTP = guanosine triphosphate; L = ligand; PDE = phosphodiesterase; R_i , R_s = inhibitory, stimulatory receptor.

cleaved by PLP-C β or PLP-C γ to yield three products: DAG, a small fraction of a cyclic triphosphate, and mostly IP₃ (see Figure 1-14).

Diacylglycerol. Diacylglycerol, formed from phospholipids by the action of the phospholipase C family, is a second messenger in its function as an activator of the **protein kinase C (PKC)** family. Activated PKCs phosphorylate proteins and promote, among others, Ca⁺⁺-ATPase activity, gene expression and activation of cell proliferation, ion channels, and exocytosis. They also provide negative feedback by suppressing phospholipase C activation and down-regulating receptors of the adenylate cyclase cascade.

As suggested in Figure 1-5, DAG can be cleaved by phospholipase A₂ to yield **arachidonic acid (AA)**. Arachidonic acid can be metabolized by five separate pathways to yield the **prostaglandins** (the cyclooxygenase pathway), the **leukotrienes** (the 5-lipoxygenase pathway), and other **eicosanoids** (from the cytochrome P-450 mono-oxygenase pathway or the 15-lipoxygenase and

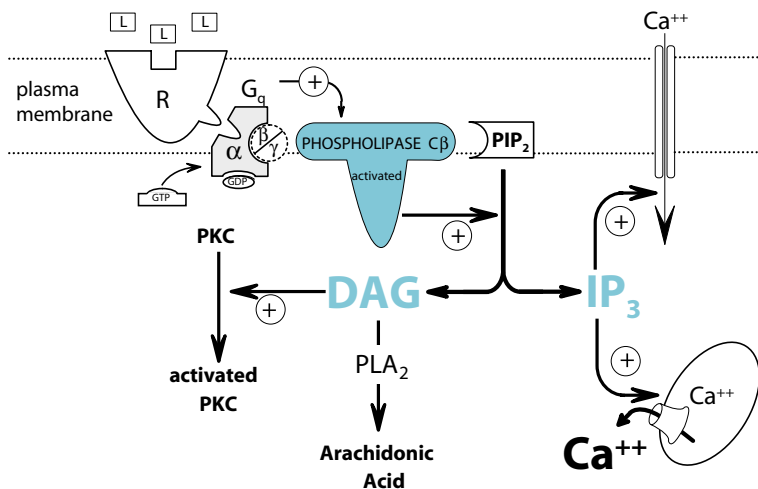


Figure 1–14 The phospholipase C system by which the second messengers diacylglycerol (DAG) phosphatidylinositol 1,4,5-trisphosphate (IP₃), and Ca⁺⁺ are formed. Binding of a ligand (L), to its receptor activates one of the G_q proteins and that activates membrane-associated phospholipase C β . Activated phospholipase C β hydrolyzes the minor membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP₂) to yield DAG, and inositol 1,4,5-trisphosphate (IP₃) binds and activates a Ca⁺⁺ release channel in the endoplasmic reticulum; it also increases membrane Ca⁺⁺ conductance. This latter action might be due to an IP₃ metabolite. Diacylglycerol activates protein kinase C (PKC) and can be cleaved by phospholipase A₂ (PLA₂) to yield arachidonic acid.

12-lipoxygenase pathways in platelets and leukocytes). All of these AA metabolites have important physiologic actions.

Inositol 1,4,5-trisphosphate and metabolites. The metabolic fate of IP₃ is that it eventually becomes inositol. This happens in several steps, the first of which is mostly a dephosphorylation that yields inositol 1,4-bisphosphate. However, there is an alternative path whose first step is phosphorylation of IP₃ to yield inositol 1,3,4,5-tetrakisphosphate (IP₄). Inositol 1,4,5-trisphosphate operates by a receptor-mediated mechanism to elevate cytosolic [Ca⁺⁺] (see Figure 1–14). The IP₃ receptor is similar to the ryanodine receptor (Ca⁺⁺ release channel) found in the sarcoplasmic reticulum of cardiac muscle. Inositol 1,3,4,5-tetrakisphosphate may enhance Ca⁺⁺ influx from the extracellular space by opening a membrane Ca⁺⁺ channel.

Ionized calcium (Ca⁺⁺). Ionized calcium acts as an intracellular second messenger in several cellular responses. It is released from intracellular stores and brought in from the extracellular space down a steep electrochemical gradient when the Ca⁺⁺ channels are open.

- **Ca⁺⁺ stores:** The main intracellular Ca⁺⁺ stores are the mitochondria and the endoplasmic reticulum, and it is the latter that is most important for signaling functions. Release from stores occurs by one of two mechanisms: ryanodine receptors or IP₃ receptors. Both may be present in the same cell. After release, the stores are refilled by a Ca⁺⁺-ATPase.
- **Ca⁺⁺ influx:** There is both a voltage gradient and a steep concentration gradient** for Ca⁺⁺ to enter cells provided that Ca⁺⁺ channels are open. It has been hypothesized that IP₄ or IP₃ or one of its isomers can modulate conductivity in membrane Ca⁺⁺ channels.

Ionized calcium that has been released into the cytosol binds to intracellular receptors such as **calmodulin** (most mammalian cells) or **troponin C** (striated muscle cells). The Ca⁺⁺-calmodulin complex controls a large number of enzymes (including phosphodiesterases), transporters, ion channels (including Ca⁺⁺ channels), and calmodulin-dependent kinases that exert their biologic effects by way of protein phosphorylation.

Cyclic GMP. Cyclic GMP is formed from GTP by the enzyme **guanylate cyclase**. Activated guanylate cyclase can also accept ATP to form cAMP when GTP is not available. Guanylate cyclase exists in two forms: **particulate** and **soluble**.

Particulate guanylate cyclase (pGC). This form is associated with membranes and is present in the plasma membrane as well as the membranes of ER, Golgi apparatus, and nucleus. It is part of a complex that spans the membrane only once and is located on the intracellular end, near the carboxy terminus (Figure 1–15). The amino end is on the extracellular side and includes the receptor. Particulate guanylate cyclase is activated by a variety of peptides, including the atrial natriuretic peptides (ANP).

Soluble guanylate cyclase (sGC). This is found in the cytosol and includes a heme group (see Figure 1–15). It is activated by several agents, including nitric oxide (NO), organic nitrates, and free radicals. It is inhibited by several agents, including those that contain ferrous iron (Fe⁺⁺) (hemoglobin and myoglobin).

The cellular effects of cGMP are mediated by three types of intracellular proteins. They are

1. cGMP-sensitive ion channels such as (a) the nonselective cation channel in rod photoreceptor cells of the retina and (b) the amiloride-

**Intracellular Ca⁺⁺ concentration is normally near 10⁻⁷ M, whereas extracellular [Ca⁺⁺] is about 2 × 10⁻³ M.

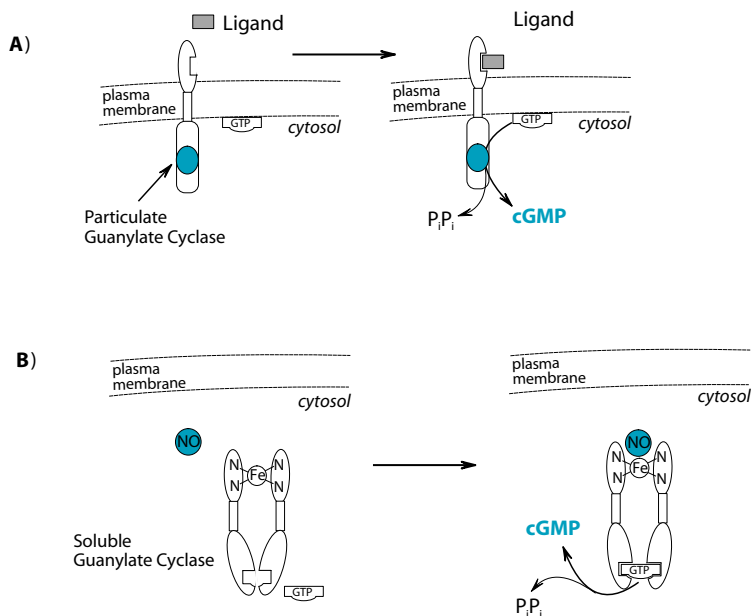


Figure 1–15 Synthesis of cGMP is catalyzed by two types of guanylate cyclase: *A*, Particulate guanylate cyclase is part of the cytosolic domain of the plasma membrane receptors of certain peptide hormones. Ligand binding to such receptors promotes activation of particulate guanylate cyclase and causes formation of cGMP. *B*, Soluble guanylate cyclases are activated by nitric oxide (NO). These guanylate cyclases are heterodimers and include a bound heme molecule that interacts with both subunits. Nitric oxide binding to the heme leads to a conformational change in the enzyme subunits and stimulates catalytic activity.

sensitive Na^+ channel of the inner medullary collecting duct of the nephron;

2. cGMP-dependent protein kinases, such as myosin light chain kinase in smooth muscle; and
3. cGMP-regulated phosphodiesterases like phosphodiesterase III (PDE III). Cyclic GMP inhibits PDE III and thereby inhibits breakdown of cAMP by PDE III. In this way, elevation of cGMP leads to elevation of cAMP.

Like cAMP, cGMP is inactivated by phosphodiesterases. One such diesterase, phosphodiesterase type 5, has gained recent prominence because it is inhibited by sildenafil (sold commercially as “Viagra”). Such inhibition prolongs the cGMP-mediated vasodilatation that causes penile erection.

APOPTOSIS

Apoptosis is orderly, programmed cell death. It differs from **necrosis**, in part by the complex involvement of extracellular signals and intracellular second messenger cascades and in part by its lack of phagocytic or other antigenic involvement. Cells that have undergone apoptosis leave behind no debris and activate no inflammatory response.

A normal living cell exists in a state of balance between proapoptotic and antiapoptotic survival factors. Among the proapoptotic influences are (1) DNA damage with subsequent activation of *p53*, (2) activation of a variety of receptors for apoptotic triggers like tumor necrosis factor- α (TNF- α), and (3) a variety of environmental insults, such as hypoxia. The pathways leading to apoptosis are complex and include at least two common features. The first is activation of a family of cytoplasmic proteases, called **caspases**, and the second is the distinctive degradation of nuclear DNA.

Muscle

Muscle is excitable, contractile tissue. It is classified, on the basis of its microscopic appearance, as **striated muscle** or **smooth muscle**. This difference arises from the different physical arrangements of the contractile proteins.

STRIATED MUSCLE

Striated muscle is further divided into **skeletal muscle** and **cardiac muscle**.

- Skeletal muscle typically bridges two attachment points on the skeleton and is in a relaxed state, unless there is a need for motion of one attachment point relative to the other.
- Cardiac muscle is arranged so as to form a hollow bag, suspended from a fibrous ring. It contracts and relaxes throughout life and at a rate between 35 and 200 beats per minute.

Morphology of Striated Muscle

A muscle consists of several muscle **columns**.^{*} Each column consists of several muscle fibers (Figure 2–1), and each fiber consists of several **myofibrils**, each 1 to 2 μm in diameter. Myofibrils clearly show repeating motifs of light and dark bands, bounded at intervals of about 2 μm by narrow, dark bands called the **Z-lines**. A typical cell incorporates several myofibrils, Z-lines, and nuclei and is bounded by an external membrane, called the **sarcolemma**.

Sarcolemma

The sarcolemma is the plasma membrane of muscle cells. It penetrates deeply into each cell by the system of transverse tubules (**T-tubules**). In skele-

^{*}This section will focus on skeletal muscle. The morphology of cardiac muscle is described in Chapter 6, “Cardiovascular Physiology.”

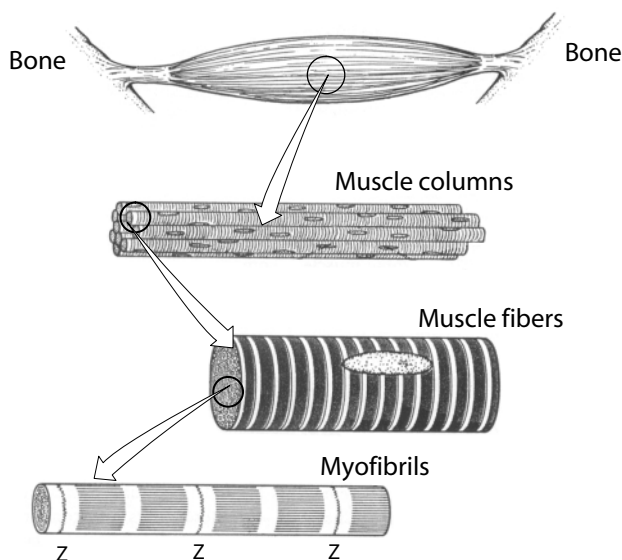


Figure 2–1 Skeletal muscle is organized into columns, fibers, and myofibrils. Z = the Z-line (or Z-disk) formed by α -actinin, an actin-binding protein.

tal muscle, each T-tubule occurs where the A and I bands join (Figure 2–2). In cardiac muscle, they occur at each Z-line. These tubular invaginations (1) allow extracellular fluid to be in close proximity to the cell interior and (2) bring the sarcolemma into close proximity with the endoplasmic reticulum, which is called the **sarcoplasmic reticulum (SR)** in muscle cells.

Sarcoplasmic Reticulum

This membrane-lined structure has evolved as a region specialized for uptake, storage, and triggered release of Ca^{++} . Its longitudinal elements are aligned with the long axis of muscle fibers and are rich in proteins that pump or store Ca^{++} . Near the T-tubules, the slender longitudinal channels broaden to form the cisternae that surround the T-tubules. These regions are rich in proteins that act as Ca^{++} release channels.

Sarcomere

The sarcomere is the contractile unit. It is bounded by two neighboring Z-lines (see Figure 2–2) and contains three types of proteins that are specialized, respectively, for structure, contraction, and regulation of contraction.

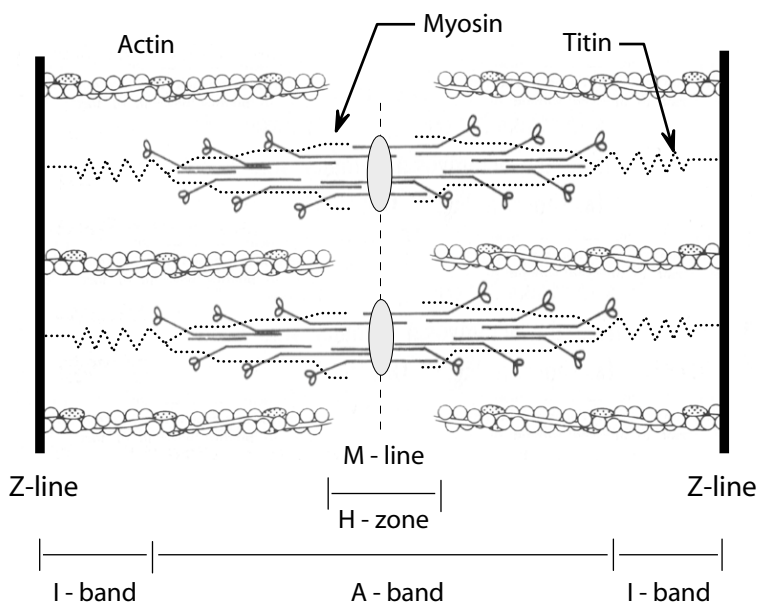


Figure 2–2 Ultrastructure of the striated muscle sarcomere. It is bounded by two Z-lines and is formed by thin filaments that contain mostly actin, the structural protein titin, and thick filaments that are formed mostly by myosin.

Structural proteins. Approximately 10% of the myofibril mass is the giant protein, **titin**. It is important for both structural integrity and the passive tension response of a stretched muscle fiber. Single titin molecules are more than 1 μm long and span from the Z-line to the M-line (see Figure 2–2). In the A-band, titin provides regularly spaced binding sites for other A-band proteins, such as light meromyosin (LMM) and C protein. The I-band region of titin is extensible and is the major contributor to the passive tension that is seen when relaxed muscle is stretched.

Contractile proteins. The thin and thick filaments of striated muscle are formed mostly and respectively by the proteins **actin** and **myosin**. They are called the contractile proteins because they will, when combined in vitro, form gel-like threads that contract when adenosine triphosphate (ATP) is added.

Actin. Actin is the major component of the thin filament (see Figure 2–2). It exists as F-actin, two slowly twisting strands of actin monomers with crossovers spaced about 36 nm at intervals of 6.5 G-actin monomers (Figure 2–3). G-actin molecules have a single polypeptide chain of 375

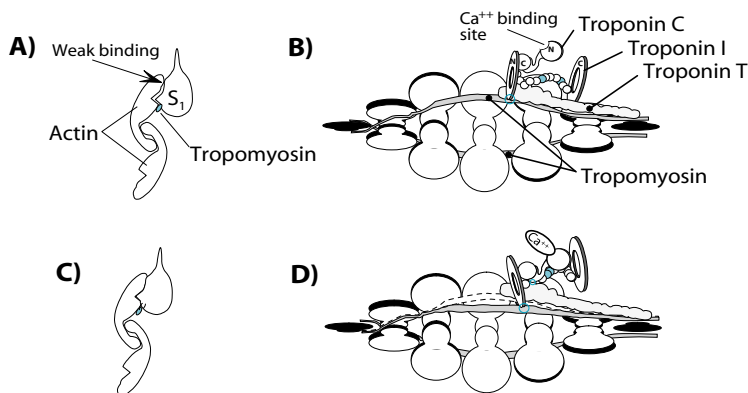


Figure 2-3 Ultrastructure of the thin filament in relaxed and activated states.

A, End view of a thin filament in the resting state. Two actin monomers joined by their coupling subdomains. Tropomyosin is in a blocking position where myosin S₁ heads are either blocked or only weakly attached by electrostatic forces between the positively charged myosin essential light chain and negatively charged residues within the C-terminal portion of actin.

B, Side view of the thin filament in the resting state. The myosin head has been omitted for clarity. (1) Tn-C is attached by its C-terminal to the N-terminal of Tn-I. (2) Tn-I attaches by its N-terminal to both the C-terminal of Tn-C and the C-terminal of Tn-T (colored circle). The central spiral of Tn-I is attached by its ATPase-inhibitory domain to actin (indicated in color). (3) Tn-T is attached by its C-terminal to the N-terminal of Tn-I, by its midregion to tropomyosin, and by its N-terminal to the head-tail junction of adjacent tropomyosin molecules.

C, The activated state. Strong, force-generating actomyosin cross-bridges are formed when tropomyosin has moved from a blocking position toward the groove formed by the intertwined actin strands.

D, Side view of the thin filament in the cocked and "on" states (with myosin omitted for clarity). Transition from the "off" state begins when Ca⁺⁺ has bound to the N-terminal of Tn-C and has triggered several Ca⁺⁺-sensitive detachments and attachments. (1) Tn-C remains attached by its C-terminal to the N-terminal of Tn-I but is also attached by its N-terminal to the central spiral of Tn-I. Furthermore, the linker region of Tn-C is attached to the C-terminal of Tn-T (indicated by colored circle). (2) Tn-I is attached by both its central spiral (colored spheres) and its N-terminal to Tn-C. The N-terminal of Tn-I is attached to tropomyosin (colored circle), and Tn-I binding to actin has been broken. (3) The binding of the Tn-T C-terminal midregion to tropomyosin has weakened, and this has allowed tropomyosin to move from its resting position (indicated by dashed lines) by 1 or 2 nm toward the actin groove. These changes in conformation and state of the thin filament proteins permit myosin S₁ heads to form actomyosin complexes that are capable of generating force provided that ATP is present and can be hydrolyzed to provide energy. (4) Removal of the Tn-I inhibitory domains from the proximity of actin allows weakly bound actomyosin cross-bridges to convert to a force-generating state.

Although the diagram suggests that only the seven actin molecules spanned by one tropomyosin molecule are released from inhibition by one Ca⁺⁺, the effect of that one Ca⁺⁺ may be mechanically coupled to adjacent tropomyosins and their associated G-actin molecules. C = COOH terminus; Tn-C = troponin C; Tn-I = troponin I; Tn-T = troponin T; N = NH₂ terminus of polypeptide chain.

amino acids, arranged in four distinct subdomains. Although, for simplicity, they are often shown as spheres, they are flat and have a diameter of 5.5 nm (see Figure 2–3). The chemical function of actin in muscle contraction is to promote the dissociation of ATP hydrolysis products ($\text{ADP} + \text{P}_i$) from the S_1 region of myosin (Figure 2–4); its mechanical function is as a ratchet-like attachment to the Z-disk. This is described more fully below under the heading “Sliding Filament Model.”

Myosin. Myosin converts chemical energy to mechanical energy. The myosin found in muscle is class II myosin. It consists of two interwoven myosin heavy chains (MHC), two myosin essential light chains (MELC) and two myosin regulatory light chains (MRELC).

- Each heavy chain (200 kDa) can be cleaved by trypsin into a tail portion (LMM) (Figure 2–4) and a portion incorporating **subfragments 1 and 2** (S_1 , S_2); (see Figure 2–4). A major role of the tail portion is to allow polymerization of myosin molecules so as to form a symmetric aggregate around the M-line in the sarcomere with the tail portion of the molecules arranging themselves in both parallel and antiparallel fashion. In each section of the thick filament the head groups of the molecule are polarized away from the center (see Figure 2–2). Such polymerization and polarization are crucial for the function of myosin, which is to move actin filaments toward the M-line.
- Each heavy chain is associated with a “head,” called S_1 and S_2 (see Figure 2–4) that can be cleaved from S_2 by papain. S_1 contains about 900 amino acids and incorporates the catalytic site for ATP hydrolysis, the surface for actin binding and attachment points for one essential and one regulatory light chain (see Figure 2–4).

Multiple isoforms of both heavy and light chains exist and allow sarcomeric myosin to convert chemical energy into work at a wide range of rates so as to meet the requirements of different types of muscle.

- The isoforms differ from one another by no more than 95 to 190 amino acids of the total 1,900 that constitute each heavy chain. The areas of difference include the light chain binding region, S_2 , and the tails, but not generally the ATP-binding pocket or the actin-binding surface.
- The isoforms differ functionally with respect to the kinetics (rate constants for attachment and detachment, maximum [unloaded] shortening velocity, rate of ATP consumption and maximal power output) but not the amplitude of the elementary force and displacement events.

Eight heavy chain isoforms are commonly found in humans: MHC1 (also called $\text{MHC}\beta/\text{slow}$) is expressed in ventricular myocardium and in

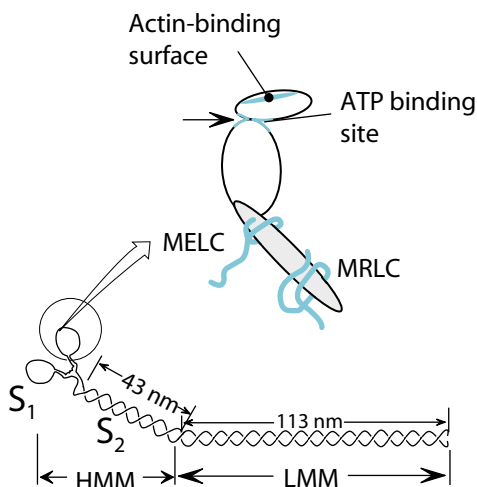


Figure 2–4 The myosin molecule and detail of one of the S_1 heads. The head consists of a 50-kDa segment and a 20-kDa segment (*shaded*) to which the essential and regulatory light chains (*in color*) are attached. The 50-kDa segment includes the ATP binding site and the actin attachment surface, which is large enough to span two actin monomers. The arrow between the upper and lower domains of the 50-kDa segment of S_1 points to the cleft, whose narrowing and widening are crucial for the “swinging lever” model of cross-bridge function. ATP = adenosine triphosphate; HMM = heavy meromyosin; LMM = light meromyosin; MELC = myosin essential light chain; MRLC = myosin regulatory light chain; S_1 , S_2 = subfragments 1 and 2 of HMM.

slow skeletal muscle fibers; $MHC\alpha$ is expressed in atrial myocardium and occasionally in skeletal muscle; $MHC2A$, $MHC2X$, and $MHC2B$ are fast isoforms expressed in fast skeletal muscle fibers; MHC_{exoc} is expressed only in extraocular muscles; whereas MHC_{emb} and MHC_{neo} are expressed only during embryologic and neonatal development, respectively.

As a rule, in fast muscle fibers, a fast heavy chain isoform associates with fast regulatory and essential light chain isoforms. In slow muscle fibers, the slow $MHC1$ associates with slow regulatory and essential isoforms. The expression of heavy- and light-chain genes is controlled by factors that include loading conditions and hormones, such as thyroid hormone.

Regulatory proteins. The actin filament, stripped of other thin filament proteins, is an intrinsic promoter of $(ADP + P_i)$ release from myosin and, by this product removal, a promoter of myosin ATPase. Therefore, controlled muscle function requires periodic inhibition of actin–myosin interactions. The proteins **tropomyosin** and **troponin** have major roles in regulating the activity states of the actomyosin complex.

Tropomyosin. Tropomyosin is a two-chain, helical, coiled coil protein, about 40 nm long. Its molecules link end to end to form a continuous strand that winds around the actin array and lies in the groove formed by the coiled actin strands (see Figure 2–3), each tropomyosin molecule interacting with seven actin monomers.

Troponin. There is one troponin complex associated with each tropomyosin molecule. The troponin complex consists of three separate polypeptide chains, troponin-C, -I, and -T (Tn-C, Tn-I, Tn-T). Many of their linkages to one another are Ca^{++} -sensitive, reversible reactions.

- Tn-C is a dumbbell-shaped molecule consisting of two globular domains joined by a central linker (see Figure 2–3B). Each globular domain contains two divalent metal binding sites. The sites in the globule containing the amino (NH_2) terminus are Ca^{++} specific and form the regulatory sites. The sites in the carboxy (COOH) terminus bind both Ca^{++} and Mg^{++} , but much less reversibly than the binding at the amino terminal. Their role lies in anchoring Tn-C tightly to the NH_2 terminus of Tn-I (see Figure 2–3B).
- Tn-I is an inhibitor of the actin–myosin reaction and shuttles between tight binding to actin (resting muscle) (see Figure 2–3B) or to Tn-C- Ca^{++} (contracting muscle) (see Figure 2–3D). It also binds to Tn-T. Its structure resembles that of Tn-C in that it is formed by two doughnut-shaped regions joined by a central spiral (see Figure 2–3B).
- Tn-T binds to Tn-C, Tn-I, and tropomyosin. It is involved in the attachment of the troponin complex to tropomyosin. It is a fist-and-finger-shaped molecule. Its bulk resides in the carboxy terminal region that is closely associated with Tn-C and Tn-I. The amino terminal region lies at the end of a finger-like extension, and it binds to the head-tail junction of tropomyosin.

Sliding Filament Model of Striated Muscle Function

At rest, the thin filament is in a **blocked state**, where momentary weak binding of myosin to actin can occur, but ATPase activity is low. However, when Ca^{++} binds to Tn-C, it triggers a sequence of protein-to-protein interactions that lead to a cycling, force-generating physical coupling between actin and myosin.

Removal of Steric Hindrance (Transition from Blocked to Cocked State)

In the resting state, cytosolic $[\text{Ca}^{++}]$ is near 100 nmol, and the physical conformation of troponin-tropomyosin permits either unattached or only

weakly attached, non-force-generating actomyosin cross-bridges (see Figure 2–3A). Cross-bridge cycling and force generation are inhibited.

When cytosolic $[Ca^{++}]$ rises from its resting value to near 1,000 nmol, the interaction of free intracellular Ca^{++} with the Ca^{++} -specific binding site on the N-terminal of Tn-C initiates the signaling cascade, in which protein constituents undergo changes of conformation and state. Of key importance are (1) induction of a high-affinity state between Tn-C and Tn-I; (2) release of the attachment between actin and the Tn-I inhibitory domain; (3) the resultant physical movement of Tn-I and an associated movement of Tn-T; and (4) physical movement of tropomyosin toward the actin-actin groove so that strongly attached, force-generating actomyosin cross-bridges can form (see Figure 2–3C).

Mechanical work is performed when neighboring Z-lines are pulled toward each other as actin filaments slide over the stationary myosin filaments.

The Power Stroke (Transition from “Cocked” to “On” State)

In the “on” state, there is strong actomyosin binding, high ATPase activity, and high force generation. In this state, there is cyclic myosin-actin interaction during which the S_1 - S_2 portion of the myosin molecule (see Figure 2–5) tilts relative to the tail of the molecule. This is called the **swinging lever model** of muscle function.

The Swinging Lever Model

The force-generating actomyosin cycle begins when Ca^{++} binding to Tn-C has allowed strongly bound actomyosin cross-bridges to form (see Figure 2–3A). One cross-bridge rotation causes a displacement of only 5 to 10 nm. A sarcomere shortens by 100 to 300 nm during contraction. To achieve this degree of shortening, repeated release and reattachment of cross-bridges is necessary. Modern techniques have permitted precise descriptions of the role of actin, the cleft between the upper and lower segments of the 50-kDa domain of myosin S_1 , and the S_2 segment. Earlier models that proposed stretching and passive recoil of the S_2 segment as a part of the force-generating process were shown to be incorrect by an experiment in which actin fibers were seen to “walk” across a “carpet” of S_1 heads only.

The sequence shown in Figure 2–5 repeats as long as sufficient Ca^{++} is present to remove the steric hindrance provided by tropomyosin and as long as sufficient ATP is present. Adenosine triphosphate has two functions: (1) it serves as a source of energy, and (2) it causes disengagement of the actomyosin cross-bridge.

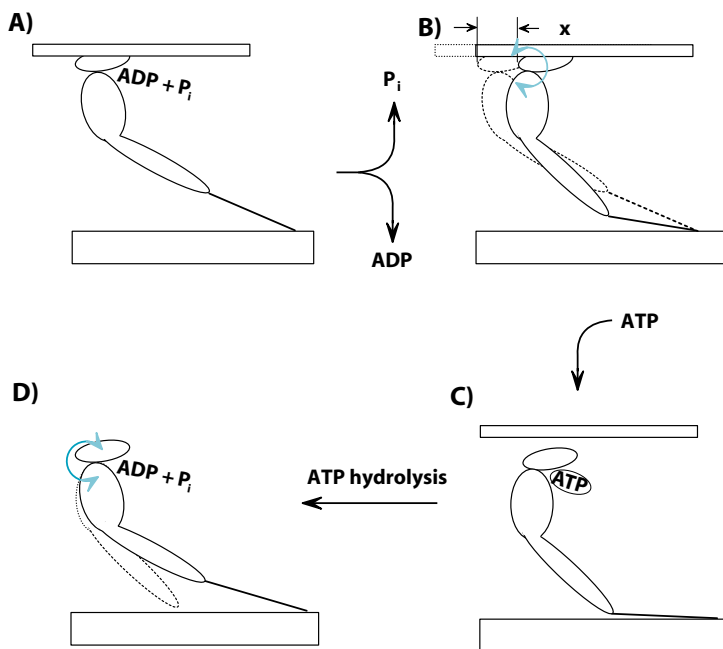


Figure 2-5 The “swinging lever” model of the muscle power stroke.

A, Steric hindrance has been removed, and a strong actomyosin cross-bridge has formed. The proximity of actin allows the products of earlier ATP hydrolysis to dissociate and to be released.

B, P_i release permits previously stored energy to slightly close the cleft between the upper and lower domains of the 50-kDa segment of S_1 (as indicated by the colored double-headed arrow). This causes the lower portion to swing in the clockwise direction, from the dashed line position to the solid line position by about 10nm, pulling the actin filament to the right by that distance.

C, ($ADP + P_i$) release allows new ATP to be bound if it is available. If ATP is not available, the cross-bridge remains fixed in the contracted position shown in *B* (the rigor complex). If ATP is available, then its binding causes cross-bridge detachment because the actomyosin-ATP complex is unstable.

D, ATP is hydrolyzed by the inherent ATPase activity of myosin, and the liberated energy is used to rotate the lower portion of the molecule (colored arrow) relative to the upper domain, thereby opening the cleft and returning the “swinging lever” to its starting position. The lever is held in this position only as long as P_i remains associated with the myosin head. Wherever portions of S_1 are shown as interrupted lines they indicated the position held in the previous frame.

Electrophysiology of Skeletal Muscle

Resting and active behavior of skeletal muscle depends critically on ion-selective channels for Na^+ , K^+ , Cl^- , and Ca^{++} . Cardiac muscle also contains a sodium–calcium exchange mechanism, concentrated in the T-tubules. This does not contribute significantly to skeletal muscle function.

Ion Currents

The inactive state. When muscle cells are at rest, their membrane currents are predominantly carried passively by Na^+ , K^+ , and Cl^- . The active Na^+/K^+ pump also participates because its stoichiometry (3 Na^+ out for 2 K^+ in) provides net outflow of positive charge.

Na^+ current. Inactivated (“closed”) Na^+ channels carry a small non-inactivating component, called the slow Na^+ current. It helps to maintain a stable resting membrane potential in the face of outward current flows provided by the K_1 potassium channel and the active Na^+/K^+ pump.

K^+ current. The dominant K^+ current at rest is $I_{\text{K}1}$. The K_1 channel normally conducts K^+ out of the cell but can carry K^+ into the cell whenever the membrane potential is more negative than the potassium equilibrium potential.

Cl^- current. At rest, there is a small, outwardly directed Cl^- current. It is believed to protect the plasma membrane from spontaneous depolarization that could result from K^+ build-up, particularly in the T-tubules.

The active state. Skeletal muscle is not spontaneously active, but it requires a stimulus. This is normally provided by the nerves of the somatic division, using **acetylcholine** as a neurotransmitter and transmitted to their target cell by a specialized synapse called the **motor end plate**.

End-plate potentials. Acetylcholine activates postsynaptic **nicotinic receptors** in the end-plate region. They form an intrinsic cation channel. Their activation causes increased local flow of Na^+ , K^+ , and Ca^{++} across the membrane. Inward flows of Na^+ and Ca^{++} dominate and depolarize the muscle cell in the region of the end plate. The localized change in postsynaptic potential is called an **end-plate potential** (or a **miniature end-plate potential [MEPP]**, such as is seen after spontaneous release of minute quanta of neurotransmitter).

When an end-plate potential is sufficiently large to depolarize the postsynaptic membrane to the gating voltage for Na^+ channels, an action potential is generated, and it spreads throughout the muscle cell (Figure 2-6).

Action potentials. A skeletal muscle action potential lasts about 10 ms. Its most significant ion currents are the result of passive fluxes of Na^+ and K^+ . L-type Ca^{++} channels, which contribute a significant current to the action potential in cardiac muscle, do not have this role in skeletal muscle.

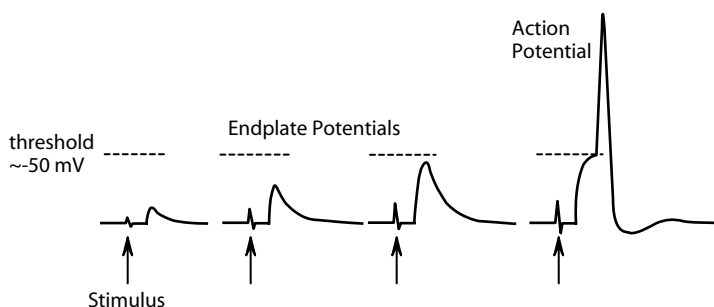


Figure 2-6 Muscle end-plate potentials are localized changes in postsynaptic potential that are caused by stimuli that are insufficient to raise membrane potential to the gating voltage for Na^+ channels (= threshold). An action potential is generated and propagated throughout the muscle cell when an end-plate potential is sufficiently large to depolarize the postsynaptic membrane to the Na^+ channel gating voltage.

Na^+ channels: I_{Na} is carried by the rapidly activating and inactivating, voltage-gated Na^+ channels that also contain a small non-inactivating component and, therefore, carry the slow Na^+ current during the resting state. Their gating voltage is typically near -40 to -50 mV.

K^+ channels: Although channels carrying I_{K1} are the major carrier of basal K^+ current in inactive skeletal muscle cells, repolarization is due to one of several delayed rectifier K^+ currents.

Ca^{++} channels: The T-tubule network of skeletal muscle is richly supplied with dihydropyridine receptors that have the structure and pharmacologic properties of L-type Ca^{++} channels. However, unlike in cardiac muscle, their Ca^{++} conductance is not essential for excitation–activation–contraction coupling in skeletal muscle. They are localized in those regions of the T-tubule membrane that directly face the terminal sacs of the sarcoplasmic reticulum (SR) and are arranged in a regular pattern, facing Ca^{++} release channels (ryanodine receptors), which are localized to the SR membrane.

Dihydropyridine (DHP) receptors in the T-tubule membrane and apposing ryanodine receptors in the SR cisternae interact directly to couple T-tubule events to the sarcoplasmic reticulum. The nature of the coupling differs between skeletal muscle and cardiac muscle, and the difference arises from the activation kinetics of the DHP receptor (Figure 2-7). Its intramembrane region contains highly mobile, charged gating domains that respond rapidly to changes in membrane potential. Their early, fast movement is followed by a slower conformational change of the whole molecule and leads, eventually, to channel opening and Ca^{++} flux through the channel.

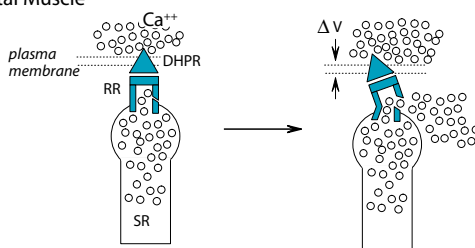
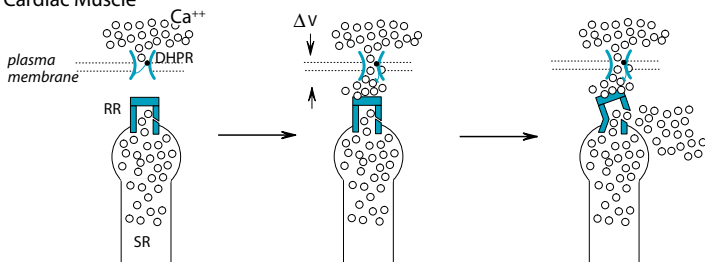
A) Skeletal Muscle**B) Cardiac Muscle**

Figure 2-7 Dihydropyridine receptors (DHPR) have the pharmacologic properties of L-type Ca^{++} membrane channels and face Ca^{++} release channels (ryanodine receptors, RR) where the T-tubule plasma membrane apposes the sarcoplasmic reticulum (SR) in striated muscle. Dihydropyridine receptors and RR interact differently in skeletal muscle and cardiac muscle. Dihydropyridine receptor is drawn here so as to emphasize functional aspects. *A*, In skeletal muscle, a change in membrane potential causes a rapid movement of DHPR gating domains that is transmitted to the RR and causes a conformational change in RR, permitting Ca^{++} release from the SR. *B*, In cardiac muscle, the longer lasting change in membrane potential opens the channel and causes extracellular Ca^{++} to enter through DHPR. The Ca^{++} that has entered the cell interior acts as a trigger for the RR to release Ca^{++} from the SR.

- A cardiac muscle twitch is delayed by almost 200 ms from the start of an action potential. Hence, cardiac muscle DHP receptors mediate long-lasting Ca^{++} currents and permit the translation of membrane depolarization into an influx of Ca^{++} that is capable of triggering intracellular responses, such as “calcium-triggered calcium release.”
- A skeletal muscle twitch, on the other hand, begins less than 20 ms after the start of an action potential. Hence, the importance of skeletal muscle DHP receptors arises from their ability to sense changes in membrane voltage. In skeletal muscle, the absolute value of the potential difference across the T-tubule membrane controls the coupling to the ryanodine receptor, not the influx of Ca^{++} ions.

Excitation–Activation–Contraction Coupling

The processes of excitation–activation–contraction coupling link electrical events of an action potential to the mechanical events of tension development and subsequent muscle relaxation. Ca^{++} plays a crucial role in these processes, rising from a resting cytosolic concentration near 100 nmol to a peak of 0.1 to 1 μmol during a normal contraction. The source of this Ca^{++} is the SR.

Sarcoplasmic reticulum. The SR is an internal membrane-lined system that forms a network of tubules aligned with the long axis of the myofibrils and lying between them (Figure 6–3). It occupies between 5 and 30% of muscle fiber volume, depending on whether the muscle is of the slow or fast type. The SR ends in blind sacs that closely abut the T-tubules. The region of approximation contains ryanodine receptors (Ca^{++} release channels) in the SR membrane, and they are apposed by DHP receptors (L-type Ca^{++} channels) in the T-tubule plasma membrane.

The SR is rich in Ca^{++} -binding proteins, such as **calsequestrin**, **calreticulin**, and **histidine-rich calcium-binding protein (HCP)**; it, therefore, holds most of the Ca^{++} that is present inside muscle cells.

Elevation of cytosolic Ca^{++} . In cardiac and smooth muscles, Ca^{++} release from the SR is proportional to $[\text{Ca}^{++}]_i$ and IP_3 , respectively. In skeletal muscle, activation of ryanodine receptors and the consequent Ca^{++} release are directly proportional to the voltage difference across the T-tubule plasma membrane. Coupling of membrane potential to the SR requires the presence of DHP receptors but not that they conduct Ca^{++} . The linkage mechanism may be a mechanical coupling between the ryanodine receptor and the DHP receptor voltage gating domains that respond rapidly to changes in membrane potential.

After a brief electrical stimulation, the Ca^{++} release channel is opened for only a few milliseconds, and Ca^{++} is released in a transient burst.

Uptake of Ca^{++} from the cytosol. Cytosolic Ca^{++} is quickly bound to troponin or to the Ca^{++} ATPases in the plasma membrane and the SR. These active transporters move two Ca^{++} per ATP. In slow skeletal muscle, the SR Ca^{++} ATPase is increased by phospholamban phosphorylation and decreased by phospholamban dephosphorylation.

Mechanics of Muscle Contraction

When muscle is stimulated adequately, it generates an action potential, and the associated change in membrane potential is translated into Ca^{++} release

from the sarcoplasmic reticulum. As described by the sliding filament model, this increased cytosolic $[Ca^{++}]$ results in muscle shortening and force generation. The magnitudes and rates of these two and other indices of muscle function are related in complex ways to the load against which the muscle must work. When a muscle, such as the biceps, is in typical use, it develops tension with a change in elbow angle while a weight is being lifted. Although the weight being lifted does not change, the load against which the muscle works changes as the elbow angle changes. Three experimental set-ups are frequently used to study this apparently simple physiologic phenomenon: **isometric**, **isotonic**, or **isokinetic** contractions.

- In an isometric contraction, the biceps develops tension, but there is no change in elbow angle.
- In an isotonic contraction, tension is developed in the biceps while moving a constant load.
- In an isokinetic contraction, the biceps contracts maximally throughout its range of motion, working against an accommodating load.

Isometric Contraction

When muscle is fixed rigidly at both ends so that it cannot shorten, stimulation will be followed by the maximum tension that is possible under the existing preload, contractile state, and rate of stimulation. The pattern of change in tension with time after a single stimulus is called a **muscle twitch**. Its total duration is about 100 ms in a fast fiber and 300 ms in a slow fiber (Figure 2–8A). Repetition of stimulation leads to a sequence of twitches that begin to merge and summate if the frequency of stimulation is so high that the muscle cannot relax completely from the preceding stimulus (see Figure 2–8B).

The length-tension relationship. Isometric experiments have revealed that the peak tension of skeletal muscle is related to its initial length. Within a range of lengths, an increase in initial length (called “preload” in cardiac muscle) will increase the peak tension developed in a subsequent twitch. A plot of the peak tension (Y-axis) against initial length will usually show a maximum at some optimal length, L_0 (Figure 2–9).

The explanation for this observation was thought to be that it was possible to increase, by sarcomere stretching, the number of actomyosin cross-bridges by improving the degree of overlap between the thick and thin filaments. A more likely explanation is that stretching alters (1) Ca^{++} dynamics, by altering some aspect of the SR function, and (2) the physical separation between the thick and thin filaments, by increasing the stretch and causing the thin filaments to be drawn closer to the thick filaments.

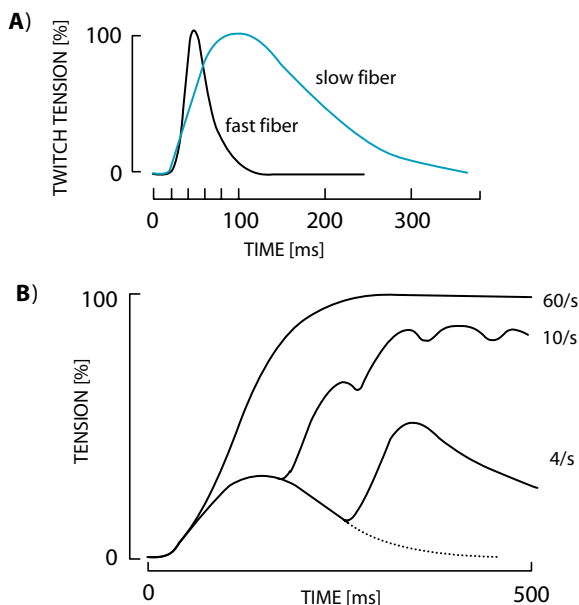


Figure 2-8 Tension development in a muscle under isometric conditions. *A*, A twitch response after a single stimulus in fast and slow muscles. The latency of tension onset is typically near 20 ms. The decay phase is typically twice as long as the rising phase. *B*, Responses to multiple stimuli at increasing frequencies. Skeletal muscle has a short cycle of electrical activity (10 to 80 ms), compared with its cycle of mechanical activity (150 to 300 ms). This makes it possible to stimulate a motor unit before the force generated by the preceding stimulus has returned to zero and the developed force can be summated. At sufficiently high stimulation rates, smooth tetanus is achieved at the maximum possible tension under the prevailing conditions of the preload and contractile state.

Isotonic Contraction

When muscle contracts against a constant load, a plot of tension versus time gives limited information because the maximum tension that is developed will be determined by the load that is being lifted. Plots of load versus velocity of shortening give more information. The general findings are that the greater the load,

- the longer is the latency from the onset of stimulation to the onset of contraction; and
- the lower is the initial shortening velocity.

The force-velocity relationship. Under isotonic conditions, the force developed by a muscle is equal to the load that is being lifted. When the

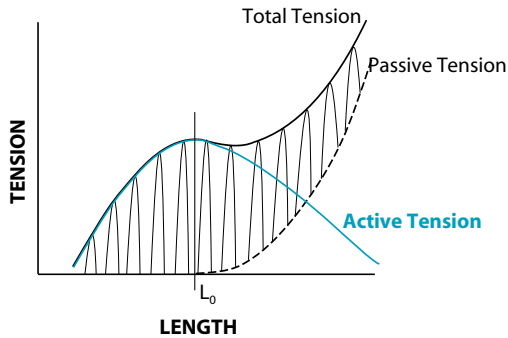
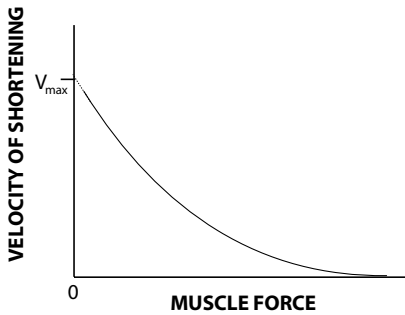
A) Length-Tension Relationship**B) Force-Velocity Relationship**

Figure 2–9 A, The length-tension relationship of muscle is derived from the peak twitch tension observed at different initial lengths. L_0 is the normal resting length and also the length at which (1) there is no passive stretch tension generated and (2) the peak amplitude of twitch tension is maximal. At initial lengths greater than L_0 , passive tension is generated by the stretch of the elastic elements and the amplitude of twitch tension decreases with increasing initial length. B, When a muscle contracts against a load, then it generates enough force to lift that load, provided that the load is of a physiologically reasonable magnitude. The maximum velocity of shortening decreases with increasing loads, and it becomes zero when the load is so large that the muscle is incapable of lifting it. V_{\max} , the maximum velocity of shortening, is shown as an extrapolation because even when no load is applied, the muscle moves itself, and, therefore, zero load can be accomplished only in gravity-free environments.

velocity of initial shortening is plotted on the Y-axis against force, a curve results that shows an inverse relationship between velocity and force (Figure 2–9B). Such curves have been used to characterize muscle performance by V_{\max} , the maximum velocity of shortening at zero load. These characterizations are criticized on the basis that the muscle itself has weight and that this makes zero load an impossible goal.

Organization of Skeletal Muscle and Skeletal Muscle Types

Motor Units

A motor unit is the functional unit of muscle contraction, and the fibers in a whole skeletal muscle are arranged in such units. A motor unit consists of one efferent spinal nerve (an α motor neuron) plus all the muscle fibers innervated by its branches. Motor units differ (1) in size (only a few in, for example, an extraocular muscle; more than a thousand in, for example, the biceps) and (2) in muscle fiber type (fast, slow, or intermediate) and, thereby, in contractile, biochemical, and fatigue properties.

Types of Skeletal Muscle Fibers

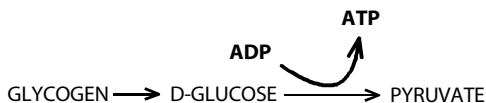
At birth, there is little difference in the Ca^{++} dynamics or contraction velocities of muscle fibers that will show clear differences later in life after muscle fibers are completely innervated and are active. In the adult human, there are three types of muscle fibers, and all fibers in a motor unit belong to one of the three types. Fiber type is driven by motor unit function and expresses itself in morphologic, molecular, histochemical, and functional differences. The molecular differences include differences in myosin isoforms.

- Conversion of fibers to another type does not occur under physiologic conditions in the adult human but is possible in experimental or pathologic settings, such as in denervation of a fast muscle.

Fast fibers. Fast fibers are functionally characterized by a short-lasting twitch time course (see Figure 2–8A). They are divided on the basis of metabolic and functional aspects into two subtypes: **fast white glycolytic** and **fast pink oxidative**.

Fast white glycolytic fibers (type 2-B). These are large fibers with an extensive SR and few mitochondria. They are white in appearance (**white muscle**) because they contain little myoglobin.[†] The muscles of the larynx contain a high proportion of type 2-B fibers.

- Biochemical features:
 1. The glycolytic pathway of ATP production dominates.



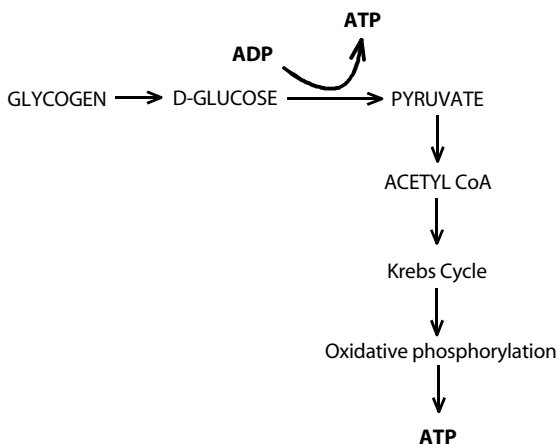
[†]Myoglobin is a heme-containing muscle protein. The presence of the heme moiety permits reversible binding of O_2 .

It produces relatively little ATP but produces it quickly.

2. The Ca^{++} transient is brief and has both a fast onset and a fast offset.
 3. There is high activity of lactate dehydrogenase, which catalyzes breakdown of pyruvate and low activity of the Krebs cycle enzyme succinate dehydrogenase, which catalyzes the conversion of succinate to fumarate in the steps that lead to ATP production by oxidative phosphorylation.
- Functional features:
 1. Large force can be generated quickly, but not maintained because fatigue sets in equally quickly.
 2. Relaxation is rapid because actomyosin cross-bridges detach rapidly.

Fast pink oxidative fibers (type 2-A). Such fibers are sparse in human muscles and are also called **intermediate fibers**. They are of small diameter and contain many mitochondria. The presence of myoglobin makes them pink or red in appearance.

- Their dominant biochemical feature is that ATP is produced by both glycolytic and oxidative activity.



- Their dominant functional feature is that large force can be generated quickly and maintained for a period of time that is intermediate between type 2-B and type 1 (slow) fibers.

Slow oxidative fibers (type 1). These fibers are red in appearance because they have high capillary density and high myoglobin content. Their SR is

less prominent than it is in fast white glycolytic fibers. The extraocular muscles are rich in type-1 fiber muscles.

- Biochemical features:
 1. Metabolism is characterized by high oxidative activity.
 2. The Ca^{++} transient is prolonged because these fibers have a lower Ca^{++} -ATPase activity.
 3. They express myosin heavy chains with low ATPase activity.
 4. Points 2 and 3 above, with the presence of many mitochondria, mean that slow fibers have a much greater capacity to generate ATP than to consume it.
 5. Lactate dehydrogenase activity is low, and succinate dehydrogenase activity is high, indicating dominant Krebs cycle activity and ATP production by oxidative phosphorylation.
- Functional features:
 1. Large force can be generated and maintained for long periods of time because these fibers are fatigue resistant.
 2. The response to nervous stimuli is a slow membrane depolarization that is caused by summation of end-plate potentials and leads to a slow but graded contraction.

Types of Whole Skeletal Muscle

Although all the fibers in a given motor unit are of the same type, any given region of muscle will show considerable anatomic intermixing of fibers from different motor units. As a result, most human muscles contain both fast glycolytic and slow oxidative fibers. There are few intermediate fibers. The proportion of fibers is determined by the nature of the long-term muscle activity:

- Activity that is chronically in a phasic manner and at high frequencies (more than 40 per second) will lead to the formation of fast fibers.
- Activity that is chronically tonic and at low frequencies favors the formation of slow fibers.

Muscle is termed “slow” or “fast,” depending on the proportion of slow or fast fibers in its motor units.

Type I (red) muscle. This contains mostly slow oxidative fibers. Muscles controlling posture are red muscle.

Type II (white) muscle. This contains mostly fast glycolytic fibers. The vocal cords are white muscle.

Regulation of Skeletal Muscle Contraction

Grading of Contractile Force

In any one active fiber, maximal contractile force is affected by (1) the frequency of action potentials in the attached motor nerve, (2) the initial stretch (preload or length–tension relationship), (3) its preceding activation history (facilitation or disfacilitation, depending on the frequency of preceding stimuli), (4) the temporal patterning of stimuli (catch-like property, whereby a change in just one stimulus interval in the middle of a long train of stimuli can change force output over a long time), and (5) the biochemical environment (contractility, or degree of activation). Of these, the one most readily understood is grading by frequency of action potentials (**temporal summation**). An additional factor is changing the number of active motor units (**recruitment**).

Temporal summation (tetanus). If the rate of stimulation is so high that there is insufficient time for complete relaxation between successive action potentials, the muscle is said to be in a state of tetanization and developing the maximum force possible under the existing biochemical conditions. As shown in Figure 2–8B, increasing stimulation frequency increases the maximal force developed until smoothly fused tetanus is achieved.

Recruitment. In normal muscle action, small motor units are activated first because their neurons are small and, therefore, reach the critical number of total ion flux before it is reached in larger neurons. If the generated force is not sufficient for the task, activity is recruited in additional motor units.

Neural Regulation

Effector mechanisms. Skeletal muscle contraction is initiated by action potentials in α motor neurons of the somatic nervous system. When the motor nerve stimulus is adequate to elicit a muscle action potential, all the fibers in that motor unit contract synchronously.

An extensive neural network of sensory and motor structures ensures both integration of activity with neighboring motor units and appropriate grading of activity relative to the desired muscle force and velocity of contraction.

Sensory structures. Afferent information regarding muscle tension and length is sensed by receptors located in tendons (**Golgi tendon organs**) and by **muscle spindles**, which are special sense organs, widely interspersed among the working fibers (Figure 2–10).

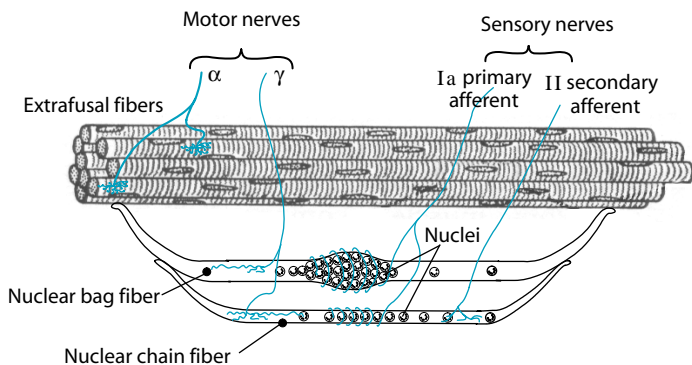


Figure 2–10 Muscle fibers and muscle spindle (not to scale). Extrafusal fibers form the contracting fibers of a motor unit. They are innervated by an α motor neuron. Intrafusal fibers are innervated by γ motor nerves and form the origin of two kinds of sensory nerves. Rapidly conducting Ia afferents originate from spiral endings near the center of each fiber. Group II sensory fibers originate from a branching network located near the end of nuclear chain fibers.

Golgi tendon organ. Golgi tendon organs are the extensively branched termination of a large group Ib myelinated nerve fiber. They are woven into the tendons of a bundle of muscle fibers. The nerve from the tendon organ synapses with a spinal column interneuron that is directly inhibitory to α motor neurons innervating that muscle.

Golgi tendon organ firing patterns are directly related to muscle tension, averaged over several motor units. Activation of the tendon organs in a muscle inhibits the α motor neurons supplying that muscle.

Muscle spindle. Muscle spindles consist of specialized fibers, named **intrafusal fibers**. They are smaller than the working (**extrafusal**) fibers that make up the bulk of the muscle, and their striations are less obvious. A muscle spindle consists of two nuclear bag fibers (see Figure 2–10), one with high and the other with low ATPase activity and up to four nuclear chain fibers. Nuclear chain fibers are thinner and shorter and lack the central “bag” that is filled with nuclei. The connective tissue capsule surrounding the spindle is attached to the tendons at either end of the muscle or to the sides of the extrafusal fibers (see Figure 2–10). Spindles function as (1) reflex devices for maintaining muscle length, (2) indirect initiators of muscle contraction, and (3) transducers of muscle stretch amplitude and velocity.

Maintenance of muscle length: The frequency of action potentials in spindle sensory nerves increases when the spindle is stretched and decreases when it is unloaded by muscle shortening. Encoded in the responses of the

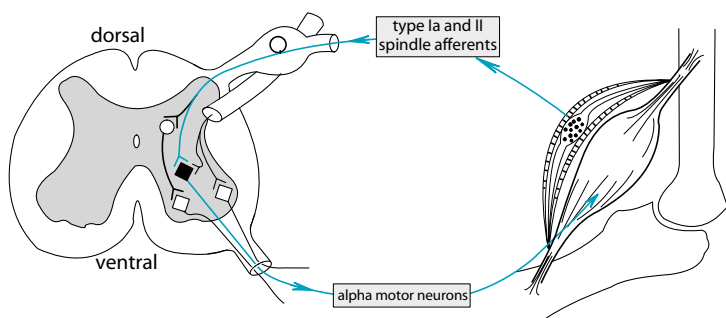


Figure 2-11 Action potential frequency in spindle sensory nerves (types Ia and II) increases when the spindle is stretched and decreases when it is unloaded by muscle shortening. Muscle length is maintained in part by reflex changes in α motor neuron discharge and in part by appropriate α motor neuron discharge to antagonist muscles (not shown).

primary afferent nerves is information regarding changes in length and the velocity of stretch.

The nature of the muscle reflex response is to shorten (in response to α motor neuron discharge) when the spindle is stretched and to relax when the spindle is unloaded (Figure 2-11). Such a response is counterproductive during a muscle contraction and is, therefore, counteracted by γ motor neuron discharge during volitional muscle contraction.

Effects of γ motor nerve activity: (1) When there is *no* prior activation of α motor nerves, then increased activity in γ motor neurons causes the muscle spindle to contract but does not directly shorten the muscle because the intrafusal fibers are too weak and too sparse. However, as the nuclear bag fibers contract on both sides of the central bag, the bag portion is stretched, the primary afferents are activated, and subsequent reflex activation of α motor nerves causes whole muscle contraction. Thus, spindle shortening in excess of whole-muscle shortening can amplify whole-muscle shortening. (2) When there is prior activation of α motor nerves, then shortening of the whole muscle unloads the spindle and would cause reflex relaxation. If the spindle is contracted by concomitant increased activity in γ motor neurons, the primary goal of the activity in α motor nerves is not counteracted. Thus, spindle contraction during whole-muscle contraction prevents inhibitory reflexes and maintains spindle sensitivity (Figure 2-12).

Muscle Fatigue

Muscle fatigue is experienced as a reduction in the force-generating capacity and power of a muscle during sustained performance of a task. The major loci

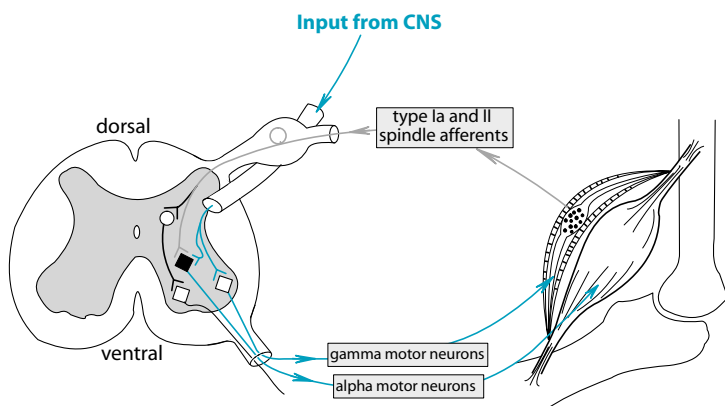


Figure 2–12 During a volitional muscle contraction, reflex maintenance of muscle length is prevented. The central nervous system (CNS) signals that direct muscle shortening by way of α motor neuron activity simultaneously maintain constant muscle spindle length by way of appropriate γ motor neuron activity.

at which fatigue develops are thought to lie within the muscle itself, beyond the motor end plate and to include both chemical and physical aspects.

Metabolic factors. Whereas ATP concentrations are usually well maintained, the concentration of creatine phosphate decreases, and the concentration of inorganic phosphate (from ATP hydrolysis) increases. Similarly, there is an increase in $[H^+]$ as the metabolism becomes increasingly anaerobic when contracting muscle occludes its own blood supply. The local acidosis will lead to increased extracellular $[K^+]$, and this will be exacerbated by the ion currents that characterize the action potentials driving the sustained muscle effort. The net effects of these changes include decreased cytosolic $[Ca^{++}]$ and disturbed excitation–activation–contraction coupling.

Altered excitation–activation–contraction coupling. Accumulation of K^+ outside the plasma membrane, as well as changes in intracellular $[K^+]$ or in the $[Na^+]$ gradient, may lead to electrophysiologic changes that include depolarization, reduction in both amplitude and conduction velocity of the action potential, changes in action potential shape, changes in Na^+ channel dynamics, and diminished voltage sensitivity of the dihydropyridine receptor. All of these changes have possibly deleterious effects on the SR Ca^{++} release. In addition, intracellular accumulation of H^+ might affect both the Ca^{++} release properties of the ryanodine receptor and the dynamics of the two Ca^{++} ATPases.

Altered actomyosin cross-bridge function. Elevation in both cytosolic $[H^+]$ and $[P_i]$ will decrease Ca^{++} sensitivity of Tn-C and thereby decrease the force generated at a given $[Ca^{++}]_i$.

Muscle injury. Functional impairment may result from microtears, disrupted sarcomeres, or physical alteration of intracellular organelles by altered ionic composition.

Long-Term Changes in Skeletal Muscle Function

Influence of hormones. Thyroid hormone exerts long-term effects on striated muscle because it promotes the expression of myosin heavy-chain genes. As a result, hypothyroidism is associated with muscle weakness. Hyperthyroidism is also associated with muscle weakness, but this probably arises from a generally increased breakdown of proteins.

Influence of training and exercise. Most athletic activity involves aspects of coordination, strength, and endurance. Training improves all three, or it can accentuate only certain aspects.

Coordination. Training leads to reduction of “wasteful” muscle activity as well as improved efficiency of exercise performance. This is believed to result from improved central nervous system-directed coordination so that there is better coordination of action potentials in all involved muscles and greater inhibition of antagonist muscles.

Strength. Pure strength training consists of brief, maximal efforts involving all motor units in the affected muscle. High tissue pressure associated with such intense effort tends to compress blood vessels in the muscle and thereby reduce oxygen supply. As a result, strength training favors fast, glycolytic motor units.

The prominent adaptive response of muscle to brief, maximal efforts is hypertrophy. This is especially noticeable with isometric exercises.

Endurance. Endurance training differs from strength training in that the former consists of sustained, submaximal efforts. Such activity leads to some anatomic changes, but its major effect on muscle is to increase the capacity for metabolic activity. This is seen as an increase in the number of mitochondria and increased stores of oxidative enzymes.

Plasticity of skeletal muscle fiber types. In spite of the frequent use of the motor units, exercise does not cause conversion of slow units to fast units. The reason may lie in training-induced electrophysiologic changes:

with training, there is a gradual increase in average duration of action potentials but a concomitant and progressive diminution in their average frequency.

In laboratory experiments, stimulus-induced conversion has been accomplished after maintained elevation of nerve action potential frequency.

Assessment of Skeletal Muscle Function

Electromyographic Assessment of Whole Muscle

Qualitative information about muscle function can be obtained by recording electrical activity with a pair of electrodes placed on the surface of the muscle. The record obtained consists of motor unit action potential trains and is called an **electromyogram (EMG)** (Figure 2–13). Its interpretation is counterintuitive in that (1) changes in the amplitude of EMG deflections are directly related to changes in firing frequency of active motor units in the muscle and (2) changes in the time interval between neighboring pulses in the EMG are inversely related to changes in the number of active motor units in the muscle.

SMOOTH MUSCLE

Smooth muscle differs from striated muscle in at least three important aspects. It (1) lacks the regular striated pattern, (2) develops tension

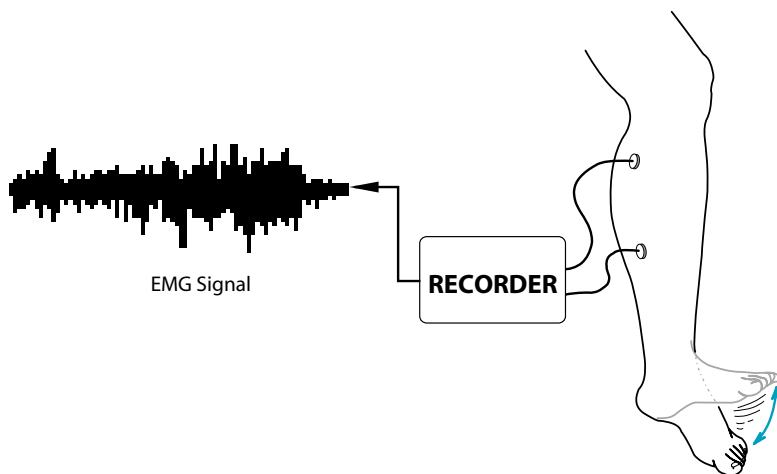


Figure 2–13 An electromyogram (EMG) is a record of the voltage fluctuations that can be recorded from the surface of working muscle. Both the amplitude of the recorded signal and the time interval between neighboring deflections carry information that is related to the activity of muscle motor units within “view” of the electrodes.

extremely slowly but can maintain it for long periods of time with a very low energy cost, and (3) has membrane receptors and transduction mechanisms for many neurotransmitters and hormones.

Morphology of Smooth Muscle

The organization of smooth muscle is diverse and ranges from **multiunit** smooth muscle (in which cells are arranged as discrete muscle fibers, each fiber innervated by an individual nerve) to **unitary** smooth muscle (in which cells are arranged in sheets with multiple gap junctions providing extensive electrical and metabolic contact with neighbors). Between these two extremes are types of smooth muscle that exhibit the spontaneous activity characterizing unitary smooth muscle but also show superimposed, neurally mediated activity that characterizes multiunit smooth muscle.

Smooth Muscle Cells

Smooth muscle cells are spindle shaped and short (100 to 500 μm long; 3 to 10 μm in diameter). They have no T-tubules, and their SR is less elaborate than that of striated muscle. They contain both thin (actin) and thick (myosin) filaments but also intermediate filaments made up of the proteins, **desmin**, **vimentin**, and **filamin**. The intermediate filaments form an intracellular network interconnected by **dense bodies**, and they attach to the plasma membrane at **dense patches**. Neighboring smooth muscle cells are often electrically coupled by gap junctions.

Plasma membrane. The plasma membrane of smooth muscle cells has several distinct regions:

- One portion has surface invaginations (**caveolae**). These caveolae appear to have no function other than to increase the surface area of smooth muscle cells, and they are different from the receptor-containing pits that can detach and form intracellular, receptor-lined vesicles.
- Another portion has closely apposed SR. This region shows electron-dense structures that appear to couple the plasma membrane to the SR, and it probably forms a major site of signal transduction by way of voltage-gated or receptor-mediated mechanisms.
- A third portion forms the attachment patches that link intermediate filaments from the intracellular network of filaments to the plasma membrane.
- A fourth portion contains the gap junctions that link neighboring cells.

Sarcoplasmic reticulum. The SR is the major intracellular depot for Ca^{++} . It stores Ca^{++} while the muscle is relaxed and releases it during excita-

tion–activation–contraction coupling. The electron-dense processes that appear to couple the SR to the plasma membrane are probably the cytosolic domains of ryanodine receptors (Ca^{++} -release channels) in the SR membrane.

Contractile Elements

The contractile machinery of smooth muscle resembles that of striated muscle, but it is arranged differently. Thin filaments, composed mainly of actin, are attached to the dense bodies or to membrane attachment patches and interdigitate with myosin filaments in such a way that a contractile mesh is formed among attachment patches and dense bodies (Figure 2–14).

Thin filaments. Thin filaments in smooth muscle are composed mostly of F-actin and tropomyosin. They contain no troponin but, instead, contain **caldesmon**, a calmodulin-binding protein. The actin found in vascular smooth muscle is α -actin, the same as in striated muscle; that found in enteric smooth muscle is a γ -actin. Many thin filaments are attached at one end either to a dense body or to a dense patch on the plasma membrane.

The dense bodies and patches are rich in **α -actinin**, an α -actin-binding protein, and appear to serve a role analogous to that of Z-lines in striated muscle. Thin filaments radiate like spokes on a wheel from each dense body.

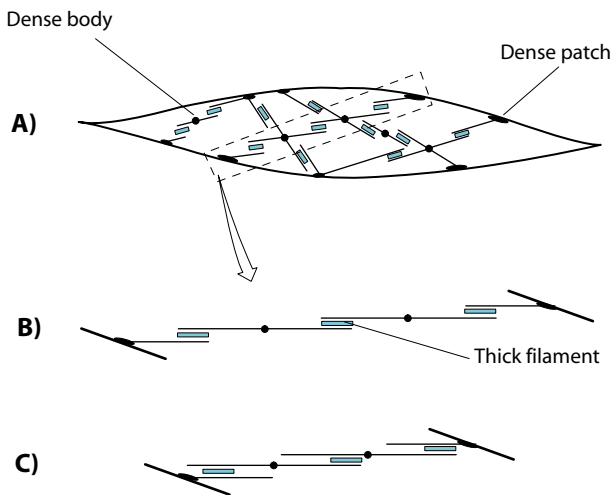


Figure 2–14 Arrangement of thin and thick filaments as well as dense bodies and patches in smooth muscle. *A*, Thin filaments are shown radiating from dense bodies or attached to dense patches at the plasma membrane. Thick filaments, lying between thin filaments, are shown in color. Note that diagonal contractile units can be formed between dense patches in the plasma membrane. Note also that smooth muscle myosin has a rectangular rather than round cross-section. *B*, Enlargement of rectangle in *A*, showing one contractile unit. *C*, The contractile unit of *B* shown in its contracted state.

Thick filaments. Thick filaments consist of smooth muscle myosin. Its amino acid sequence differs slightly from that of striated muscle myosin. However, it has two S_1 heads, attached to a coiled coil tail and is formed by two heavy chains, two “essential” light chains, and two “regulatory” light chains. Smooth muscle myosin differs from striated muscle myosin in two important aspects: (1) It is arranged differently. Rather than the parallel/antiparallel arrangement, smooth muscle myosin molecules are oriented in one direction on one face of the filament and in the opposite direction on the other (Figure 2–15). This is called a “side-polar” arrangement; it means that a thin filament can completely overlap a thick filament and can be pulled over the whole of its length. At the level of a whole smooth muscle it means that operation near maximum tension is possible over a wide range of lengths. (2) It has very low ATPase activity. This results not only in low rates of actomyosin cross-bridge cycling but also in low rates of energy expenditure.

Smooth Muscle Function

As it is in striated muscle, a rise in cytosolic $[Ca^{++}]$ is the trigger for the activation of smooth muscle contraction. However, the mechanisms by which Ca^{++} is released from the SR and in which Ca^{++} transients are coupled to contraction are different in smooth muscle.

Elevation of Cytosolic $[Ca^{++}]$

$[Ca^{++}]_i$ is increased either by a primary change in membrane potential (**electromechanical excitation**) or by chemical events that do not necessarily involve a change in membrane potential (**chemomechanical excitation**).

Electromechanical excitation. This is initiated by a depolarization of the cell membrane that is not necessarily sufficient to elicit an action potential but must be sufficient to activate voltage-gated Ca^{++} channels to conduct

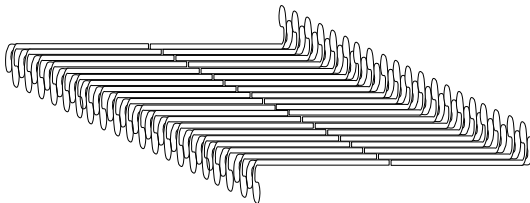


Figure 2–15 Polarized arrangement of myosin on opposite faces of a smooth muscle thick filament.

Ca^{++} flux into the cell interior. Both T- and L-type channels are present in smooth muscle. The amount of Ca^{++} entering through voltage-gated channels is insufficient to activate contraction. It is probably augmented by calcium-triggered calcium release through ryanodine receptors in the SR.

Chemomechanical excitation. These processes account for chemically induced contractions of smooth muscle. They are mediated by plasma membrane receptors and involve either direct gating of a membrane Ca^{++} channel or the action of a second messenger, most commonly inositol 1,4,5-trisphosphate (IP_3). The IP_3 receptor is located in the SR membrane and is similar to the ryanodine receptor in its Ca^{++} release properties.

Excitation-Activation-Contraction Coupling

Once cytosolic $[\text{Ca}^{++}]$ has increased from its normal resting level of 100 nmol/L to about 500 to 1,000 nmol/L, the processes of excitation–activation–contraction coupling lead to contraction and the development of force by a sliding filament process resembling that described for striated muscle (see Figure 2–5), except that there is no troponin. The process involves a physical change in tropomyosin followed by a repeating cycle of strongly attached actomyosin cross-bridges, actin-catalyzed release of the products of previously hydrolyzed ATP, a power stroke, and detachment of the cross-bridge as new ATP is bound to the S_1 ATP binding site. Relaxation occurs either when Ca^{++} is removed from the cytosol or when the myosin regulatory light chain is dephosphorylated.

Functions of Ca^{++} . Ca^{++} activates calmodulin, a highly selective, cytosolic Ca^{++} -binding protein with four high-affinity Ca^{++} binding sites. When at least three of them are occupied, the molecule undergoes a conformational change, allowing it to modulate both caldesmon and myosin light-chain kinase (MLCK) (Figure 2–16). The probable insignificance of the caldesmon effect is further described under “Thin Filament Regulation” below.

Effects on MLCK. The Ca^{++} /calmodulin complex activates MLCK. Activated MLCK phosphorylates the regulatory light chain of the myosin head, and this increases myosin ATPase activity, a necessary and sufficient step for smooth muscle contraction. Usually, the regulatory light chain is phosphorylated at the serine-19 position, but additional phosphorylation can occur at the adjacent threonine-18 position. It is not known how any changes that are initiated by regulatory light-chain phosphorylation in the neck region of the S_1 head (see Figure 2–4) are transmitted to the head region where actin binding and ATP hydrolysis take place.

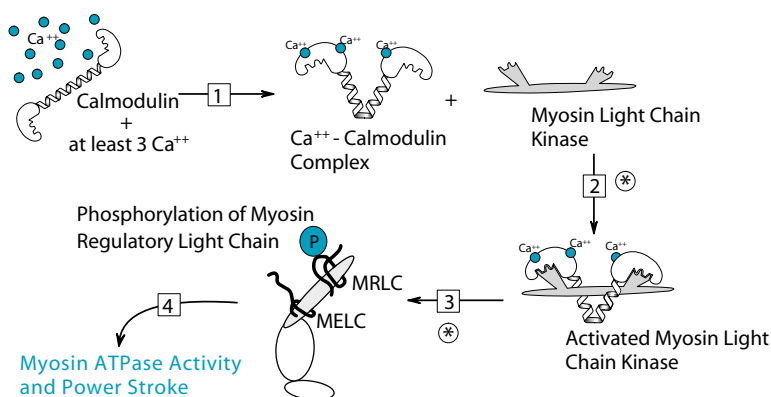


Figure 2-16 Steps in activation-contraction coupling of smooth muscle. Calmodulin is a cytosolic protein. When at least three of its four Ca^{++} binding sites are occupied, calmodulin undergoes a conformational change (step 1) that permits interaction with and activation of myosin light chain kinase (step 2). Activated myosin light chain kinase catalyzes phosphorylation of the myosin regulatory light chain (step 3), which increases myosin ATPase activity in the myosin head. Phosphorylation of MRLC is a necessary and sufficient condition for ATPase activity and the power stroke. Steps marked with * identify sites where Ca^{++} sensitivity can be modulated. MRLC = myosin regulatory light chain; MELC = myosin essential light chain.

Electrophysiology of Smooth Muscle

Ion Currents in Smooth Muscle

Smooth muscle has a variety of selective and nonselective ion channels. Among the selective channels, those carrying Ca^{++} or K^{+} have been investigated most intensively, but Cl^{-} and Na^{+} channels are equally important. Three functional types can be identified: voltage-gated channels, ligand-gated channels, and stretch-activated channels.

Voltage-gated channels. Ca^{++} channels. L-type Ca^{++} channels are the most important contributors to the upstroke of smooth muscle action potentials and to excitation–activation–contraction coupling.

K^{+} channels. At least two types of voltage-gated K^{+} channels are important for smooth muscle function: (1) one or more kinds of delayed rectifier channel conduct the repolarizing current at the end of an action potential, and (2) the inward rectifier K_1 channel helps to maintain resting membrane potential in electrically stable cells.

Na^{+} channels. Voltage-gated Na^{+} channels have been identified in some smooth muscle. When they are present, they contribute to the change in membrane potential during the upstroke of the action potential.

Ligand-gated channels. Such channels are influenced by chemical rather than electrical changes. The influence of the ligand is direct in some cases (e.g., in the ATP-sensitive K^+ channel, K_{ATP} , which is activated by lack of ATP, or in the Ca^{++} -sensitive K^+ channel, which is activated by increased $[Ca^{++}]_i$), and it is indirect in others where interaction of the ligand with its membrane receptor produces a second messenger that can gate ion channels.

Stretch-activated channels. These tend to be nonselective cation channels, conducting both Na^+ and Ca^{++} .

Resting Membrane Potential

Smooth muscle cells have a more positive resting membrane potential than do striated muscle cells. It is between -40 and -60 mV, which is more positive than the potassium equilibrium potential, E_K . The most likely explanation for this is greater contributions from Na^+ and Cl^- currents. Most vascular smooth muscle has, in addition to the ubiquitous Na^+-K^+ pump, an active mechanism that transports Cl^- into the cell as well as a $3Na^+-Ca^{++}$ exchanger that normally functions in the Ca^{++} -out mode.

Action Potentials

Ca^{++} entering a smooth muscle cell serves a dual function in that it depolarizes the membrane potential and initiates contraction. It is often true that the amount of Ca^{++} that has entered is sufficient for a contraction but not sufficient to raise the membrane potential to the threshold for triggering an action potential. As a result, two electrically distinct types of smooth muscle have been identified: (1) normally quiescent muscle, in which a small excitatory stimulus elicits a sustained, nonregenerating electrical response resembling a skeletal muscle end-plate potential, while a sufficiently large stimulus triggers action potentials; and (2) spontaneously active muscle, which displays slow wave electrical activity. When these slow wave potentials reach the threshold, one or more spontaneous action potentials are generated, spread over neighboring cells, and cause a stronger contraction than that associated with the slow waves (Figure 2–17).

In general, the upstroke of the action potential, when it occurs, is carried by a Ca^{++} current through L-type channels, and repolarization is mostly due to delayed rectifier K^+ currents.

Regulation of Smooth Muscle Function

At the tissue level, smooth muscle tension is influenced by neural and chemical factors as well as by physical stretch. At the cellular level, these influences

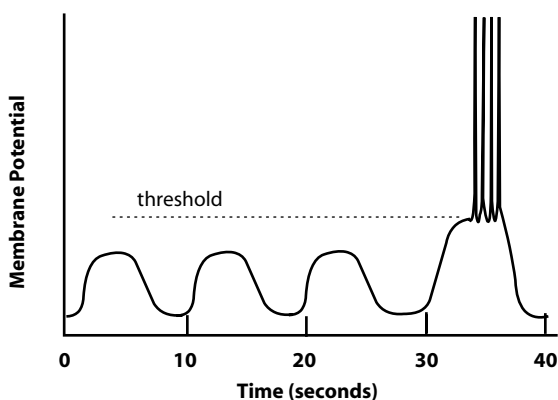


Figure 2-17 Smooth muscle shows slow wave activity where the peak of each wave is below the threshold for opening the Ca^{++} channels that are responsible for generating action potentials. When that threshold is reached, then a burst of action potentials is generated at the peak of the triggering slow wave until the cell repolarizes and resumes its slow wave activity.

are translated into changes of cytosolic Ca^{++} concentration $[\text{Ca}^{++}]_i$ or sensitivity to a given $[\text{Ca}^{++}]_i$.

Regulation at the Cellular Level

Regulation by cytosolic $[\text{Ca}^{++}]_i$. $[\text{Ca}^{++}]_i$ depends on membrane Ca^{++} current and Ca^{++} release from sarcoplasmic reticulum (Figure 2-18).

Membrane calcium current. Ca^{++} flux through L-type membrane channels is modulated by agents that alter membrane potential (such as K^+) and by agents that affect channel conductance. Such agents include cyclic adenosine monophosphate (cAMP) (which stimulates the L-type channel) and cyclic guanine monophosphate (cGMP) (which inhibits the L-type channel).

SR release and uptake. Many agents influence SR release and uptake of Ca^{++} . They include (1) IP_3 (which promotes Ca^{++} release), (2) cGMP (which inhibits Ca^{++} release), (3) cAMP (which promotes Ca^{++} uptake into the SR), and (4) agents that modulate phospholamban phosphorylation (the SR Ca^{++} ATPase activity is increased by phospholamban phosphorylation and decreased by phospholamban dephosphorylation).

Regulation of Ca^{++} sensitivity. A variety of mechanisms can influence force development at a given $[\text{Ca}^{++}]_i$ (Table 2-1).

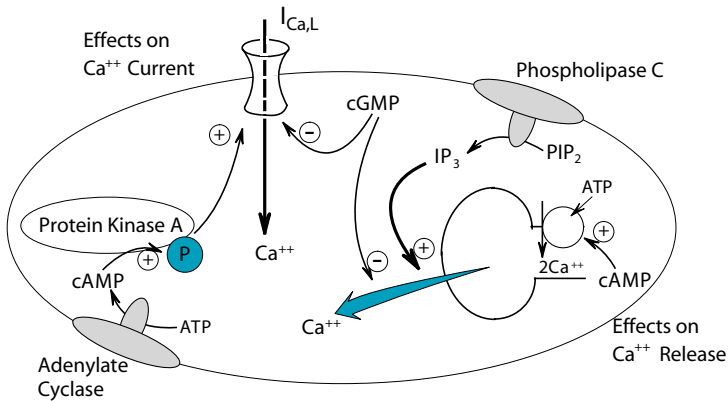


Figure 2–18 Cellular mechanisms of modulating smooth muscle function by way of modulating intracellular [Ca²⁺]. Both Ca²⁺ entry through L-type channels and Ca²⁺ release from sarcoplasmic reticulum can be regulated. In most smooth muscle, the dominant effect of cAMP is relaxation. The strongest stimulus for increasing [Ca²⁺]_i is inositol 1,4,5-trisphosphate (IP₃). ATP = adenosine 5'-triphosphate; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; I_{Ca,L} = L-type Ca²⁺ current through L-type channels; PIP₂ = phosphoinositol bisphosphate.

Regulation by phosphorylation and dephosphorylation. (1) *MLCK phosphorylation:* Myosin light chain kinase (MLCK) can be phosphorylated at up to six sites. Of these, phosphorylation at serine-815 by cAMP-dependent protein kinase is appreciable. Such phosphorylation causes a marked decrease in the affinity of MLCK for Ca²⁺/calmodulin binding and results in a shift of the

Table 2–1
Regulation of Smooth Muscle Function by Ca²⁺ Sensitivity or Thin Filament Dynamics

Regulatory Factor	Cellular Site	Effect
Ca ²⁺ Sensitivity	Phosphorylation of myosin light chain kinase (MLCK)	MLCK phosphorylation decreases MLCK affinity for Ca ²⁺ calmodulin
	Phosphorylation of myosin regulatory light chain (MRLC)	Myosin light chain phosphatase and other phosphatases reverse phosphorylation of MRLC and decrease Ca ²⁺ sensitivity
Thin Filament Dynamics	Caldesmon (??)	Caldesmon at very high concentrations inhibits myosin ATPase activity
	Calponin	Calponin inhibits myosin ATPase activity

Ca^{++} dependency of muscle force to a higher level of $[\text{Ca}^{++}]_i$. This is called a decrease in Ca^{++} sensitivity. (2) *MRLC phosphorylation*: Both shortening velocity and force are dependent on phosphorylation of serine-19 in the myosin regulatory light chain (MRLC). This reaction is catalyzed by Ca^{++} /calmodulin-dependent MLCK and reversed by myosin light chain phosphatases (MLCP). As a result, the ratio of activated MLCK to active MLCP is an important determinant of smooth muscle activity. When the ratio is high, more actomyosin cross-bridges are formed, and they will quickly cycle between the attached and detached states. When the ratio is low, a greater proportion of cross-bridges cycle slowly in a **latch state**. A feature of smooth muscle function is that an increase in $[\text{Ca}^{++}]_i$, MLCK activity, MRLC phosphorylation, and associated force development is often followed by a decline in $[\text{Ca}^{++}]_i$ and MRLC phosphorylation but maintained force in spite of low MRLC phosphorylation. The latch state is characterized by slowly cycling actomyosin cross-bridges and allows maintenance of force at low energy expenditure. A latch bridge is formed only when the MRLC is dephosphorylated while the associated myosin head is still attached to actin. It requires that both $[\text{Ca}^{++}]_i$ and MRLC phosphorylation be above resting levels. (3) *MRLC dephosphorylation*: Regulation of phosphatase activity is a potential mechanism for changing the Ca^{++} sensitivity of MRLC phosphorylation. This is an area of active investigation, both with respect to the phosphatases involved and the mechanisms by which they are regulated in smooth muscle.

Regulation by the thin filament. (1) *Caldesmon*: Caldesmon is a thin filament protein. It binds to actin, tropomyosin, and calmodulin. There is one caldesmon molecule per 16 to 25 actin monomers. Both its ends are attached to the thin filament. Caldesmon inhibits the actin-activated ATPase activity of phosphorylated myosin, and both this inhibition and caldesmon's affinity for actin are reduced by Ca^{++} /calmodulin. This is unlikely to have regulatory significance because (a) the relative affinities of caldesmon and MLCK for Ca^{++} /calmodulin dictate excessively high calmodulin levels before there is significant reduction in caldesmon-based inhibition of ATPase activity, and (b) there is probably not enough caldesmon to interact with every myosin molecule. (2) *Calponin*: Calponin binds calmodulin, actin, and tropomyosin. It is present at the same concentration as tropomyosin and inhibits myosin ATPase activity in a Ca^{++} -independent manner. A role for it in the regulation of smooth muscle contraction has been suggested but not yet demonstrated.

Regulation at the Organ Level

Neural influences. In spontaneously active (unitary) smooth muscle, nerves can modulate activity, and in nonspontaneous (multiunit) smooth muscle, nerves can initiate activity. The dominant smooth muscle neuro-

transmitters are acetylcholine and norepinephrine. When they activate their respective postsynaptic receptors, they have at least three effects: (1) they change membrane permeability to Ca^{++} , (2) they change membrane potential, and (3) they may cause muscle contraction without necessarily generating a smooth muscle action potential.* Smooth muscle in different regions differs in its mechanical responses (contraction or relaxation) to each of the neurotransmitters.

Chemical influences. Local tissue factors, such as partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), concentration of hydrogen ion [H^+], as well as paracrine and endocrine agents, too numerous to list, influence smooth muscle activity. One of the key differences between smooth and striated muscles is that smooth muscle contains a great variety of plasma membrane receptors whose activation by specific ligands will modulate contractile behavior.

Mechanical influences. Stretching of smooth muscle cells may activate mechanosensitive ion channels. It makes the average membrane potential less negative and, thereby, increases excitability. This causes an increased number of spontaneous action potentials and leads to increased spontaneous muscle contraction. This automatic constrictor response of some smooth muscle to increased stretch is called the **myogenic reflex**.

*Whether or not a muscle action potential is generated depends only on whether the number of Ca^{++} ions needed for contraction is large enough to have moved the muscle cell membrane to its threshold for an action potential.

Blood

Blood is that portion of the extracellular fluid volume that is confined to the blood vessels. It is a normally liquid suspension of **formed elements** (cells and cell fragments) in **plasma** and functions as a medium of **transport**, **communication**, and **organism preservation** (Table 3–1).

COMPOSITION OF BLOOD

Blood is a normally liquid suspension of formed elements. Table 3–2 shows the relative abundance and major functions of blood components.

FORMATION OF BLOOD (HEMOPOIESIS)

In children, blood cells are produced in the marrow of all bones. After the age of 20 years, only the marrow of the vertebrae, sternum, and ribs remain significantly active (red marrow) in the production of erythrocytes, many leukocytes, and platelets. Inactive marrow becomes yellow marrow because of fat infiltration.

Active marrow contains **pluripotential stem cells** that are capable of replacing the bone marrow completely (self-renewal) or can be diverted from self-renewal toward separate pools of committed **progenitor cells** (Figure 3–1).

Stem Cells and Progenitor Cells

Progenitor cells differ from stem cells in two ways: (1) they have lost the capacity for self renewal and (2) they are not pluripotential but are committed to produce (under the proper growth conditions) daughter cells of a particular type.

During maturation, each cell line, promoted by a variety of stimulating factors, acquires distinctive properties.

Table 3–1
Functions of Human Blood

Function	Details
Transport	Gases; nutrients; metabolic waste; heat; defense agents; buffers; enzymes; hormones
Communication	“Information” is transported by chemicals including hormones.
Organism preservation	<ul style="list-style-type: none">• Clotting factors operate to prevent blood loss.• Phagocytes inactivate foreign cells or cellular debris.• Antithrombic agents prevent inappropriate blood clotting.• Hemostatic mechanisms prevent blood loss after blood vessel injury.• Immunoglobulins protect against molecular threats.

Erythrocytes (Red Blood Cells)

The main function of the red blood cell is to transport respiratory gases between the lung and other tissues. This is supported by three physical attributes:

1. They are a 330 g/L solution of **hemoglobin** (the major O₂-transporting protein of the body) plus some **carbonic anhydrase** (a facilitator of CO₂ packaging).
2. Their exterior membrane is pliable. In humans, they have no mitochondria, few structural elements, and no nucleus. These aspects give them great cellular deformability and allow them to recover after each deformation that occurs as they are squeezed through capillaries.
3. Their biconcave shape yields maximum surface area for a given volume and, thereby, provides greatest surface area for exchange phenomena.

Erythropoiesis

In the adult human, about 200 × 10⁹ red cells are formed each day provided that (1) there are proper cell growth conditions, (2) the appropriate growth factors are present, and (3) erythropoietin and iron are available.

The **erythroid colony-forming unit** (CFU_e) represents the earliest committed cell in the erythroid series. Conversion of CFU_e cells to hemoglobin-synthesizing erythroblasts and, eventually, to erythrocytes requires the presence of **erythropoietin**. Other growth factors generally participate, but only erythropoietin is obligatory.

Table 3–2

Composition of Human Blood

Component	Major Function	Normal Values	
		(% by volume)	(% of all leukocytes)
Plasma	Carrying medium; protein-associated functions*	52–58	
Erythrocytes	Transport of O ₂ ; CO ₂	42–48	
Leukocytes		<1	
Granulocytes (PMNs)			
Eosinophils	Participate in allergic reactions		1–4
Basophils			0.4–1
Neutrophils	Defense against bacterial infections; mediation of inflammatory responses		50–70
Monocytes	Modulate immune responses; scavenge cellular debris		2–8
Lymphocytes	Mediate immune responses		20–40
Platelets	Form hemostatic plugs	<1	

*The major plasma proteins are **albumin** (4.5 g/dL), several **globulins** (2.5 g/dL), and **fibrinogen** (0.3 g/dL). Most are synthesized by the liver, and they have five major functions: (1) **carriers** for hormones, trace metals, or drugs; (2) **proteolytic agents** in the cleavage of various hormonal or enzymatic precursors; (3) **protease inhibitors**; (4) source of **plasma colloid osmotic pressure**; (5) source of the **humoral immunity** portion of the immune system.

PMNs = polymorphonuclear leukocytes.

Erythropoietin (EPO). Erythropoietin is a 165-amino-acid glycoprotein that is produced mostly by endothelial cells in renal cortical peritubular capillaries. The hormone is produced constitutively, and hypoxia causes recruitment of additional synthesizing cells. Erythropoietin acts through membrane receptors and (1) increases the number of committed erythroid stem cells in the bone marrow and (2) promotes conversion of these committed stem cells to erythrocyte precursor cells (erythroblasts, normoblasts, and reticulocytes).

The most significant intracellular event during this conversion is the synthesis of **hemoglobin**. It begins in the committed stem cell (CFU_e) and increases progressively to a plateau in reticulocytes.

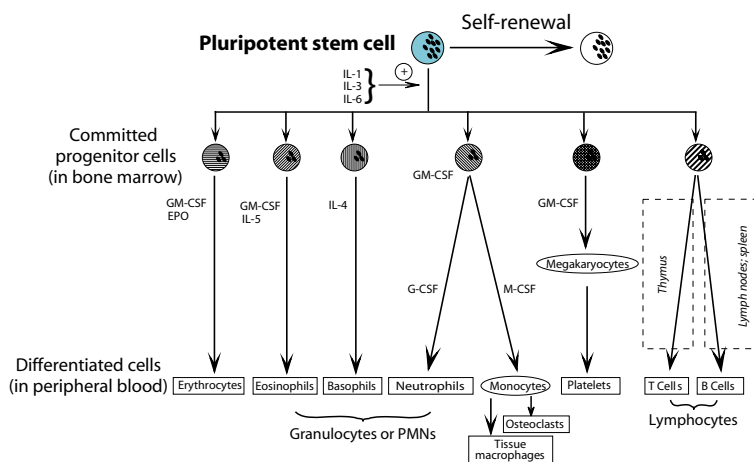


Figure 3–1 Formation of various formed elements in blood from bone marrow cells under the influence of several stimulating factors. A pluripotent stem cell can differentiate in a few divisions into one of six classes of progenitor cells that go on to produce blast cells. Blast cells are the earliest morphologically distinct precursors of specific cell types. EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; M-CSF = monocyte colony-stimulating factor; PMNs = polymorphonuclear monocytes.

Hemoglobin. Hemoglobin (Hb) is a globular molecule that is made up of four subunits. Each subunit contains a heme moiety (Figure 3–2) that is conjugated to a polypeptide (see Figure 3–2).

Hemoglobin synthesis. Hemoglobin is synthesized in all cells of the pre-erythrocyte line in a process that begins in the mitochondrion, using **succinate** as a substrate, continues in the cytoplasm, where **porphyrinogen** is formed, returns to the mitochondrion for the formation of **heme**, an iron-containing pigment, and, finally, goes to the cytoplasm for the combination of heme with **globin** subunits.

The final Hb molecule consists of two pairs of heme-containing polypeptides.

Structure and function of hemoglobin. Six types of polypeptide chains are found in human hemoglobin: α (141 amino acids + heme), β (146 amino acids + heme), γ (also 146 amino acids + heme, but 37 of the residues differ from those found in β chains), δ (also 146 amino acids + heme, but 10 of the residues differ from those found in β chains), as well as ϵ and ξ chains that are found in embryos up to 3 months of gestation.

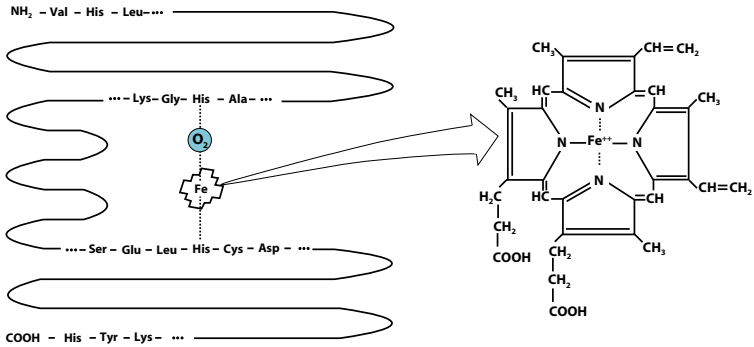


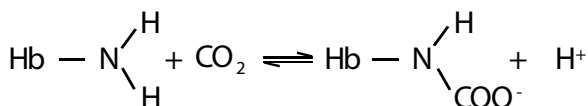
Figure 3–2 One subunit of oxygenated hemoglobin (oxyhemoglobin), showing the heme group in detail. When hemoglobin reacts with O_2 to form oxyhemoglobin, the O_2 is carried between Fe^{++} and a histidine in an adjacent polypeptide chain.

Adult hemoglobin: In the adult human, three types of chain are found. They are designated α , β , and δ . About 98% of adult hemoglobin is **hemoglobin A**, a combination of two α -chains and two β -chains. The remainder is hemoglobin A_2 (two α - and two δ -chains).

Fetal hemoglobin: Fetal hemoglobin (hemoglobin F) is present in significant concentration up to about 6 months of age. It differs from the adult form in both structure and O_2 affinity: hemoglobin F contains two γ -chains instead of β -chains; it has higher O_2 affinity at a given pO_2 than does hemoglobin A because its γ -chains bind 2,3-DPG* less avidly than do the β chains of adult Hb.

Reactions of hemoglobin: (1) *Oxygenation and deoxygenation:* Each of the four Fe^{++} ions can bind rapidly and reversibly with one O_2 molecule to form oxyhemoglobin. The amount of O_2 carried by hemoglobin is decreased by increasing temperature, increased $[H^+]$ (this is called the **Bohr effect**) or increased [2,3-DPG].* (2) *Carbon dioxide:* About 25% of the CO_2 carried by red cells reacts with the NH_2 terminal of hemoglobin (see Figure 3–2) to form **carbamino hemoglobin**:

*2,3-Diphosphoglycerate, an intermediary product in the conversion of glucose to pyruvate. It is plentiful in red blood cells; is increased by each of thyroid hormone, growth hormone, and androgens; and binds to the beta chains of hemoglobin, thereby decreasing its O_2 affinity.



The remaining 75% is carried in the form of dissolved $\text{H}_2\text{CO}_3/\text{HCO}_3^-$. (3) *Carbon monoxide*: Hemoglobin has a much higher affinity for carbon monoxide (CO) than for O_2 . Consequently, CO displaces O_2 and thus reduces the oxygen-carrying capacity of erythrocytes. Carbon monoxide and Hb form **carbon monoxyhemoglobin**, also called carboxyhemoglobin. (4) *Methemoglobin*: A variety of nitrites or oxidant agents can convert the ferrous iron (Fe^{++}) in hemoglobin to the ferric form, Fe^{+++} , thus forming methemoglobin. Methemoglobin cannot bind O_2 .

Red Blood Cell Membrane

Membrane structure. The red cell membrane resembles other plasma membranes in that it is a bilayer of phospholipids, glycolipids, and cholesterol. Peripheral and integral proteins are associated with the bilayer.

Mechanical properties. The erythrocyte membrane is highly deformable. This property arises from interactions between cytoskeletal elements (particularly **spectrin** and **ankyrin**) and the membrane-spanning protein **glycophorin**. Glycophorin accounts for nearly 75% of membrane protein in erythrocytes, and its presence is crucial for membrane fluidity.

Immunologic properties. The red cells of different individuals differ to a very small extent in the structure of some carbohydrates that are part of membrane glycolipids. These differences bestow antigenic properties on red blood cells and cause red cell **agglutination** if bloods of sufficiently different antigenic properties are mixed.

ABO antigens. The A and B antigens are the most important of the more than 100 different blood group antigens that have been identified. They are inherited and are the basis for dividing individuals into the four blood groups: O, A, B, and AB (Table 3–3). In neonatal life, we quickly develop antibodies against the antigens that are *not* present on our red cells, and these antibodies, called **agglutinins**, are carried in plasma.

The antigens are called **agglutinogens** and are carried on the red cells in the blood as well as on cells in many other tissues. In red cells, they are glycosphingolipids that differ by only the last sugar in the carbohydrate chain that is attached to a membrane sphingolipid (Figure 3–3). When red cells from an

Table 3–3

Details of the ABO System

Blood Type	Agglutinogens on Red Cells	Agglutinins in Plasma	Plasma Will Agglutinate Red Cells of Type	Occurrence (percent of population)
O	None*	Anti-A; anti-B	A; B; AB	45
A	A	Anti-B	B; AB	40
B	B	Anti-A	A; AB	10
AB	A; B	None	No agglutination Universal recipient	5

*Type O individuals are called “universal donors” because their red cells carry neither A nor B antigens. Their plasma will agglutinate recipient red cells of types A, B, and AB, but in a transfusion, the donated plasma will normally be diluted by the donor’s plasma.

individual are mixed with plasma from another individual, an immune response (transfusion reaction) will occur, in which the red cells will clump together (**agglutinate**) and burst (**hemolyze**), releasing their hemoglobin.

Rh antigens. In addition to the ABO system of antigens, there are many others, though they are rarer. After the ABO antigens, those of the Rh system are important. Within the Rh system, the C, D, and E antigens are most important. They are found only in red cells. D is the most antigenic component, and the presence or absence of D is designated as “Rh-positive” or

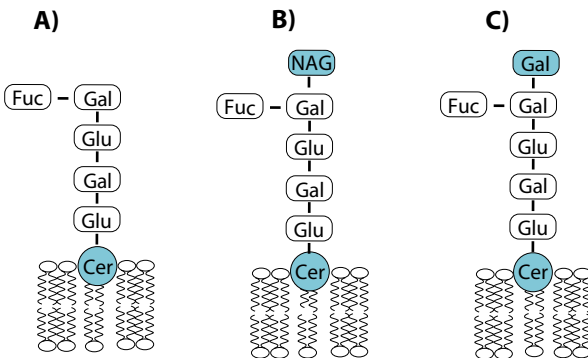


Figure 3–3 Antigens (agglutinins) of the ABO group are formed by glycosphingolipids on the surface of erythrocytes. (All sphingolipids contain the fundamental long-chain fatty acid building block ceramide [Cer]). *A*, The H antigen that is present in individuals with type O blood. *B*, The A antigen (type A blood) has a terminal N-acetylgalactosamine (NAG). *C*, The B antigen (type B blood) has a terminal galactose (Gal). Cer = ceramide; Fuc = fucose; Gal = galactose; Glu = glucose.

“Rh-negative,” respectively. Eighty-five percent of Caucasians and more than 99% of Asians are Rh+. Unlike antibodies to the AB antigens, anti-D develops only when the blood of a D− individual is exposed to D+ red cells. This can occur as a result of transfusion or when Rh+ fetal blood mixes with the circulation of an Rh− mother.[†]

Life Cycle of Erythrocytes

Normal erythrocytes have a life span of about 120 days. Aging cells undergo membrane changes that allow mononuclear phagocytes in the marrow, liver, and spleen to recognize and remove the deteriorating cells. In the course of these processes, (1) heme is dissociated from the globin portion and is oxidized. This separates Fe^{++} from the pigment portion. **Transferrin**, the iron-transporting protein, carries the iron back to the **erythroid colony-forming units** and erythroblasts for incorporation into new erythrocytes. The pigment portion of heme is reduced to **bilirubin** and is excreted via bile into the gastrointestinal (GI) tract, giving stool its characteristic brown color. (2) The globin chains are broken down into their amino acids and released to the body pool of amino acids.

Leukocytes (White Blood Cells)

There are normally only 4,000 to 11,000 white cells per μL of human blood, compared with 5,000,000 red cells per μL . They are classified according to their microscopic appearance or affinity for certain stains. Their major function is as a rapid and specific defense mechanism against infectious molecular agents or microorganisms. The largest group is the **granulocytes** (polymorphonuclear leukocytes [PMNs]), so named because they all contain cytoplasmic granules that carry substances involved in allergic or inflammatory responses.

Granulocytes

Formation of granulocytes. Granulocytes arise from three populations of committed stem cells in the bone marrow and arrive in the tissues fully differentiated as **eosinophils**, **basophils**, or **neutrophils** (see Figure 3–1).

[†]When an Rh− mother carries an Rh+ fetus and small amounts of fetal blood mix with maternal blood during delivery, the mother may develop significant levels of anti-Rh antibodies in her plasma. During the next pregnancy, the mother's Rh agglutinins cross the placenta into the fetus and can cause severe hemolytic disease in the fetus.

Eosinophils. Eosinophils are especially abundant in mucosal tissues of the respiratory, lower urinary, and GI tracts. Their major role is to attack parasites that are too large to be engulfed by phagocytosis. They are also involved in allergic reactions because their circulating level is increased in allergic diseases.

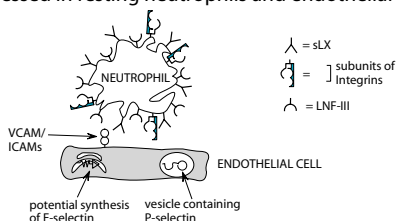
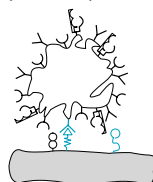
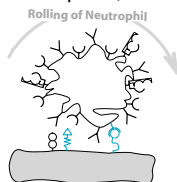
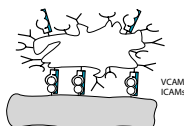
Basophils. Basophils are rich in histamine and heparin. They release inflammatory mediators when they are activated.

Neutrophils. Neutrophils are the first line of defense against infections and play a crucial role in inflammation.

Functions of granulocytes. Granulocytes, especially neutrophils, contain mechanisms by which they can progress rapidly from a harmless circulating intravascular cell to a specific phagocytic cell and killer of foreign particles, including bacteria.

Inflammation. In acute inflammation, neutrophils are captured and mobilized within minutes to hours and accumulate locally to form the initial defense in a locally restricted area (Figure 3–4). They are followed by monocytes within 1 day and by lymphocytes within several days. Neutrophil involvement in acute inflammation can be broken down into eight distinct phases:

1. *Recognition:* When tissue macrophages recognize foreign particles that have invaded tissue, they release a variety of inflammatory mediators, including tumor necrosis factor alpha (TNF- α), colony-stimulating factors for granulocytes (G-CSF) or granulocyte-macrophages (GM-CSF), leukotriene B₄ (LTB₄), complement fragment C5a, interleukin-8 (IL-8), and others. These soluble mediators can act as priming or activating factors for neutrophils and vascular endothelial cells.
2. *Expression of adhesion molecules and inflammatory mediators:* Neutrophils are large cells and, therefore, travel near the axis of microvessels. They need to be captured and drawn toward the margins of the flowing stream. This function is performed by a variety of adhesion molecules, expressed cooperatively on the surface of endothelial cells and activated neutrophils (see Figure 3–4). The adhesion molecules involved in leukocyte–endothelium interactions include selectins, integrins, immunoglobulins, and other molecules like CD44 and VAP-1. They mediate cell-to-cell and cell-to-substrate interactions by recognizing and binding specific ligands, such as other adhesion molecules.
3. *Hydrodynamic margination, capture, and rolling of neutrophils:* Radial displacement (hydrodynamic margination) and retardation of neutrophils by the endothelium are required as initial steps in the inflam-

A) Proteins expressed in resting neutrophils and endothelial cells**B) Activation of endothelium (selectins)****Capturing and rolling of neutrophils (selectins)****C) After 6 to 24 hours enough VCAM and ICAMs have been induced to bind integrins and flatten the neutrophil.**

Flattened neutrophils put out pseudopodia, force apart endothelial cells at intercellular junctions and begin diapedesis.

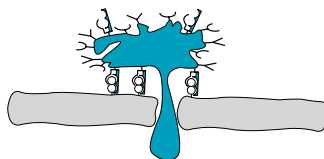


Figure 3-4 Neutrophils are involved in the early stages of acute inflammation. They are large cells that normally travel near the center of the flowing blood stream. **A**, Neutrophils are covered with integrins and the complex carbohydrate ligands for the selectins. Endothelial cells constitutively express some VCAM and ICAM-1 and -2. P-selectin is contained in cytosolic granules and the endoplasmic reticulum is poised to synthesize E-selectin. **B**, Inflammatory mediators initiate synthesis and translocation of selectins to the endothelial surface and they bind to their respective ligands on the neutrophil. Periodic breaking and release of the bonds causes neutrophil rolling over the endothelial surface. **C**, After a few hours, enough cell adhesion molecules, VCAM and ICAM-1 and -2, have been synthesized to bind the α and β subunits of the neutrophil surface integrins to draw the neutrophil close to the endothelium, causing them to flatten in the process. Flattened neutrophils extend pseudopodia that widen one of the intercellular clefts so as to permit emigration of the neutrophil to the interstitial space. LNF-III = lacto-N-fucopentaose; sLX = sialylLewisX; ICAM = intercellular cell adhesion molecule. Two forms exist: ICAM-1 (CD 54) and ICAM-2; VCAM = vascular cell adhesion molecule.

matory response. Once the neutrophils and endothelial cells are within a critical proximity, contact is made primarily through the E- and P-selectins, adhesion molecules that are induced (E-selectin) or translocated (P-selectin) to the surface of endothelial cells in postcapillary venules by a number of chemical signals. Their ligands are complex carbohydrates that are constitutively expressed on the neutrophil surface. Intermittent breaking of these contacts causes rolling (see Figure 3-4B). Nevertheless, the neutrophils are now moving across the endothelium at reduced speed and are exposed to endothelial inflammatory mediators.

4. *Activation, adhesion, and spreading:* Neutrophil activation is enhanced by exposure to the endothelium, and further expression of adhesion molecules leads to firm neutrophil adhesion to and spreading across the endothelial cell.
5. *Diapedesis:* Adhesion and spreading are prerequisites and lead to migration of the activated neutrophil through the intercellular junctions of neighboring endothelial cells (see Figure 3–4C). Neutrophils and monocytes migrate preferentially from postcapillary venules.
6. *Migration:* After passing through the endothelial junction and the basement membrane, the activated neutrophils, guided by chemotactic stimuli, migrate toward the foreign particles that initiate the inflammatory response. This migration is guided by interactions between adhesion molecules on the neutrophil surface and elements of the interstitial matrix.
7. *Phagocytosis:* Once the neutrophils reach the foreign particles, they attach to the opsonized[‡] surface of the agent (if it is large), or they engulf the agent within a phagocytic vacuole. Destruction of foreign material is chiefly by reactive oxygen metabolites (superoxide radicals[§] [O_2^-]) and granule contents including elastases, cathepsin G, proteases, and others.
8. *Apoptosis and elimination of neutrophils:* Among the β_2 integrins that are activated in the inflammatory response are those that trigger apoptosis of activated neutrophils so that they can be eliminated. Apoptotic neutrophils are specifically recognized and eliminated by macrophages.

Phagocytosis. Phagocytosis is a process of immobilization, ingestion, and digestion of foreign agents by granulocytes and monocytes. A vital first step in phagocytosis is the **activation of the complement system**.

Complement system: This is a system of 11 plasma enzymes identified as C1 to C9; C1 consists of the three subunits C1q, C1r, and C1s. The enzymes circulate in the inactive form but can be activated to lyse foreign cells. The activation proceeds in a step-like fashion, each activated enzyme hydrolyzing a peptide bond in the next inactive enzyme (Figure 3–5).

The complement system is activated by one of two pathways: (1) The **classical pathway** is triggered when immunoglobulin G or M binds to cell

[‡]Opsonization is a process by which the surface of a foreign invader is altered so as to make it more vulnerable to phagocytic action.

[§] O_2^- is formed when an electron is added to O_2 . It quickly forms two metabolites, hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^*). These have little inflammatory or bactericidal activity by themselves but can react with other substances to form effective destroyers of bacteria.

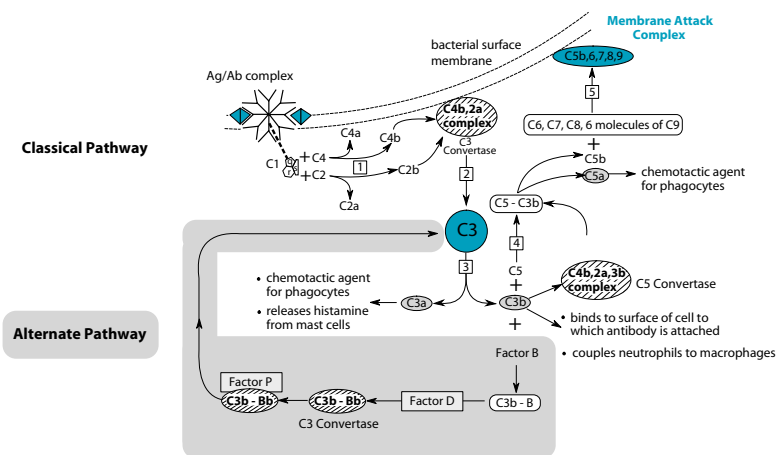


Figure 3–5 Complement activation by the classical pathway or the alternate pathway differs in the convertase that splits C3. The classical pathway is triggered by an antigen/antibody complex that has formed on, for example, a bacterial surface membrane. Such a complex binds the q component of C1 and activates C1 so that it can bind first C4, which is cleaved into C4a and C4b, and then C2, which is cleaved into C2a and C2b (step 1). A C4b,2a complex is then formed on the bacterial surface membrane and acts as the C3 convertase in the classical pathway (step 2), producing C3a and C3b (step 3). Antibody synthesis is not required for activation of the alternate pathway. This pathway begins with C3b, a moiety that is normally formed spontaneously to the extent of a few molecules. C3b complexes with factor B and the C3b-B complex are activated by the enzyme, factor D, which cleaves B to yield Ba and Bb. The complex C3b-Bb is the active convertase for C3. It is stabilized by factor P (properdin). Progression and amplification of the alternate pathway occur only if C3b-Bb is formed or deposited on a foreign surface. The membrane-bound C3 convertases cleave C3 into a small, soluble fragment, C3a and the larger C3b. C3b has a recognition site for C5, and the two form a C5-C3b complex (step 4). C3b also complexes with C4b and C2a to form C4b,2a,3b, which acts to convert C5 in the C5-C3b complex into the fragments, C5a, and C5b. C5a is a major inflammatory mediator and C5b complexes with C6, C7, C8, and 6 molecules of C9 to form the membrane attack complex, C5b,6,7,8,9 that lyses the membrane to which the antibody had originally bound (step 5).

surface antigens and then promotes activation of the three subunits of C1. The consequent activation cascade eventually leads to (a) activated C3, a cell surface-associated factor that promotes opsonization,¹¹ and (b) activated (C5, C6, C7, C8, C9), which is associated with production of chemotactic substances, release of histamine, and insertion of **perforins** into the plasma membrane. Perforins form pores that permit the free movement of ions. (2) The **alternate pathway** of complement activation does not require binding of immunoglobulins to cell surface antigens. It is triggered when the cir-

¹¹Opsonization is a process by which the surface of a foreign invader is altered so as to make it more vulnerable to phagocytic action.

culating protein factor I attaches to specific surface polysaccharides in a bacterium or virus. This pathway also leads to activation of C3 and (C5, C6, C7, C8, C9) and their associated opsonization or cell lysis.

Monocytes

Monocytes are formed in the bone marrow (see Figure 3–1), enter the blood, and circulate for about 3 days before they enter the tissues by diapedesis and become **tissue macrophages** that differentiate to perform specific functions in different tissues.[#] They persist in that form for about 3 months. They are phagocytic cells and perform many of the same actions that are performed by neutrophils. By secreting a large number of lysosomal, chemotactic, complement-activating, and pyrogenic factors, they are key effectors in the elimination of microorganisms and play an important role in immunity and blood clot formation. They sometimes fuse and form giant cells that coalesce into **granulomas**.

Mast Cells

Mast cells are found in tissues, and although they resemble basophils in some respects, they are different and derive from a different marrow stem cell. They are markedly granulated and are frequently found under epithelial surfaces. They are especially rich in heparin and histamine, and the granules containing these substances are released when immunoglobulin E (IgE)–coated antigens bind to receptors on the mast cell surface. They trigger hypersensitivity reactions and participate in inflammatory responses.

Lymphocytes

Lymphoid precursor cells migrate in fetal or early postnatal life to either the thymus or lymph nodes and spleen. Cells originating from thymus-routed precursors become T cells whereas the others become B cells. The two populations of lymphocytes respond differently to antigens, but they form the **specific** immune mechanisms of the body as opposed to **nonspecific** mechanisms, such as phagocytosis.

Production of lymphocytes. A single lymphocyte carries only one unique specificity. If it is triggered to increase the number of its unique receptors (in the case of T cells) or antibodies (in the case of B cells), the increase can be accomplished only by clonal multiplication of the original cell.

[#]The system of tissue macrophages was previously called the reticuloendothelial system.

B cells. B cells carry **immunoglobulins** as surface receptors. Antigens can stimulate these cells to clone into **plasma cells** that synthesize and secrete large quantities of a specific immunoglobulin antibody, different from the antibodies synthesized by all other B-cell clones.

Immunoglobulins. Structure: Immunoglobulins consist of two identical “heavy” amino acid chains and two identical “light” chains, assembled into a Y-shaped molecule (Figure 3–6). There are five different heavy chains, determining whether the immunoglobulin isotype is IgA, IgD, IgE, IgG, or IgM and differing from one another by the variable domain of the pair of heavy chains. There are only two variants of the light chain.

Function: While Ig bound to the B-cell surface act as receptors, freely circulating Ig can be antibodies, and as such, they recognize and bind antigens in order to (1) precipitate antigen from solution or (2) attach antigen to phagocytic/cytotoxic cells for subsequent destruction.

T cells. T cells are grouped into two classes, depending on their functions (Table 3–4): (1) cytotoxic T cells (T_C), which destroy hostile cells; and (2) helper T cells (T_H), which assist B cells in their immunologic tasks. Helper T cells are further divided into two subclasses, partly on the basis of the

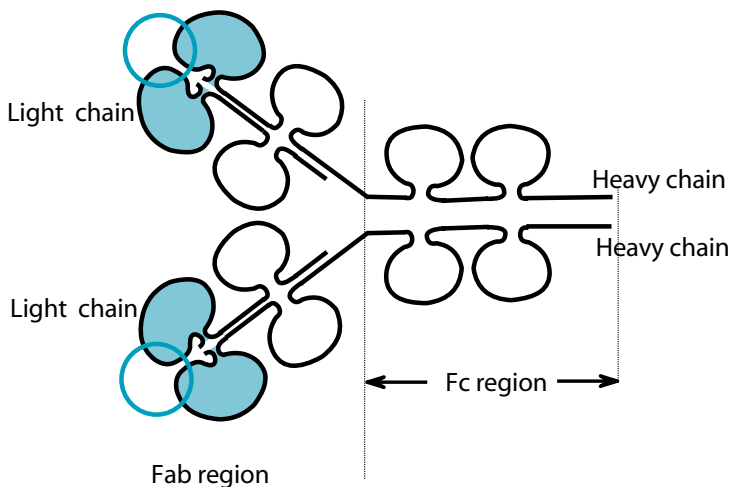


Figure 3–6 Structure of a typical immunoglobulin molecule. Each light chain forms two domains, and each heavy chain forms four or five domains of about 110 amino acids. Some domains occur in all immunoglobulins (constant domains), and some occur only in certain classes of immunoglobulins (variable domains, *shown in color*). Papain cleaves immunoglobulin molecules at a point called the “hinge.” The region to one side of the hinge is named the Fc region; that on the other side of the hinge is named the Fab region. The colored circles identify the antigen-binding regions (paratope).

interleukins they secrete once they are activated and partly on the basis of their functions: (i) T_{H1} cells secrete IL-2 and γ -interferon and help cytotoxic T cells and macrophages (Figure 3–7), and (ii) T_{H2} cells secrete IL-4, IL-5, and IL-6, which promote B-cell activation, and IL-10, which is an inhibitory cytokine in many settings (see Figure 3–7).

Table 3–4
Classification of T Lymphocytes

Class	Subclass	Differentiation by Secreted Cytokines	Function
Cytotoxic (T_C)			Destroy foreign cells
Helper (T_H)	T_{H1}	IL-2; γ -interferon	Assist T_C and macrophages
	T_{H2}	IL-4, -5, -6, and -10	Promote B-cell activation

IL = interleukin.

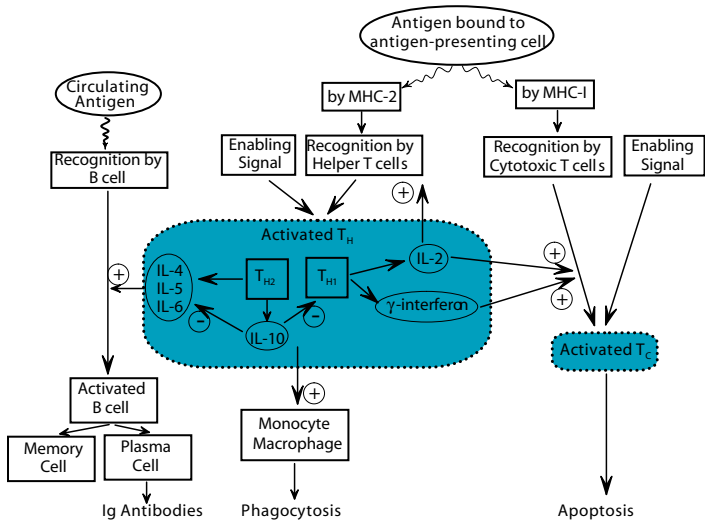


Figure 3–7 Summary of immune responses involving B cells and T cells. The T-cell independent response is shown on the left as resulting from antigen recognition by B cells. Most immune responses involve T cells, and these are summarized on the right. They require that the antigen be presented to T cells as part of an MHC on the surface of an antigen-presenting cell, and they lead ultimately to apoptosis, phagocytosis, and cloning of IgG, IgM, IgA, and IgE antibodies by plasma cells. CD = cluster of differentiation; Ig = immunoglobulin; IL = interleukin; MHC = major histocompatibility complex; T_C = cytotoxic T cells; T_H = helper T cells.

T cells carry two types of receptor proteins on their surfaces. They are named the **T-cell receptor** and CD** molecules. Different forms of these two are combined differently and specifically on T_H and T_C. This selectivity is bestowed on T cells while they are being processed in the thymus.

T-cell receptors: These receptors consist of two chains (α and β) that are anchored in the plasma membrane, and the extracellular region of each is folded into two domains (Figure 3–8). The most distal tip of the chains forms the recognition and binding sites (called the **paratope**). The T-receptor paratope recognizes as an epitope^{††} only a specific portion of the molecules of the **major histocompatibility complex** (MHC) on the surface of other cells.

CD molecules: These molecules also recognize a specific portion of the MHC on other cells, but it is a different portion from that recognized by the T-cell receptor. Important CD molecules are named CD3, CD4, and CD8, and many others have been identified. CD3 is present in all classes of T cells. Helper T cells carry only CD4,^{‡‡} T_C carry only CD8. The specific association of CD4 with T_H and CD8 with T_C helps ensure discrimination in the association of T cells with other cells.

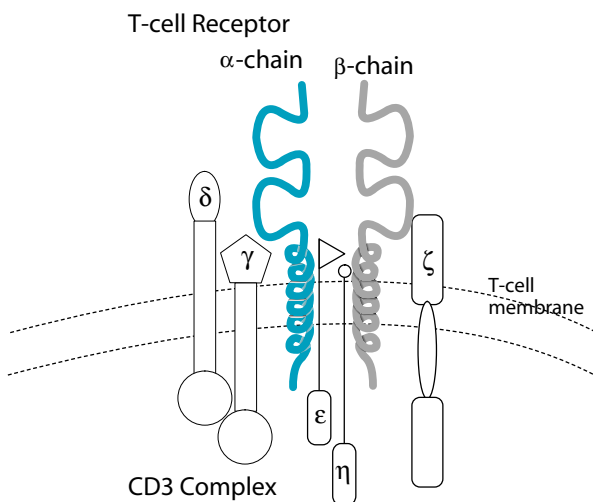


Figure 3–8 The T-cell receptor in normally functioning T cells is closely associated with CD3, a complex consisting of five subunits that are formed by five different peptides, labeled δ , γ , ϵ , η , and ζ . CD3 functions to transmit to the cell interior the signal that was received by the T-cell receptor.

**CD = cluster of differentiation.

††Epitope = that region of a molecule that determines its antigenic properties.

‡‡CD4 also acts as a receptor for the acquired immune deficiency syndrome (AIDS) virus and initiates destruction of helper T cells in immune deficiency syndromes.

CD molecules are polypeptides with a single membrane-spanning domain. They and a variety of co-receptors cooperate with the T receptor in transducing the extracellular binding event into the intracellular signals of the immune response.

Major histocompatibility complex. MHC molecules are proteins that are anchored to the extracellular surface of cells. Their function is to bind antigen for presentation to T cells. There are two classes of MHC molecules: MHC-I and MHC-II. MHC-I are present on practically all nucleated human cells. They are epitopes only for cytotoxic T cells. MHC-II molecules are normally confined to specialized cells, such as B cells, macrophages, and other antigen-presenting cells that take up antigens from the extracellular space. MHC-II are epitopes only for helper T cells. MHC-I and MHC-II differ in structure, but both present, in their three-dimensional structure, a groove to the extracellular space. These grooves can bind a variety of peptides and act as presenters of antigens.

Immune responses. Immune responses consist of defense mechanisms that are characterized by recognition of nonself, specificity, and memory. Mechanisms of **natural immunity** reside in circulating components, such as interferon or properdin, that are capable of acting directly and immediately on foreign matter. Of far greater importance are the mechanisms of **acquired immunity**. They are normally dormant but can be activated in response to specific stimuli. Passive activation (by the injection of previously activated components) is possible, but the essence of the immune system is **active acquired immunity**, derived from circulating lymphocytes. These responses mature within the organs of the immune system (bone marrow, lymph nodes, spleen) with a delay of 5 to 10 days, and they exhibit **memory**. Immune memory resides in circulating lymphocytes called **memory cells**. If they are present, exposure to the remembered antigen will quickly give a large immune response.

At the cellular level, an immune response is initiated when a sufficient number of B cells or T cells have bound an antigen. Such binding provides the **initial signal**, and it must be followed by an adequate **second signal** for a full response to occur. The second signal often is either a secreted signaling molecule of the interleukin family or some consequence of cell-to-cell contact.

Although there are some immune responses that occur by way of B cells alone, without the involvement of T cells, the vast majority of B-cell activations require help from T cells.

T-cell-independent immune responses. There are some antigens that can stimulate B cells to proliferate and differentiate into antibody-secreting **plasma cells** without the involvement of T cells. These antigens characteristically bind the B-cell receptors at several points and are capable of gener-

ating a sufficiently strong signal to activate some B cells. However, these reactions do not produce memory B cells and generally lead to the production of only low-affinity IgM antibodies rather than the full Ig complement.

T-cell-dependent immune responses. When T cells are involved, the cells to which they attach are either being assisted or destroyed, depending on whether the attaching T cell is a helper or cytotoxic cell. Cells that are generally useful for body defense mechanisms carry MHC-II, and MHC-II binds only helper T cells. Other cells carry MHC-I, and MHC-I binds cytotoxic T cells.

Helper T cells: Activated T_H stimulate macrophages to make them more effective destroyers of pathogens and help other lymphocytes to respond to antigen.

Activation of helper T cells: The usual pathway is that a microbe is ingested by an antigen-presenting cell, such as a macrophage, digested, and degraded by cytosolic lysosomes. The resulting protein fragments of 10 to 15 amino acids are then bound to MHC-II that was synthesized in the endoplasmic reticulum of the antigen-presenting cell. The MHC-II/antigen unit is transported to the surface of the antigen-presenting cell, where it can be recognized by the T receptor of a helper T cell. Such recognition is the first step leading to T_H activation.

In addition to MHC-II, antigen-presenting cells express other surface molecules, and these lead to both enabling and modulating signals. Enabling signals are required in addition to immune recognition (the first signal) if there is to be T-cell activation. Such signals include cytoskeletal rearrangement and transmembrane signal conduction. Modulating signals derive from activation of neuropeptide receptors in the T-cell membrane or from mechanisms that modulate membrane ion channels or cytosolic $[Ca^{++}]$.

Once T_H are activated, they stimulate their own proliferation by simultaneous secretion of the growth-promoting factor, IL-2, and synthesis of IL-2 receptors on the T-cell surface. Selective cloning of only those T cells that were stimulated by the antigen is ensured by the fact that only antigen-stimulated T cells up-regulate the IL-2 receptor.

Activated T_H fall into two categories, T_{H1} and T_{H2} , according to their secretion products and their primary functions: T_{H2} help activate B cells and macrophages (see Figure 3–7), and T_{H1} help activate cytotoxic T cells (see Figure 3–7).

Activation of B cells by helper T cells: Whereas macrophages are nonselective in the antigens they present because they derive them from any and all ingested pathogens, B cells present only antigens that they specifically recognize in their extracellular environment. The steps to this presentation are as follows:

1. The foreign molecule (antigen) is recognized and bound by the specific immunoglobulin receptor on the outside of the B cell.

2. The receptor/antigen combination is internalized and degraded into peptide fragments that can be bound to MHC-II proteins.
3. The MHC-II/peptide fragment unit is transported to the surface of the B cell so that it can become an antigen-presenting cell recognizable by the T receptor of a helper T cell.
4. Once a T_H has been activated, it directs at least some of its membrane-bound and secreted products toward the surface of the antigen-presenting B cell. Among these is a ligand for the CD40 transmembrane molecule on the B-cell surface. CD40 and its ligand are crucial for normal T_H -B cell interaction.

Suppressor T cells: The concept of suppressor T cells is not universally accepted. Suppression is provided by cytokines like IL-10, and these are secreted by the T_{H2} group of helper T cells.

Cytotoxic T cells: Cytotoxic T cells (T_C) act directly to kill infected cells or eliminate microorganisms, such as viruses, that proliferate inside cells where they cannot be detected by antibodies. T_C are activated either by the infected cell or by helper T cells. Once T_C are activated, they destroy the target cell by mechanisms that induce apoptosis.

Activation of cytotoxic T cells by infected cells: All proteins in a cell, including viral proteins, are continuously degraded. The fragments are actively transported into the endoplasmic reticulum, where they can be recognized and bound by MHC-I molecules that are being synthesized in the endoplasmic reticulum. They are subsequently transported to the cell surface. Peptide fragments that are derived from healthy cells and normal cellular constituents and are held on the cell surface by MHC-I are not antigenic because they are recognized as self. Nonself products on MHC-I will be recognized by T receptors on T_C , and coactivation of T receptor and CD8 on T_C will lead to the activation of T_C .

Activation of cytotoxic T cells by helper T cells: Interleukin secretion by activated helper T cells is an important signal for T-cell proliferation. The T_{H1} subgroup of T_H is distinguished from T_{H2} by secreting mostly IL-2 and γ -interferon, as opposed to other interleukins. This subgroup of T_H , when activated, activates cytotoxic T cells preferentially (see Figure 3-7).

Platelets

Platelet Structure

Platelets are small, disc-shaped granulated cells without nuclei. They normally circulate freely but can be triggered within seconds to form self-aggregates by adhering to one another.

Granules. Platelets contain many granules. Of greatest significance are (1) the electron-dense granules containing one or more of adenosine diphosphate (ADP), Ca^{++} , or serotonin, and (2) the α -granules containing, most importantly, fibrinogen, fibronectin, von Willebrand's factor, thrombospondin, and a variety of growth factors.

Interior membrane systems. In addition to the many granules, they contain a variety of organelles as well as two internal membranous systems: (1) the **open canalicular system** is a continuation of the plasma membrane and gives platelets a large surface area through which substances may be absorbed or secreted; (2) the **dense tubular system** does not communicate directly with the cell surface. It is analogous to the endoplasmic reticulum and is rich in stored Ca^{++} .

Plasma membrane. The plasma membrane is a phospholipid bilayer. It is densely covered by carbohydrates (glycocalyx) and contains receptors for several substances. Of greatest significance for normal platelet function is GP IIb-IIIa, a complex that functions as a receptor for fibrinogen, thrombospondin, and vitronectin. Many of the surface receptors belong to the **integrin** family.

Formation of Platelets

Platelets are formed as fragments of large bone marrow cells, the megakaryocytes (Figure 3–9). Proliferation and maturation of megakaryocytes are promoted by **thrombopoietin**, and each megakaryocyte produces about 1,000 platelets by pinching off a little cytoplasm and extruding it into the circula-

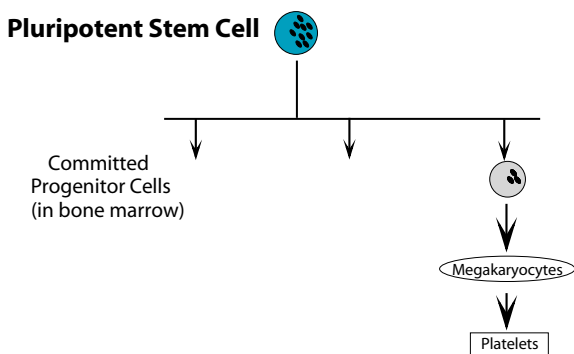


Figure 3–9 Platelets are fragments of megakaryocytes. They, in turn, derive from one of six classes of committed bone marrow progenitor cells. The other five classes lead to erythrocytes and leukocytes.

tion. Once produced, platelets have a half-life of about 4 days in blood, much of it spent circulating slowly through the red pulp of the spleen.

Function of Platelets

Platelets are necessary for blood clotting. They normally circulate freely. However, when they come in contact with stimulating agents, such as collagen or fibrogen, they aggregate, secrete a variety of factors, and attract other platelets to the region in order to form a hemostatic plug.

Whether platelets clump together depends entirely on surface forces governing interactions among platelets and between platelets and the vascular endothelium. These surface forces are ruled by products of arachidonic acid, nitric oxide (NO), and nucleotides, such as ADP and adenosine triphosphate (ATP).

Hemostasis

Blood vessel injury initiates a sequence of defensive responses that includes, at the site of injury, formation of a **platelet plug** and transformation of liquid blood into a stationary gel, called a **blood clot**.

Formation of the Platelet Plug

Circulating platelets are kept in a nonaggregated, free-flowing state because (1) adhesion receptors have a low affinity for their ligands unless they are triggered to bind them, (2) some receptors are shielded from their extracellular matrix ligands by an intact endothelial layer, and (3) endothelial cells secrete nucleotidases that prevent build-up of ADP or ATP in the region of platelets.

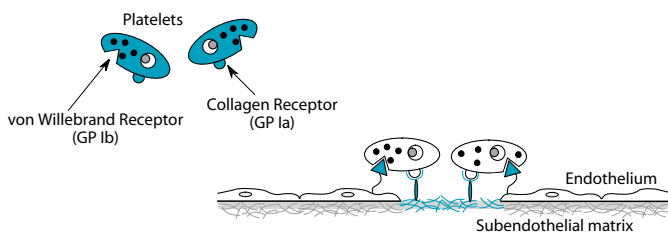
Interactions between platelets and vascular endothelium. Endothelial cells secrete prostacyclin (prostaglandin I_2 [PGI_2]) and NO, two short-ranging substances that act to suppress Ca^{++} -mediated platelet reactions. Both do this by receptor-mediated mechanisms that produce the second messenger cyclic adenosine monophosphate (cAMP) in the case of prostacyclin and cyclic guanosine monophosphate (cGMP) in the case of NO. The importance of Ca^{++} in platelet behavior is described more fully under “Thromboxane A_2 , Ca^{++} , and Aspirin®” later in this chapter.

Platelet activation and formation of the hemostatic plug.

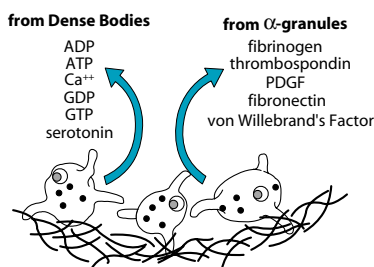
Adhesion to a foreign surface. When vascular endothelium is disrupted, platelets are exposed to nonendothelial elements, such as collagen and

laminin. This triggers the activation of the integrin family of platelet receptors and causes platelet adherence to the exposed ligands (Figure 3–10). The von Willebrand receptor complex is of special importance. Its activation leads to binding of von Willebrand's factor, which is expressed by endothelial cells. In the subsequent steps, the platelet shape changes from a smooth disc to a sphere with long, finger-like extensions that arise out of the canalicular membrane system.

A) Adhesion



B) Secretion



C) Aggregation

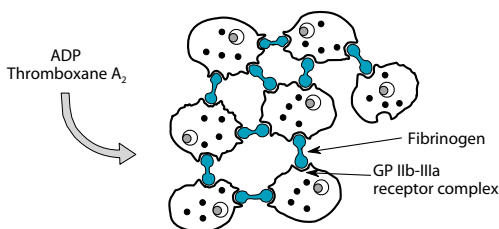


Figure 3–10 Platelets normally circulate freely in plasma. *A*, When endothelial injury exposes the subendothelial matrix, platelet receptors are activated, exposed collagen binds the GP Ia receptor, and von Willebrand's factor, synthesized by endothelial cells, binds the GP Ib receptor. *B*, As the platelets change from a discoid to a spherical shape with long extensions they are stimulated by thrombin or collagen to secrete a variety of substances from their two types of storage granules, the most important being ADP, fibrinogen, and thrombospondin. *C*, Under the influence of ADP and thromboxane A_2 , the GP IIb-IIIa receptor complex is created on the platelet surface and binds fibrinogen, thereby causing platelets to adhere to one another by way of fibrinogen links and to begin the formation of a hemostatic plug. PDGF = platelet-derived growth factor.

Simultaneously, a cascade of reactions is initiated that will cause most of the platelets accumulating at the injury site to adhere to one another (aggregation) rather than adhere to the subendothelial ligands.

Platelet aggregation and formation of hemostatic plugs. Exposure of platelets to thrombin or immobilized fibrinogen will, within seconds, convert the GP IIb-IIIa receptor complex for fibrinogen, thrombospondin, and vitronectin to a high-affinity state and also initiate up-regulation of the complex.^{§§} Simultaneously, there will be secretion of a variety of substances from the platelet α -granules and dense bodies, the most important being ADP, fibrinogen, and thrombospondin. Platelet aggregation requires fibrinogen and ADP as well as the GP IIb-IIIa receptor complex. A variety of adhesion molecules and a meshwork of fibrin that is formed locally from fibrinogen cause platelet aggregation in a hemostatic plug (see Figure 3–10).

Thromboxane A₂, Ca⁺⁺, and Aspirin®: Clinical studies have shown that acetylsalicylic acid (ASA), the active ingredient in Aspirin®, can be effective in reducing certain clotting complications of vascular diseases. Acetylsalicylic acid is a specific inhibitor of cyclooxygenase-1 (COX-1), an enzyme responsible for the formation of prostaglandins from arachidonic acid. The mechanisms of ASA actions involve interference in a positive feedback mechanism by which platelet activation causes increased platelet cytosolic [Ca⁺⁺] (Figure 3–11). Five steps are involved in that feedback mechanism:

1. Thrombin and other ligands activate their respective receptors and cause inositol trisphosphate (IP₃)[†]-mediated release of Ca⁺⁺ from the dense tubular system. Receptor activation also produces diacylglycerol (DAG).
2. Elevated [Ca⁺⁺]_i activates phospholipase A₂, an enzyme that cleaves arachidonic acid from DAG (see Chapter 1).
3. Platelets are rich in COX-1 and, therefore, metabolize the arachidonic acid to prostaglandins.
4. Platelets are also rich in thromboxane synthetase, an enzyme that converts prostaglandin H₂ to thromboxane A₂ (TXA₂).
5. Thromboxane A₂ diffuses out of the platelet, activates TXA₂ receptors on the platelet plasma membrane, activates phospholipase C, and thereby produces more IP₃ and DAG, yielding more Ca⁺⁺ release and more arachidonic acid.

^{§§}The receptor complex is also activated, though to a lesser degree, by epinephrine, thromboxane A₂, and platelet activating factor, a cytokine that is secreted by neutrophils, monocytes and platelets.

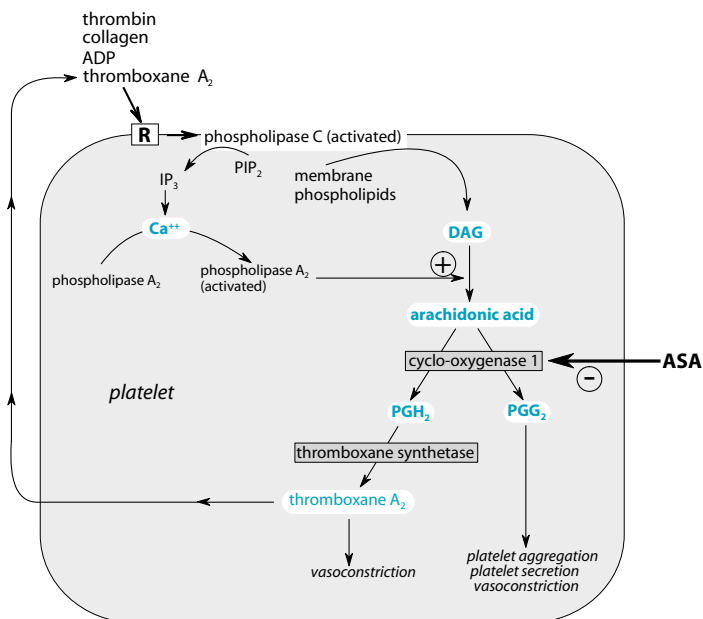


Figure 3-11 Derivatives of arachidonic acid play a crucial role in platelet adhesion to the endothelium, and the clotting process can be disrupted by interruption of arachidonic acid metabolism. Activation of phospholipase C by thrombin and other ligands elevates cytosolic [Ca⁺⁺] and diacylglycerol (DAG). Elevated [Ca⁺⁺] activates phospholipase A₂, the enzyme that cleaves arachidonic acid from DAG, and cyclooxygenase 1, an enzyme that is present in platelets in high concentration, metabolizes arachidonic acid to prostaglandins, including PGG₂ and PGH₂. Platelets also contain thromboxane synthetase, which converts PGH₂ to thromboxane A₂ (TXA₂). TXA₂ diffuses out of the platelet, activates membrane receptors, and establishes a positive feedback mechanism for the production of more prostaglandins. Agents like acetylsalicylic acid (ASA, the active ingredient in Aspirin®) and indomethacin inhibit platelet aggregation by inhibiting cyclooxygenase 1.

The five steps described above can be significant when platelets are quiescent or only mildly stimulated. The COX-1 antagonism of ASA exerts its clotting inhibition at step 3.

Clotting of Blood

Blood vessel injury leads not only to the formation of a platelet plug but also, within seconds and in a circumscribed area, to the transformation of fluid, flowing blood into a gel. This transformation is the result of a cascade of activations of circulating **procoagulants** (clotting factors) in excess of influences from **anticoagulants**.

On the basis of historical observations, the initiation of the clotting cascade is described in terms of an **intrinsic pathway** and an **extrinsic pathway** (Figure 3-12). The intrinsic pathway was so named when it was

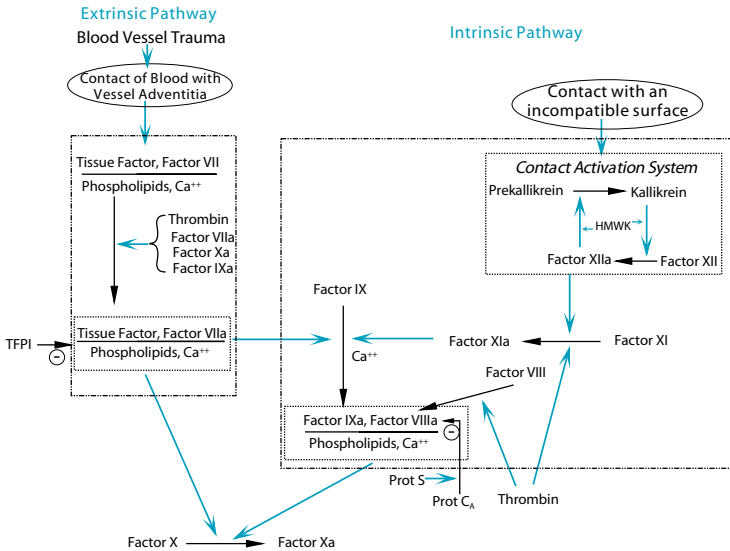


Figure 3-12 Generation of activated factor X by way of the intrinsic or extrinsic pathways. The extrinsic pathway requires contact between blood and tissue factor, which is found in blood vessel adventitia and is accessible to blood after vascular injury. The intrinsic pathway is triggered when blood contacts a negatively charged surface, such as glass, or a comparable in vivo activating surface. Upon such contact, prekallikrein and factor XII of the contact activation system reciprocally activate each other in the presence of high-molecular-weight kininogen (HMWK) as a cofactor. Two essential enzymes in the cascade, VIII and IXa, are themselves physiologically inert but become catalytically effective when they are bound to cofactors. As shown in the illustration, these cofactors are tissue factor and factor VIIIa, respectively. In addition, Ca⁺⁺-dependent association with a phospholipid surface is required. Anticoagulant influences derive from tissue factor pathway inhibitor (TFPI) and activated protein C (Prot C_a). Protein S (Prot S) is a cofactor in the inhibitory actions of Prot C_a. Colored arrows indicate promoting or enzymatic activity.

observed that blood clotted when it was placed into a container and nothing else was added. The observation was taken to mean that all factors required for clotting were intrinsically present in blood. The extrinsic path was so named when it was observed that blood clotted more quickly when it was exposed to damaged tissue. The observation was interpreted to mean that external factors could be added to the blood to hasten the clotting process.

Both the intrinsic and extrinsic pathways lead to activated factor X, which is the active principle of **prothrombinase**, also called the **prothrombin activation complex**. Once initiation has produced activated factor X, the clotting cascade follows a common path to the formation of cross-linked fibrin threads (Figure 3-13).

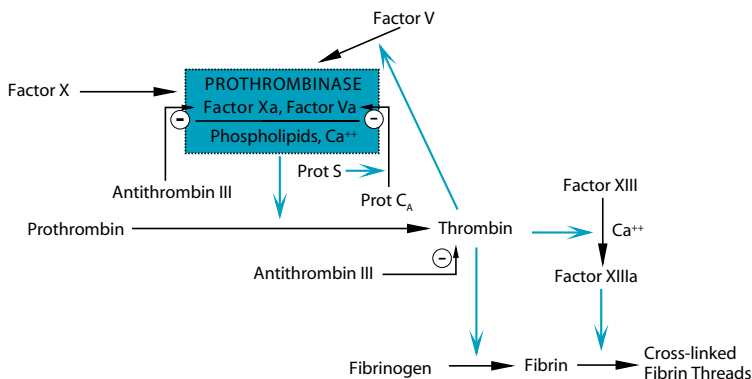


Figure 3-13 The common pathway by which a fibrin clot is formed by the action of the prothrombinase complex, which is Factor Xa and others. Antithrombin III complexes most importantly with activated factor X and activated factor V and blocks their biologic activity. This action is enhanced by heparin. Prothrombinase can also be inhibited by activated protein C (Prot C_A). Colored arrows indicate promoting or enzymatic activity.

Procoagulant factors. Most clotting factors are proenzymes whose active forms are created sequentially by proteolytic cleavage. These proenzymes are synthesized in the liver and are also found in platelets. Some clotting factors, such as phospholipids, Ca⁺⁺, or factor V, have no enzymatic activity but act as cofactors. Four clotting factors can be synthesized only if vitamin K is present. These are prothrombin and factors VII, IX, and X.

Generation of prothrombinase. Prothrombinase is a complex whose active principle is activated factor X. Its formation after vascular injury normally follows the extrinsic pathway (see Figure 3-12).

The extrinsic pathway is initiated by blood vessel trauma and leads to prothrombinase after the activation of only one factor, factor VII. It requires **tissue factor**, which is a transmembrane glycoprotein found, in tight association with phospholipid, in certain cells of blood vessel adventitia, though not in cells to which circulating blood is normally exposed. Tissue factor comes in contact with blood after vascular injury. Its extracellular domain is a high-affinity receptor for factor VII, and after blood vessel injury, they both form a complex if Ca⁺⁺ is present. The complex of tissue factor–factor VIIa is, in isolation, a weak activator of either of its biologic substrates, factor IX and factor X. However, activation of small amounts of factor X will initiate a positive feedback mechanism by which Xa preferentially activates factor VII that is complexed to tissue factor. The extrinsic pathway is inhibited by tissue factor pathway inhibitor (TFPI).

The intrinsic pathway is initiated when blood contacts negatively charged surfaces, such as glass and others. It can also be activated in vivo, but there in

the intrinsic path, the initiating surfaces have not yet been clearly identified. The first step is the contact activation system by which prekallikrein and factor XII (Hageman factor) reciprocally activate each other in the presence of high-molecular-weight kininogen (HMWK) as a cofactor.

Sufficient activation of factor XII then rapidly activates factor XI. This step is further accelerated in the presence of thrombin (see Figure 3–12). Factor XIa activates factor IX, provided that Ca^{++} ions are present. The resulting factor IXa, which is bound to phospholipid, forms a complex with factor VIIIa and Ca^{++} , and this complex participates in subsequent clotting steps as an activator of factor X. The relatively lesser importance of the intrinsic pathway to normal *in vivo* clotting is shown by the observation that patients with a deficiency of factor XI show excessive bleeding after surgical interventions, but only some of them will show abnormal bleeding after tissue trauma. The intrinsic pathway is inhibited by antithrombin III and activated protein C. Antithrombin III operates by inhibition of factor IXa. Activated protein C inhibits the cofactor activity of factor VIIIa.

Conversion of prothrombin to thrombin. Prothrombin is a circulating protein. Its synthesis (in the liver) requires vitamin K and can be inhibited by substances that compete with vitamin K (such as warfarin).

Prothrombinase is the only known physiologic activator of prothrombin (see Figure 3–13). Its enzymatically active component is factor Xa. The prothrombinase complex is formed by Ca^{++} -dependent assembly of factors Xa and Va on a phospholipid surface, such as the plasma membrane of platelets. It acts by cleaving prothrombin and yields thrombin. Thrombin lacks the domain that is required for phospholipid binding and, therefore, leaves the phospholipid surface, enters the blood, and performs its subsequent actions from there. In the coagulation cascade, its actions include (1) promotion of the activation of factors V, VIII, and XI; (2) clot formation by promoting formation of fibrin from fibrinogen (see Figure 3–13); and (3) activation of factor XIII (see Figure 3–13).

Prothrombin cleavage can be inhibited by antithrombin III, and this inhibition is promoted by the anticoagulant heparin.

Conversion of fibrinogen to fibrin. The last step in clot formation is the conversion of the circulating protein fibrinogen to fibrin monomers that are subsequently polymerized and cross-linked to form the visible clot. The enzymatic activity of thrombin produces fibrin monomer (see Figure 3–13) by cleavage of amino terminals from fibrinogen. Polymerization and stabilization of the fibrin monomer are promoted by activated factor XIII, and its activation is, in turn, promoted by thrombin and requires Ca^{++} .

Anticoagulant factors. Circulating plasma contains not only procoagulant factors but also a variety of protease inhibitors that contribute to the

regulation of blood coagulation. The most important of these are **antithrombin III**, **tissue factor pathway inhibitor**, and the **protein C** system.

Antithrombin III. This neutralizes almost all activated procoagulation factors but is most active in inhibiting thrombin and activated factor X (see Figure 3–13). The mechanism of inactivation involves formation of one-to-one complexes between antithrombin III and the target procoagulation factors.

Tissue factor pathway inhibitor (TFPI). This inhibitor has many different names, including lipoprotein-associated inhibitor and extrinsic pathway inhibitor. It circulates in plasma in association with lipoproteins. About 10% of total stores is carried by platelets and is released from them following stimulation by thrombin. Its inhibitory action results from specific interaction with the complex that consists of tissue factor and factor VIIa (see Figure 3–12).

Protein C. Endothelial cells are the loci for the constitutive synthesis of thrombomodulin, a glycoprotein that is localized to the luminal side of the vascular endothelium. It serves as an endothelial receptor for thrombin. When thrombin is complexed with thrombomodulin, it no longer possesses procoagulation activity but becomes capable of activating protein C, a naturally occurring anticoagulant. Activated protein C then inactivates both factor Va and VIIIa. This inhibitory function of protein C is enhanced by protein S, an endothelial surface protein.

Regulation of coagulation. Several factors ensure that coagulation normally occurs only at sites of injury and only at times of injury.

Localization to sites of injury results from the requirement for suitable membrane surfaces for the assembly of coagulation complexes. Such surfaces are normally found only near injury sites or when there has been damage to the vascular endothelium.

Restriction of coagulation to times of injury is the result of balanced pro- and anticoagulant factors when there has not been an injury. Antithrombin III, protein C, and the anticoagulant factors secreted by endothelial cells (thrombomodulin and glycosaminoglycans) are the most significant coagulation inhibitors.

The role of the vascular endothelium. The endothelium has both procoagulant and anticoagulant properties, and both play a significant role in maintaining blood in its normal fluid state (Table 3–5).

The procoagulant actions of the vascular endothelium include three features: (1) the expression of **tissue factor** as a surface protein when it is stimulated by (a) certain toxins, (b) viruses such as herpes simplex, (c) mechanical shear, or (d) factors such as thrombin, interferon, interleukin-1, and others. Expression of tissue factor can initiate the extrinsic clotting path; (2)

Table 3–5

Role of the Vascular Endothelium in Hemostasis

Procoagulants secreted	Tissue factor von Willebrand's factor Factor V
Anticoagulants secreted	Thrombomodulin Prostacyclin (PGI ₂) Nitric oxide (NO) Competitive inhibitors of clotting factors

synthesis of von Willebrand's factor^{|||} and factor V; and (3) binding of factor X, which permits assembly of the prothrombinase complex.

The anticoagulant actions of the vascular endothelium include four aspects: (1) the provision of heparan sulfates at the luminal surface. Anticoagulant actions of antithrombin III are enhanced dramatically when it binds to them; (2) the constitutive expression of the thrombin receptor, thrombomodulin. Its activation by thrombin binding, in turn, activates the anticoagulant actions of protein C when protein S, also secreted by endothelial cells, is present; (3) the secretion of prostacyclin (PGI₂) and nitric oxide (NO). They inhibit platelet aggregation by receptor-mediated mechanisms that act to decrease cytosolic [Ca⁺⁺] in platelets; and (4) the secretion of several binding proteins that competitively occupy binding sites required for activation of clotting factors.

Anticoagulation Therapy

Ca⁺⁺ Chelators

Clotting can be prevented if Ca⁺⁺ is removed from the blood by substances, such as citrates and oxalates, that form insoluble Ca⁺⁺ salts or by chelating agents that bind Ca⁺⁺.

Heparin

Heparin is a naturally occurring proteoglycan that is synthesized by mast cells and hepatocytes. It binds to antithrombin III and converts it from a slow to a rapid inhibitor of thrombin.

^{|||}von Willebrand's factor is an important "bridge" that allows platelets to adhere to collagen after vascular injury. It also serves as the carrier for factor VIII.

Inhibitors of Vitamin K

Vitamin K is required for the synthesis of several clotting factors, including prothrombin. They all contain 10 to 12 residues of the unique amino acid, γ -carboxyglutamic acid, in their NH_2 terminals, and their presence permits these coagulation proteins to bind to negatively charged phospholipids, which is an essential step in the coagulation process. Vitamin K is essential for the formation of γ -carboxyglutamic acid by carboxylation of glutamate. Coumadin derivatives, such as dicumarol and warfarin, inhibit coagulation by competing with vitamin K for reactive sites in the processes by which γ -carboxyglutamic acid is formed.

Hirudin

Hirudin is a potent inhibitor of thrombin. It is the active ingredient in the saliva of medicinal leeches.

Fibrinolysis

Once a clot has been formed, it can (1) become invaded by fibroblasts and be reorganized by them into fibrous tissue or (2) be gradually resorbed by the processes of **fibrinolysis**. The proteolytic action of **plasmin** is essential for fibrinolysis because it lyses fibrin and fibrinogen. Plasmin is formed from plasminogen, a freely circulating, inactive proenzyme. Its conversion is accomplished by **plasminogen activators**. Two such activators are released from cells: tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Tissue-type plasminogen activator is secreted from vascular endothelial cells in its active form. Urokinase-type plasminogen activator is also secreted from vascular endothelial cells but as an inactive precursor from which the active enzyme urokinase is formed by either kallikrein or factor XIIa, both of the contact activation system (see Figure 3-12).

Inhibition of Fibrinolysis

The fibrinolytic system is controlled by several inhibitors, including plasminogen activator inhibitor-type 1 (PAI-1) and type 2 (PAI-2),^{##} α_2 -antiplasmin, and α_2 -macroglobulin.

Fibrinolytic Therapy

Streptokinase (a bacterial enzyme), urokinase (produced from kidney cells), and human t-PA (produced by recombinant DNA techniques) are among the agents frequently used in the treatment of myocardial infarction.

^{##}Both PAI-1 and PAI-2 are secreted by vascular endothelial cells. Thus, the endothelium plays a role in fibrinolysis as well as in processes of coagulation and anticoagulation.

Autonomic Nervous System

NERVOUS REGULATION OF PHYSIOLOGIC FUNCTIONS

The central nervous system (CNS) performs three types of functions: (1) mental processes, such as thought or emotion; (2) actions on the external environment, such as locomotion, or other actions requiring skeletal muscle work; and (3) actions on the internal environment, such as cardiac slowing or gastrointestinal (GI) peristalsis.

Mental processes are required as an antecedent to all actions on the external environment, and the success of such actions is constantly being checked against a volitional goal. However, such references to higher processes are not generally required for maintenance of the internal environment or for involuntary reactions to external stimuli. The portion of the nervous system that governs these latter responses acts with considerable autonomy and is, therefore, named the **autonomic nervous system**. It should be noted, though, that processes at the highest cortical level provide the cultural and ethical boundaries within which autonomic responses are permitted to express themselves.

The interior milieu is maintained in a steady state by the nuclei and nerves of the autonomic nervous system. This system integrates and coordinates all reflex mechanisms that maintain a living person in a steady state with the environment. It used to be thought of as that part of the human nervous system by which efferent information is conveyed to tissues other than skeletal muscle. It is now more correctly described as a portion of the nervous system that controls cardiac muscle, smooth muscle, and certain secretory organs and includes sensing elements, central nervous nuclei, and efferent paths.

PATTERNS OF AUTONOMIC CONTROL

The functional unit of the autonomic nervous system, the **reflex arc**, is focused on a parameter that is to be controlled, and it functions to correct

deviations of the parameter from a **set point**. This involves a sequence of three steps:

1. The status of the parameter is sensed in the periphery and is transformed and transmitted as action potential patterns along an afferent path to the CNS.
2. A central nervous reflex center determines whether there is a difference between the present status of the parameter and its desirable state under the present circumstances (the set point). Any deviation is named an **error signal**.
3. A pattern of action potentials is transmitted along efferent paths to peripheral effector mechanisms. They act to change the status of the parameter in such a direction that the magnitude of the error signal is reduced.

Steps 1 to 3 are reiterated until the error signal has been reduced to zero. The typical pattern of activity described above requires six functional components: a sensor, an afferent path, a reflex center, a set point, an efferent path, and an effector mechanism (Figure 4–1).

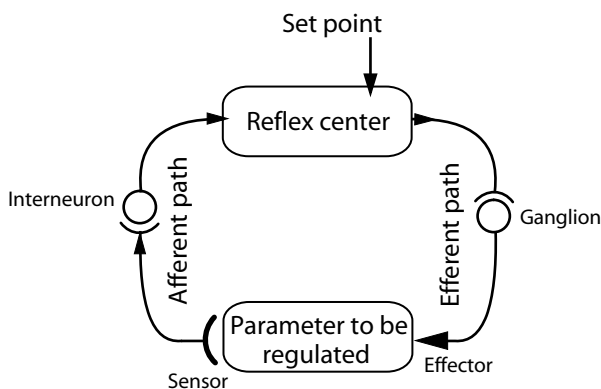


Figure 4–1 Components of a typical autonomic reflex arc, operating to maintain one physiologic parameter within its normal limits.

COMPONENTS OF AUTONOMIC NERVOUS FUNCTION

Central Autonomic Nervous System and Reflex Centers

Patients who have suffered damage to the upper spinal cord are often incapable of regulating many autonomic variables, especially under extreme conditions. This demonstrates the importance of CNS participation even though spinal segmental reflex loops are capable of maintaining a steady state in controlled environments and in response to mild stimuli. Central

nervous system mechanisms function to initiate, coordinate, and anticipate autonomic responses. They also provide set points and adapt them to circumstances when that is warranted.

Hierarchy of Central Autonomic Control

Limbic cortex and amygdala. These very high centers function both as a brake on automatic responses that may accompany emotional states, such as fear, rage, embarrassment, or sexual desire, and as direct activators of the system. The latter is seen prominently in two circumstances: (1) in the responses of blood pressure, sweat glands, or genitalia to dreams and fantasies and (2) in the volitional control of resting autonomic functions during states of deep meditation. In this state, metabolic rate, heart rate, arterial blood pressure, and distribution of blood flow can all be modified by application of conscious mental effort.

Autonomic responses that are coordinated at this high CNS level are physically and emotionally complete whole-body responses in that they include the subjective feelings of fear, joy, pleasure, and pain.

Hypothalamus. The hypothalamus provides two basic functions relative to the autonomic nervous system: (1) it is an interface between the autonomic nervous system and higher nervous centers, on the one hand, and the endocrine system, on the other; (2) it coordinates whole-body autonomic responses to behavioral drives (such as fear) or to input from autonomic and environmental sensors. This coordination involves the following:

- Integration of responses to hunger, thirst, and sexual drives
- Integration of thermoregulation
- Integration of defence reactions
- Control of several endocrine secretions, including adrenal medulla, posterior pituitary, and anterior pituitary

Responses that are coordinated at the level of the hypothalamus, but not higher, are physically complete and involve the whole body.

Brainstem. The brainstem consists of three anatomically distinct regions: **midbrain**, **pons**, and **medulla** (Figure 4–2). They are linked at the core by the **reticular formation**.

Midbrain. The midbrain acts as a conduit for ascending and descending fibers. It also harbors nuclei that are associated with complex neurologic patterns that are not normally controlled by autonomic activity but do have autonomic correlates.

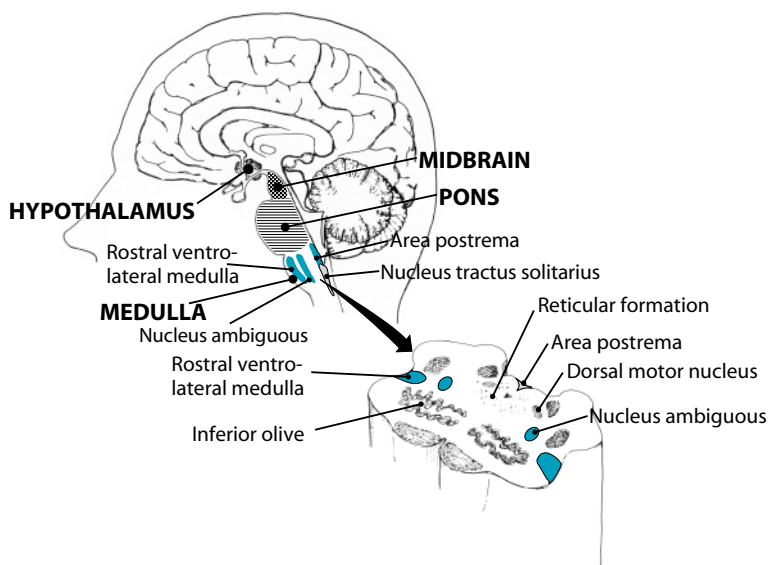


Figure 4-2 Functional anatomy of important autonomic structures. Although structures in the section of the medulla are labeled only once, they each occur on the left as well as on the right side and in the same position. The left and right inferior olives are dominant structures in the medulla. They are intermediary stations between the somatosensory cortex and the cerebellum.

Pons. The pons contains nuclei for several cranial nerves as well as reflex centers for cardiovascular and respiratory control.

Medulla. This region contains many nuclei, among them the nucleus ambiguus and dorsal motor nucleus (see Figure 4-2), which are the origins of cranial nerves IX and X. It also contains the rostral ventrolateral medulla, which is a major originating site for sympathetic outflow to the spinal cord.

The pons/medulla region is an autonomous center for reflex responses to afferent signals from respiratory, cardiovascular, or GI receptors. The physiologic responses to the activation of neurons in these midbrain areas are physically complete and system specific.

Reticular formation. This is a collection of both ascending and descending fibers, located near the dorsal side (see Figure 4-2). Their major functions are (1) determining the state of consciousness and (2) balancing autonomic and somatic activities with the level of consciousness.

Spinal cord. The spinal cord is a collection of nerve cell bodies and axons; it is encased within the vertebral column and extends to the level of the

first lumbar vertebra (L1), where it terminates in the **cauda equina**. Within each cord segment, two distinct regions can be recognized on the basis of coloring: **gray matter** and **white matter**.

Gray matter. Gray matter (Figure 4–3) consists mostly of neuronal cell bodies and is subdivided on each side into three regions: (1) the **dorsal horn** is the region where sensory afferents synapse with spinal neurons, (2) the **ventral horn** contains groupings of motor neurons that supply skeletal muscle, and (3) the **intermediate zone** lies between the other two and contains local afferent or efferent interneuron linkages as well as the cell bodies of autonomic preganglionic nerves.

White matter. The white matter of the spinal column is the nervous tissue that surrounds the gray matter. It is composed chiefly of ascending and descending axons, arranged into fascicles and columns: (1) the **dorsal column** contains principally ascending fibers, (2) the **ventral column** contains mainly descending fibers, and (3) the **lateral column** contains a mixture of ascending and descending fibers.

Peripheral Autonomic Nervous System

Spinal Nerves

At each spinal segment, two spinal nerves connect with the cord, one on the left and the other on the right, and each of these two nerves branches into a dorsal root and a ventral root (Figure 4–4). The dorsal root contains

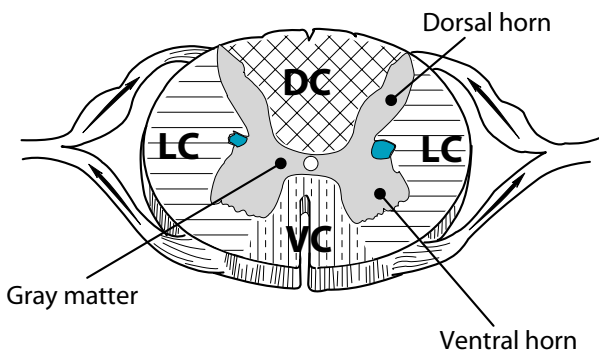


Figure 4–3 Structure of the spinal cord. The intermediolateral gray matter is shown in color. This is the region in which sympathetic preganglionic neurons are located. DC = dorsal column; LC = lateral column; VC = ventral column.

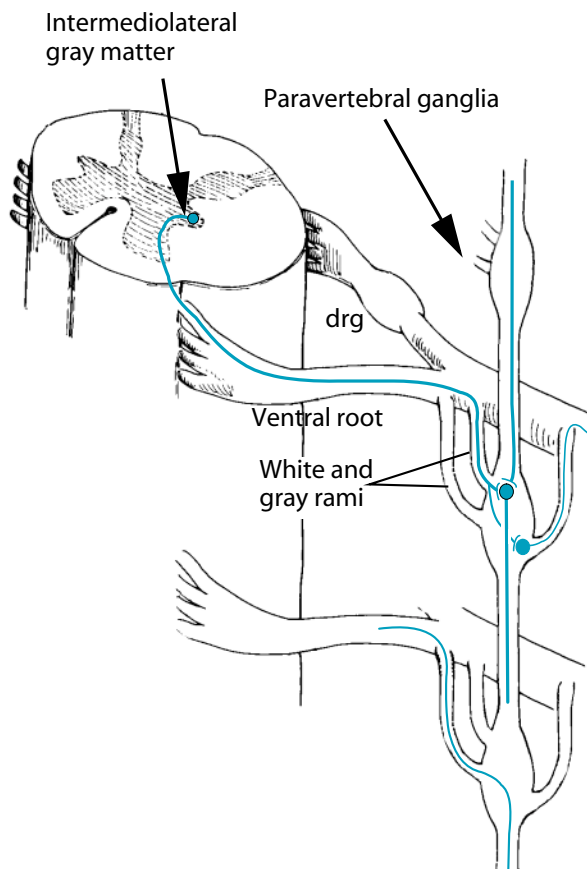


Figure 4-4 Afferent nerves enter the spinal cord through a dorsal root. Efferent nerve cells lie in the intermediolateral column and leave the cord by way of ventral roots and then synapse in a paravertebral ganglion (*upper portion*) or traverse the ganglion without synapsing there (*lower portion*), but synapsing in a distant visceral ganglion. drg = dorsal root ganglion.

afferents from a specific region of the body, and the ventral root contains somatic and sympathetic preganglionic efferent nerves for a specific region of the body.

Sensory structures and afferent fibers. The autonomic nervous system is mostly concerned with regulation of body temperature, blood pressure, blood gases, blood flow distribution, local distentions, and sphincter diameters. Accordingly, its major sensors are classified as thermosensors, mechanosensors (or stretch-sensors), and chemosensors because those are the modalities to which each class shows the greatest response.

Thermosensors are nerve endings, located in the hypothalamus, skin, and mucous membranes, that display pronounced discharge sensitivity to temperature changes. Mechanosensors respond to changes in physical deformation of their environment, such as vibration, acceleration, or stretch. Receptors relevant to the function of the autonomic nervous system are found in skin, skeletal muscle, GI tract, blood vessels, cardiac chambers, and lung interstitium. Chemosensors are capable of converting into action potential trains the changes in concentration of chemicals like hydrogen ions (H^+), oxygen (O_2), serotonin, and others.

At the simplest level, sensors generate action potentials in proportion to the strength of a specific stimulus, and their nerves conduct the potentials toward the CNS. Sometimes, the relationship between the activating stimulus and the antecedent physiologic change is direct; in other instances, physiologic variables must first be transformed.

Structure of afferent fibers. Almost all organs that receive efferent autonomic innervation also have afferent fibers. Afferent fiber cell bodies lie in a dorsal root ganglion or, in the case of some cardiopulmonary afferents, in cranial ganglia, such as the nodose ganglion. They are small, unmyelinated fibers that generally run in mixed peripheral nerves and can be distinguished from other small fibers by several features. They (1) have a darker appearance, which arises from a particular distribution of Nissl substance and neurofilaments; (2) are sensitive to the neurotoxin capsaicin; and (3) predominantly terminate in laminae I and V in the dorsal horn of the spinal cord, whereas somatic afferents terminate in lamina II (Figure 4–5).

Functions of sensory structures and afferent fibers. (1) *Transformation of physical or biologic phenomena:* Transformation involves conversion of a physical or biologic phenomenon into a form that is recognizable by a receptor. For example, respiratory chemoreceptors are not directly sensitive to carbon dioxide (CO_2) but are sensitive to H^+ . Transformation in this case involves conversion of changes in $[CO_2]$ to proportional changes in $[H^+]$.

(2) *Transduction of physical or biologic phenomena:* When a stimulus impinges on a sensory nerve ending, it sets up a receptor current by opening ion channels in a local region of the receptor membrane. The sum total of individual channel currents gives rise to a graded change in membrane potential, called the **receptor potential** or **generator potential**. Receptor potential amplitude is directly related to stimulus intensity, though not necessarily in a linear way. If the amplitude of the receptor potential is sufficient to trigger an action potential, further transmission of sensory information is by **action potentials**, and information about stimulus strength is encoded in the frequency of these action potentials, also in some directly proportional relationship. However, most receptors show **adaptation**, whereby a contin-

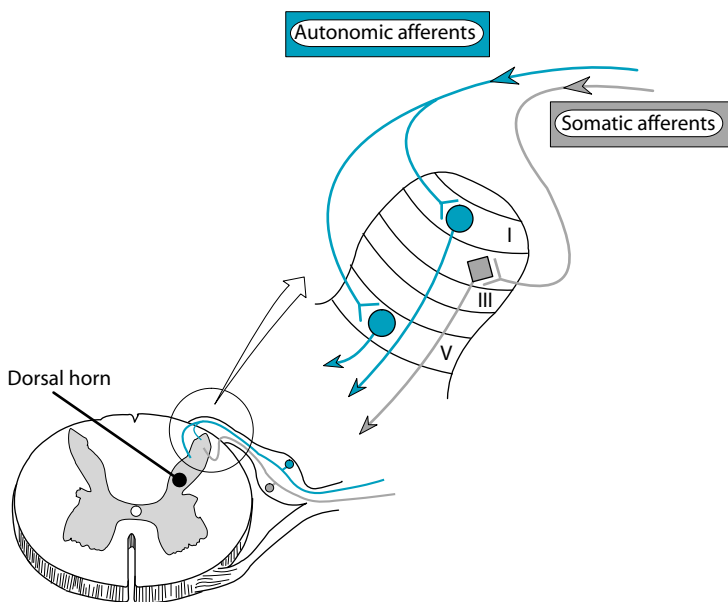


Figure 4-5 The dorsal horn is organized into laminae. Afferent autonomic fibers terminate in laminae I and V whereas afferent somatic fibers terminate in lamina II.

uously applied stimulus elicits, over a time period that ranges from milliseconds in some receptors to many minutes in others, a progressively diminishing response (Figure 4-6).

Primary sensory axons usually synapse with interneurons before they reach central nervous nuclei, where the receptor information is decoded in a postsynaptic cell.

Complex functions of sensory structures and afferent fibers. Sensors and their afferents are not simply generators of stimulus-specific action potentials that are conveyed to higher centers for processing. They may carry chemically coded messages, perform dual afferent and efferent functions, and control their own plasticity.

Afferent nerves contain neuropeptides, such as calcitonin gene-related peptide as well, but not as vital as above, and substance P, and the relative proportion of each type of afferent differs among organs. The significance of these peptides or tissue-to-tissue differences in the relative abundance of afferent fibers containing them is not yet clear.

Many fibers whose anatomic features would designate them as afferents also show efferent function in that they respond to stimulation with local release of chemicals that lead to circumscribed responses, such as localized

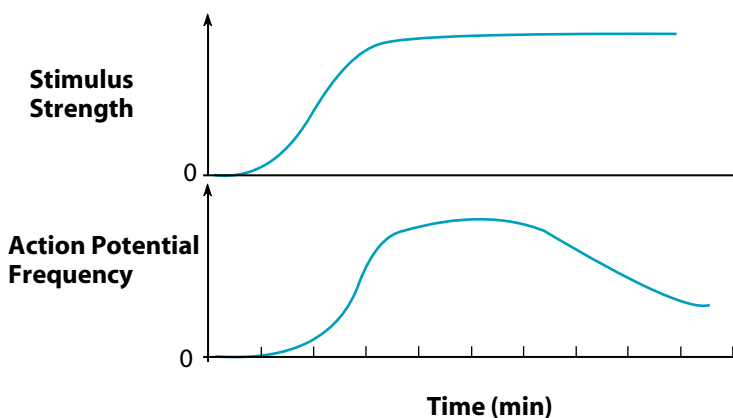


Figure 4-6 Example of adaptation in a sensory unit. The frequency of action potentials in the nerve decreases with time even though the stimulus strength is maintained. The time required for adaptation ranges from a few milliseconds to a few minutes.

edema (neurogenic inflammation). Although such responses sometimes involve stimulation of adjacent mast cells by antidromic conduction, direct reactions of the stimulated nerve do occur.

Intense stimulation of afferents induces postsynaptic changes in spinal cord cells that include expression of cellular proto-oncogenes like *c-fos* and *c-jun*. The products of these genes include transcription factors that could have long-term effects on their host cells.

Efferent fibers. The autonomic nervous system differs from the somatic nervous system in anatomy and tonic activity (Table 4-1). Autonomic, but not somatic, efferents have a ganglion interposed between the central nervous* cell body and the target cell. Autonomic, but not somatic, nerves have a baseline neural activity that can be increased or decreased as required.

Preganglionic fibers. The cell bodies of autonomic efferent nerves are located in the brainstem or the spinal cord. Their location and the location of the associated ganglion form two of the criteria by which the system is classified into sympathetic or parasympathetic divisions.

Thoracolumbar preganglionic fibers: The cell bodies of sympathetic preganglionic neurons are in the intermediolateral gray matter of the spinal

*The spinal cord is considered to be part of the CNS.

Table 4–1

Differences between Autonomic and Somatic Efferent Nerves

System	Structure	Baseline Activity	Function
Autonomic	Ganglion interposed between cell body and peripheral target cell	Tonic activity is present and is increased or decreased as needed	Controls smooth muscle and secretory units
Somatic	Motor neurons run directly from CNS to peripheral target cell	None	Controls muscles of locomotion

cord (see Figure 4–4) at segments T1 to L2 of the thoracolumbar cord. Their axons emerge at the segment level of the cell body as a ventral root. Most enter the paravertebral chain of ganglia and synapse there with one or more postganglionic neurons (see Figure 4–4); some only pass through the paravertebral chain without synapsing but synapse with postganglionic fibers in one of the visceral ganglia.

Cranial and sacral nerves: Parasympathetic preganglionic axons are long and generally synapse on postganglionic cells in or near the target organ.[†] Their cell bodies are located in the brainstem or S2, S3, and S4 segments of the sacral spinal cord.

The parasympathetic nerves of most widespread significance for control of body function are the vagus and the pelvic nerve. (1) Vagus: Efferent vagal fibers innervate the heart, lungs, and GI tract. Their cell bodies are clustered in specific areas of the **dorsal motor nucleus** (for abdominal viscera, heart, and lungs) or the **nucleus ambiguus** (for palate, larynx, pharynx, esophagus, and heart). (2) Pelvic nerve: The parasympathetic preganglionic cell bodies in the sacral spinal cord are not arranged in a distinct column, comparable with the intermediolateral column that supplies the preganglionic sympathetic fibers. Efferents in the pelvic nerve control the lower GI and urinary tracts, the urinary bladder, and aspects of sexual function.

Ganglia. All autonomic efferent paths have a ganglion interposed between the spinal cord and the effector cell (Figure 4–7). They are sites at which preganglionic fibers synapse with postganglionic fibers, and they offer the oppor-

[†]The nerves supplying the salivary glands are an exception.

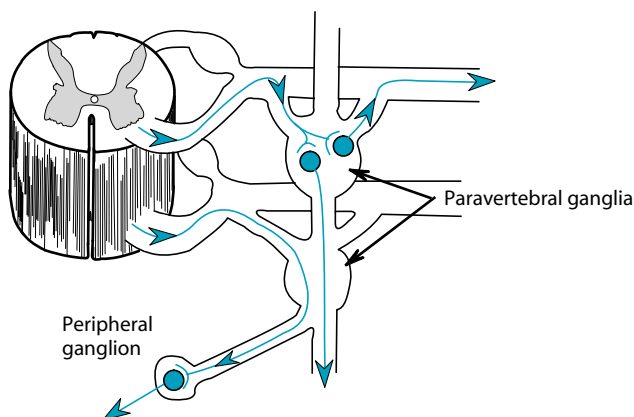


Figure 4-7 Pre- and postganglionic autonomic fibers synapse either in a paravertebral ganglion or a peripheral ganglion.

tunity for modulation of efferent signals either by convergence and divergence[‡] or by signals in other preganglionic fibers synapsing in the same ganglion.

Sympathetic ganglia: Sympathetic ganglia are found (1) in the sympathetic trunks alongside the vertebral column (see Figure 4-7) and (2) in the viscera in structures such as the celiac, superior, and inferior mesenteric ganglion. Preganglionic fibers that synapse in a visceral ganglion pass through the ganglia of the sympathetic trunk without synapsing there.

Parasympathetic ganglia: The fibers of the parasympathetic division, with the exception of the eye, the secretory glands of the head region, and, possibly, the intrinsic GI plexus, are not collected in distinct peripheral ganglia but are distributed in the walls of the effector organs and synapse there with individual **ganglion cells**.

Postganglionic fibers. Postganglionic fibers project directly to the effector organ target cells where they form a synapse. In sympathetic postganglionic nerves, this synapse takes the form of several varicosities, each forming a site of neurotransmitter synthesis and release to postsynaptic receptors on the target cell. In parasympathetic neurons, the synapse is in the form of a terminal bouton.

[‡]Convergence: The number of preganglionic fibers is larger than the number of postganglionic fibers. Divergence: The number of postganglionic fibers is larger than the number of preganglionic fibers.

Synaptic Processes

Synapses are specialized points of communication where a presynaptic structure is closely apposed to a postsynaptic structure across a narrow synaptic cleft.

Synapses in the autonomic nervous system are chemical. Their presynaptic side, but not their postsynaptic side, contains all the elements that are required for the synthesis and packaging of **neurotransmitters** into cytosolic vesicles (on average 40 to 50 nm in diameter) for subsequent release on stimulation.

Neurotransmitters

The major transmitters in the peripheral portions of the autonomic nervous system and at low frequencies of nerve activity are acetylcholine and the biogenic amine norepinephrine. However, at higher rates of stimulation or in specific fibers, either acetylcholine nor norepinephrine can be co-released with a variety of other transmitters. These include ATP, amino acids, other biogenic amines, or neuropeptides.

Release of neurotransmitters. Action potentials in a nerve lead to release of neurotransmitters from storage vesicles in the nerve terminal. The coupling between the two phenomena is action potential-mediated Ca^{++} entry through two populations of presynaptic Ca^{++} channels: (1) Ca^{++} channels in the region away from the synapse and (2) Ca^{++} channels at the active zones within the synapse.

The role of extrasynaptic Ca^{++} channels. These voltage-gated channels are activated first because they are closer to the source of the action potential, and although they produce elevation of cytosolic $[\text{Ca}^{++}]$, it is often less than the changes that will be produced a little later in the immediate region of Ca^{++} channels at the active zones. Extrasynaptic Ca^{++} entry has two consequences: (1) vesicles are released from a pool that is corralled by the cytoskeleton because the vesicle protein, synapsin I, which connects the vesicle to the cytoskeleton, breaks the hold when it is phosphorylated by Ca^{++} -calmodulin-dependent protein kinase II; (2) vesicles become positioned at particular sites, near voltage-gated N-type Ca^{++} channels on the presynaptic membrane. This process is called **docking**, and it crucially involves the proteins, **synaptobrevin** (also called VAMP[§]) in the vesicle membrane and both **syntaxin** and **SNAP-25**^{||} in the presynaptic membrane (Figure 4–8).

[§]VAMP = vesicle-associated membrane protein. At least two isoforms exist.

^{||}SNAP-25 = synaptosomal-associated protein, M_r 25,000.

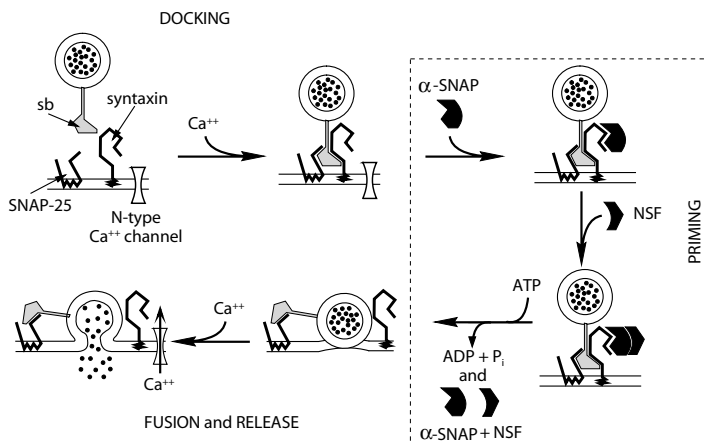


Figure 4-8 Steps (in a clockwise direction, starting top left) by which a nerve action potential is coupled to vesicle fusion and neurotransmitter release from the presynaptic terminal. The process begins after an action potential has opened voltage-gated Ca^{++} channels and is defined by four steps: vesicle docking, vesicle priming, membrane fusion, and neurotransmitter release.

Vesicle docking occurs when the vesicle protein synaptobrevin (sb) is captured by the plasma membrane proteins, SNAP-25, and syntaxin. **Vesicle priming** involves three steps: (1) binding of the cytosolic protein α -SNAP to the membrane protein syntaxin; (2) binding of the cytosolic protein NSF to the α -SNAP-syntaxin complex; (3) hydrolysis of ATP with related dissociation of the α -SNAP-syntaxin complex. During **vesicle fusion**, the membrane of the vesicle melds with the presynaptic plasma membrane of the terminal nerve, and the energy released by ATP hydrolysis is used to increase the distance between SNAP-25 and syntaxin so as to accommodate the vesicle in the presynaptic membrane. **Neurotransmitter release** occurs when Ca^{++} enters through the N-type channel in the active zone and greatly increases local Ca^{++} concentration. A fusion pore is formed through which neurotransmitter is released.

After docking, several **priming** steps occur to prepare the vesicle for fusion with the presynaptic membrane. At least two presynaptic cytosolic proteins are required for priming. They are NSF (N-ethylmaleimide-sensitive factor) and α -SNAP. The last step in priming is hydrolysis of ATP by the NSF/ α -SNAP complex.

The role of Ca^{++} channels in the active zone. Formation of a fusion pore and release of vesicle contents require high concentration of Ca^{++} (in excess of 200 μM). Such concentrations can be achieved in the cytosol with high-frequency stimulation but are generally reached only in the immediate vicinity of the active zone channels. It is thought that each active zone voltage-gated Ca^{++} channel is associated with its own synaptic vesicle just before transmitter release.

The membrane of the emptied vesicle is recycled once the vesicle contents have been released.

Diversity of neurotransmitters and function. The nervous system uses a variety of strategies to accomplish different peripheral tasks from one and the same path of innervation. This involves coding that is embedded in the diversity of transmitter agents found in the nerves (Table 4–2).

Preganglionic fibers. The dominant preganglionic neurotransmitter in all autonomic efferents is acetylcholine, and it acts on nicotinic receptors in the plasma membrane of the postganglionic cell body. However, a variety of peptides has been found colocalized with acetylcholine. These include corticotropin-releasing hormone (CRH), substance P, somatostatin, vasoactive intestinal polypeptide (VIP), and enkephalin. Moreover, differential distribution of presynaptic fibers containing certain peptides to certain portions of the intermediolateral cell column of the spinal cord may be a mechanism for peptide-specific peripheral innervation.

Postganglionic fibers. Specific peptides may also be responsible for different electrophysiologic responses that are seen in different populations of postganglionic neurons. All postganglionic neurons respond to preganglionic stimulation with a nicotinic fast excitatory postsynaptic potential (EPSP). Postganglionic neurons differ from one another with respect to additional electrical phenomena, such as (1) slow EPSPs or inhibitory postsynaptic potentials (IPSPs) that might be mediated by different comple-

Table 4–2
Strategies for Achieving Specific Differential Function by Means of Diverse Neurotransmitters

Coding Site	Coding Method
Preganglionic fibers	<ol style="list-style-type: none">1) Release of specific secondary NTs along with the primary NT, acetylcholine2) Physical grouping of fibers with specific NTs in circumscribed portions of the intermediolateral spinal cord cell column
Postganglionic fibers	<p>The mix of NTs released from postganglionic fibers could be governed by:</p> <ol style="list-style-type: none">1) Shape of postganglionic membrane potential response as governed by postsynaptic ion channels or NT receptor complement2) Frequency of stimulation

NT = neurotransmitter.

ments of ion channels or (2) delayed EPSPs and IPSPs that might be mediated by different peptides.

The mix of postganglionic neurotransmitters is frequency dependent, as a result of a mechanism that is likely to involve levels of cytosolic $[Ca^{++}]$ and differential Ca^{++} sensitivity of different secretory granules. At low frequencies of nerve stimulation, only norepinephrine or acetylcholine is released from postganglionic fibers. At progressively higher frequencies of stimulation, additional factors are released. In the sympathetic nerve endings, these include neuropeptide Y, and in the parasympathetic nerves, they include VIP and histidine isoleucine.

Receptors for neurotransmitters. Neurotransmitter receptors belong to one of two categories: they are ligand-gated ion channels or G protein-coupled activators of an intracellular second messenger. Activation of ion channels is rapid and produces a change in membrane potential that lasts only a few milliseconds. Activation of G protein-coupled receptors produces responses that last for several seconds or even minutes.

Autonomic nerves are abundantly supplied with both pre- and postsynaptic receptors. Activation of presynaptic receptors modulates neurotransmitter release. Activation of postsynaptic receptors is responsible for the biologic effects that are associated with neurotransmitter release. These effects are in the form of an electrical or chemical change in the postsynaptic cell. (1) In nerve-to-neuron synapses, the effect of interest is changes in transmembrane ion flux and subsequent generation of either an **EPSP** or an **IPSP**. (2) In nerve-to-effector organ synapses, the effect of interest is often a change in postsynaptic cytosolic $[Ca^{++}]$ because that ion governs many mechanical or secretory responses.

Effector Organs

The effector organs of the autonomic nervous system are the muscles of the eye, cardiac muscle, smooth muscle, and secretory units.

Cardiac Muscle

The autonomic nervous system does not initiate cardiac contraction but is a dominant influence in the short-term control of its rate and vigor. These aspects are described more fully in Chapter 6.

Smooth Muscle

Vascular and intestinal smooth muscles are supplied by the autonomic nervous system. The dominant influence of nervous control in these tissues is

modulation of contraction but may also be initiation of contraction. Both aspects are more fully described in Chapters 6 and 8.

Secretory Effectors

Two types of secretory effectors are controlled by the autonomic nervous system: exocrine glands (most prominently salivary glands and those modulating GI or sexual function) and endocrine glands, most prominently the endocrine pancreas and the adrenals.

DIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM

The two major divisions of the autonomic nervous system are the **sympathetic** and **parasympathetic** nervous systems.* They differ from each other in some anatomic features and in their respective target organ neurotransmitters (Table 4–3).

The effect of increased activity in either system can be excitatory in some target organs and inhibitory in others. In target organs that are innervated by both systems, sympathetic and parasympathetic effects often oppose each other. In addition to their postsynaptic effects, there is also considerable presynaptic crosstalk between the systems.

Adrenergic Control Mechanisms

Structure of Sympathetic Nerve Terminals

The endings of sympathetic postganglionic fibers are unmyelinated and show a large number of **varicosities** (Figure 4–9) that are filled with vesicles and mitochondria. The vesicles contain mostly norepinephrine and ATP but also dopamine β -hydroxylase, the enzyme that converts dopamine to norepinephrine.

Synthesis of Norepinephrine

Tyrosine is mostly of dietary origin (most proteins contain tyrosine) and enters the nerve terminal from the blood. The first two enzymes required for norepinephrine synthesis (tyrosine hydroxylase and DOPA decarboxylase) are cytosolic (see Figure 4–9). Dopamine is transported into the vesicles in exchange for 2H^+ , and the exchanger is driven by a steep H^+ concentration gradient that is maintained at a high level by active H^+ transport

*The enteric nervous system of the GI tract is sometimes described as a third division of the autonomic system.

Table 4–3

Sympathetic versus Parasympathetic Systems

	Sympathetic System	Parasympathetic System
Location of preganglionic cell bodies	Preganglionic fibers originate from neurons lying in the intermediolateral column of the spinal cord and exit at their level by way of ventral roots, mostly in the thoracolumbar region.	Preganglionic fibers originate from neurons lying in cranial nerve nuclei of the brainstem (cranial outflow) or from neurons lying in the lateral columns of the sacral spinal cord (sacral outflow).
Location of ganglia	Ganglia form separate, discrete structures either alongside the spinal column or in the viscera.	Ganglia are formed by ganglion cells within the walls of the effector organ.
Presence of neuroendocrine elements	Adrenal medulla is a collection of postganglionic chromaffin cells. They release (mostly) adrenaline on preganglionic stimulation.	None
Anatomy of postganglionic synapse	Multiple synapses with a target organ are formed by varicosities spaced at 3- to 10- μ m intervals.	Synapse with target cell is formed by a terminal bulb, called a bouton .
Major postganglionic neurotransmitter	Norepinephrine in most cases*	Acetylcholine in most cases

*Notable exceptions are the sweat glands, which have sympathetic innervation and use acetylcholine as the postganglionic neurotransmitter. In addition, sympathetic cholinergic fibers innervate blood vessels in some muscle groups in some nonhuman species.

into the nerve terminal (see Chapter 9, “Endocrine System,” for more details). If O_2 is present, norepinephrine is formed inside the vesicles and stored there.

Metabolism of Norepinephrine

Once released into the synaptic cleft, norepinephrine is either bound to postsynaptic receptors or taken up again into the secreting nerve terminal, where it is metabolized by the enzymes **monoamine oxidase**, which is located on the outside of mitochondria, or **catechol-O-methyltransferase**, a cytosolic enzyme (see Figure 4–9).

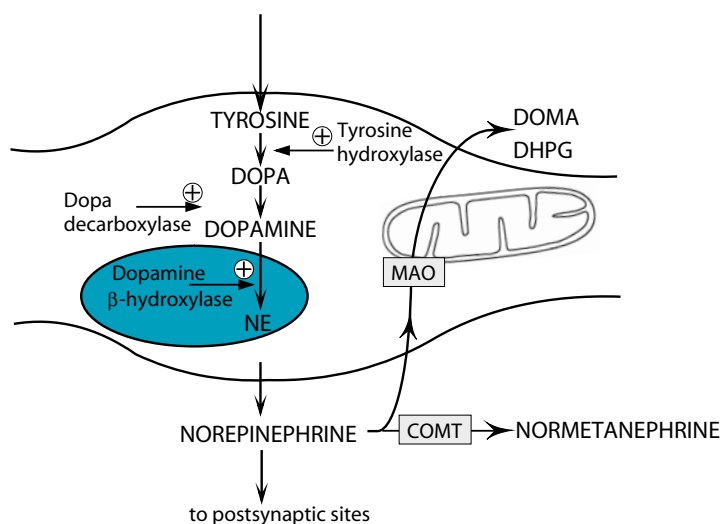


Figure 4-9 Synthesis and metabolism of norepinephrine in sympathetic nerve terminals. Tyrosine enters the nerve terminal from the blood, and dopamine is formed in the cytosol and transported into the storage granules (shown in color). There, norepinephrine is synthesized and stored for later release. Once released into the synaptic cleft, norepinephrine is either bound to postsynaptic receptors or taken up again into the nerve terminal to be metabolized by MAO or COMT. COMT = catechol-O-methyltransferase; DHPG = 3,4-dihydroxyl-phenylglycol; DOMA = 3,4-dihydroxy-mandelic acid; DOPA = dihydroxy-phenylalanine; MAO = monoamine oxidase; NE = norepinephrine.

Structure of Adrenal Medulla

The adrenal medulla contains **chromaffin** cells that are arranged in close proximity to preganglionic cholinergic fibers and, therefore, act as postganglionic cell bodies. The presence of **phenylethanolamine N-methyltransferase** (PNMT) is a unique feature of chromaffin cells.

Synthesis of Epinephrine

Chromaffin cells have all the enzymes that are present in the sympathetic postganglionic fibers and are, therefore, capable of synthesizing norepinephrine. In addition, they contain the cytosolic enzyme PNMT, which converts norepinephrine to epinephrine, provided that it is activated by high concentrations of cortisol, draining from nearby cells in the adrenal cortex.

Postsynaptic Receptors

Adrenoreceptors: In all sympathetically innervated organs, except sweat glands, the dominant neurotransmitter is norepinephrine; therefore, the

dominant postsynaptic target cell receptor type is the adrenergic receptor. This is a membrane-spanning protein with six intramembrane domains and an extracellular binding region that specifically recognizes epinephrine and norepinephrine, though not usually with the same affinity.

There are two types of adrenergic receptors, designated α and β . Both α and β receptors have several functional subtypes (Table 4–4).

Alpha receptors. α_1 Receptors are the dominant α receptor subtype on the postsynaptic target cell membrane. This subclass is further subdivided into α_{1A} , α_{1B} , α_{1C} , and α_{1D} on the basis of relative affinity for antagonists. α_2 Receptors are the dominant α receptor subtype on the presynaptic side of adrenergic nerve terminals themselves. Their function is to modulate norepinephrine release from the synapse. They are subdivided into three groups, α_{2A} , α_{2B} , and α_{2C} .

The major effector pathway of α_1 adrenoreceptor activation is activation of phospholipase C, leading to formation of inositol triphosphate (IP_3) and diacylglycerol (DAG), as well as IP_3 -mediated elevation of cytosolic $[Ca^{++}]$.

Beta receptors. β_1 Receptors are found mostly in cardiac myocytes; β_2 receptors are found in smooth muscle and in secretory effectors; and β_3 receptors have limited distribution and are present at low levels in adipose tissue (where they stimulate lipolysis) and the GI tract (where they stimulate gut motility).

Table 4–4

Adrenergic Receptors Found in Target Cell Synapses

Class	Subclass	Primary Location	Primary Transduction Mechanism (Second Messengers)
α	α_1 α_{1A-1D}	Postsynaptic membrane	Phospholipase C (IP_3 , DAG, Ca^{++})
	α_2 α_{2A-2C}	Presynaptic membrane	Adenylate cyclase inhibition (\downarrow cAMP)
	β_1	Postsynaptic membrane of cardiac myocytes	Adenylate cyclase (cAMP)
β	β_2	Postsynaptic membrane of smooth muscle and secretory effectors	Adenylate cyclase (cAMP)
	β_3	Postsynaptic membrane of adipocytes and some GI smooth muscle	Adenylate cyclase (cAMP)

β Adrenoceptor activation is coupled by way of a G protein to adenylate cyclase. Its activation promotes formation of cytosolic cAMP.

Neuropeptide Y receptors. This peptide, when it is cosecreted with norepinephrine, acts on peripheral Y_1 and Y_2 receptors. They operate predominantly through inhibition of adenylate cyclase by way of a G protein–coupled mechanism.

Cholinergic Control Mechanisms

Synthesis of Acetylcholine

Acetylcholine is synthesized in the terminal bouton of preganglionic or parasympathetic postganglionic fibers. This involves the transfer of an acetyl group from acetyl coenzyme A (CoA) to choline. It takes place in the cytosol and is catalyzed by the enzyme **choline acetyltransferase** (Figure 4–10). Acetyl CoA is produced in mitochondria; the sources of choline are partly the breakdown of membrane phospholipids and partly uptake

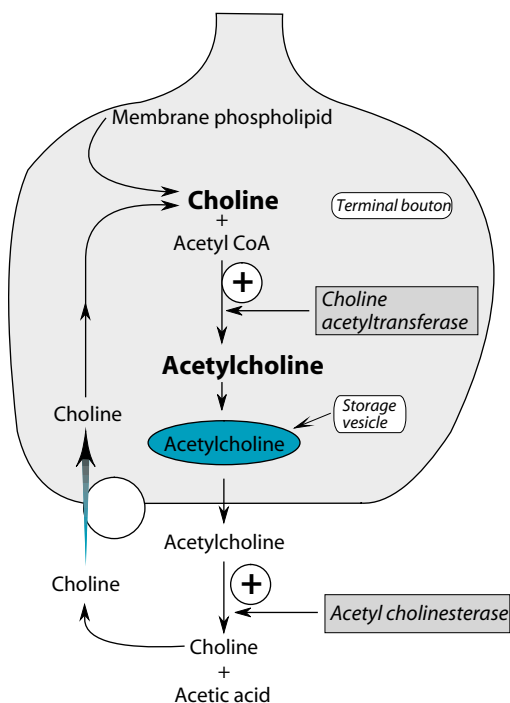


Figure 4–10 Synthesis of acetylcholine. CoA = coenzyme A.

from the synaptic cleft, where it (along with acetic acid) is produced when acetylcholine is broken down by **acetylcholinesterase**.**

Cytosolic acetylcholine is moved into presynaptic storage vesicles by a specific antiporter that exchanges acetylcholine for H^+ . Cytosolic $[H^+]$ is maintained at a high level by active H^+ transport. In addition to the neurotransmitter, the vesicles also contain ATP.

Postsynaptic Receptors

Cholinoreceptors: Cholinergic receptors are membrane-spanning proteins that function either as ligand-gated ion channels or as G protein-coupled triggers for cytosolic second messengers (Table 4–5).

Postsynaptic receptors in ganglia are **nicotinic cholinergic**, whereas those in the effector organs are **muscarinic cholinergic**. They differ in structure, identity of antagonists, and signaling mechanisms.

Nicotinic receptors. These receptors are formed by five subunits, each of them consisting of four membrane-spanning domains. The subunits are

Table 4–5

Cholinergic Receptors Found in Target Cell Synapses

Class	Subclass	Primary Location	Primary Transduction Mechanism (Second Messengers)
Nicotinic		Ganglionic postsynaptic	Na^+/K^+ channel
Muscarinic		Postsynaptic membrane of target cells in:	
	M_1	Peripheral ganglia and exocrine glands	Phospholipase C (IP_3 , DAG, Ca^{++})
	M_2	Pacemakers and myocytes in cardiac atria	Adenylate cyclase inhibition ($\downarrow cAMP$)
	M_3	Peripheral ganglia, exocrine glands, and vascular endothelium	Adenylate cyclase inhibition ($\downarrow cAMP$)
	M_4	Secretory effectors	Phospholipase C (IP_3 , DAG, Ca^{++})
	M_5		Phospholipase C (IP_3 , DAG, Ca^{++})

**A variety of insecticides are anticholinesterases and, thereby, act to prolong the action of acetylcholine.

arranged so as to form a central pore. The receptor is inhibited by ganglionic blockers, such as hexamethonium or pentolinium, and, surprisingly, by high concentrations of acetylcholine. At low acetylcholine concentration, nicotinic receptors are activated when two acetylcholine molecules are bound to extracellular sites.

The nicotinic cholinergic receptor is a nonspecific cation channel. Its activation causes increased flux of Na^+ and K^+ down their electrochemical gradients and results in bursts of fast EPSPs until the acetylcholine molecules have dissociated from the receptor.

Muscarinic receptors. Parasympathetic postsynaptic effects are due mostly to the activation of **muscarinic cholinergic** receptors. They are serpentine proteins with seven membrane-spanning domains and are inhibited by **atropine**. Five subtypes, designated M_1 to M_5 , have been identified on the basis of their relative sensitivity to different antagonists because no selective agonists and no highly specific antagonists have been found. All five types are found in the central nervous system. In the periphery, the M_2 subtype is expressed at high density in the heart; M_1 and M_3 are found in the peripheral ganglia and exocrine glands; and M_3 is found in vascular endothelium.

Muscarinic cholinergic receptors are G protein coupled to adenylate cyclase (M_2 and M_3) or phospholipase C (M_1 , M_4 and M_5), and when they are activated, they produce the second messengers cyclic adenosine monophosphate (cAMP) (M_2 and M_3) or, in the case of M_1 , M_4 , and M_5 , IP_3 and DAG plus the IP_3 -mediated release of Ca^{++} from intracellular stores. In addition, several target cells have acetylcholine-sensitive K^+ channels, whose activation leads to electrical hyperpolarization.

Nitroxidergic Control Mechanisms

The marked increase in local blood flow that is required to initiate penile erection is mediated by nerves that elaborate nitric oxide. It causes elevation of intracellular cGMP.

CENTRAL COORDINATION OF NERVOUS AND CHEMICAL ELEMENTS

The autonomic nervous system operates to restore to zero any difference between the status of any one of many controlled parameters and its centrally stored set point: (1) a variety of sensory mechanisms provide afferent input; (2) a hierarchy of central nervous mechanisms evaluate, integrate, coordinate, and generate patterns of chemical and electrical signals for the

purpose of executing appropriate effector action; and (3) sympathetic and parasympathetic efferent fibers convey the electrical information to the heart, smooth muscle, and secretory effectors.

Afferent Information

Both electrical and chemical information is used by the central nuclei.

Electrical Afferent Information

Afferent fibers enter mainly by way of the vagus and glossopharyngeal nerves to synapse in the **nucleus tractus solitarius** (Figure 4–11). Additional electrical information comes from (1) central nervous receptors of temperature and chemical status and (2) nociceptors that monitor visual, auditory, olfactory, and other ambient phenomena.

Chemical Afferent Information

Chemical agents gain access to the central nuclei by way of structures lacking the blood-brain barrier. Such areas include the **area postrema** (see Figures 4–2 and 4–11) and **circumventricular organs**.

Central Nuclei

The pons/medulla areas of the midbrain (see Figure 4–2) are the most significant sites for central autonomic regulation of individual variables. Electrical information reaches the area through the nucleus tractus solitarius (see Figures 4–2 and 4–11) and from tracts that connect to higher centers. Chemical information reaches the area mostly through the area postrema. Four other regions in the midbrain have special significance. They are (1) the rostral ventrolateral medulla (RVLM) (see Figures 4–2 and 4–11), which is a collection of cell bodies for fibers in the intermediolateral column of the spinal cord (see Figures 4–3 and 4–4); (2) the caudal ventrolateral medulla (CVLM), which contains neurons that exercise tonic inhibition of the RVLM; (3) the dorsal motor nucleus; and (4) nucleus ambiguus (see Figures 4–2 and 4–11), both of which are collections of vagal preganglionic cells.

Efferent Information

Efferent autonomic information leaves central nuclei in sympathetic and parasympathetic tracts.

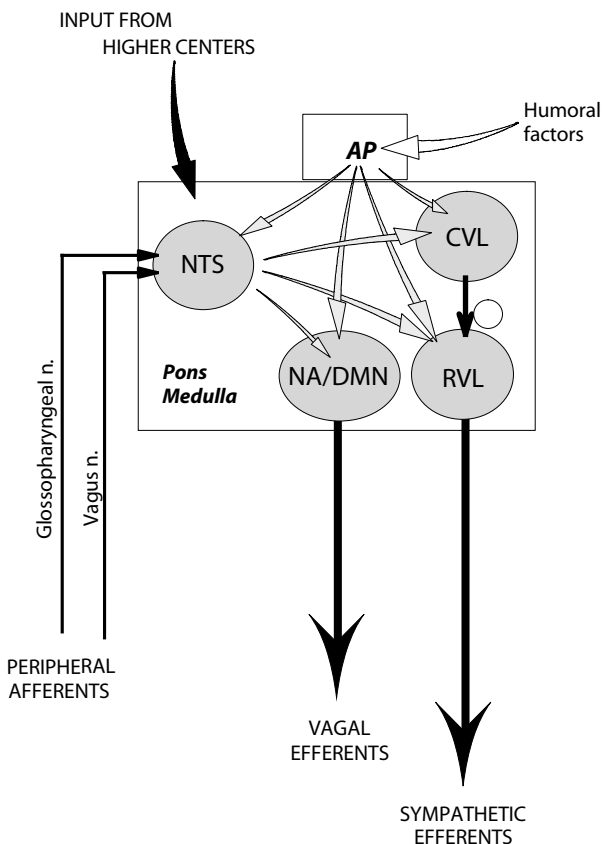


Figure 4–11 Midbrain centers of autonomic regulation. Afferent electrical information enters the nucleus tractus solitarius (NTS) by way of the vagus and glossopharyngeal nerves, whereas afferent chemical information gains access to the region mostly by way of the area postrema (AP) because it lacks a blood-brain barrier. The NTS and AP communicate extensively with the nuclei that generate efferent information, namely, the nucleus ambiguus (NA), dorsal motor nucleus (DMN), and rostral ventrolateral medulla (RVLM). CVL = caudal ventrolateral medulla.

Sympathetic Efferents

Efferent sympathetic activity descends in fibers of the intermediolateral columns of the spinal cord and is transferred from there to sympathetic pre-ganglionic neurons (see Figure 4–4).

Parasympathetic Efferents

The parasympathetic efferents leave the central nuclei mostly by way of the vagus nerves. Fibers to the sacral region of the spinal cord are not organ-

ized in a distinct spinal column but do descend in the mediolateral area, near the sympathetic fibers.

THE AUTONOMIC NERVOUS SYSTEM AND PAIN

Stimulation of the autonomic nerves does not normally activate nociceptive elements and is, therefore, not normally associated with sensations of pain. However, mechanical trauma to a peripheral nerve is sometimes followed by a syndrome that includes burning pain and disturbances of sweating and vasomotor regulation. Several factors are believed to be involved in this dysfunction of autonomic regulation: (1) damage to peripheral nerves may cause a change in the central connections of afferent nerves; (2) adrenergic receptors may appear in some afferent nerves so that local release of norepinephrine in the vicinity of such afferents can excite them; (3) inappropriate activation of afferents can lead to apparently inappropriate reflex responses involving vascular and sweat gland elements.

Respiration

PULMONARY GAS EXCHANGE

Primary Function of the Lungs

The lungs are the primary site of gas exchange between the body and the environment because all other sites, including skin, account for less than 1% of the total.

Rhythmic increases and decreases in chest volume cause air to enter and leave the lungs in a reciprocating pattern. The exchange regions of the lung consist of an easily permeated interface between air and blood.

Physics of Gases

Gases are carried in blood (1) in physical solution and (2) in chemical combination with specific carrier agents. Although the amount of oxygen (O_2) and carbon dioxide (CO_2) that can be physically dissolved in blood represents only 5% of the total amounts carried, each molecule of O_2 or CO_2 that moves into or out of the tissues is, at some time, physically dissolved and moves from one region to another by diffusion.

Physical solubility of gases. The amount of gas that is dissolved in a liquid depends on the product of its partial pressure and its solubility coefficient α . Alpha is measured in mL of gas per mL of solvent per 760 mm Hg and ranges from 0.024 for O_2 to 0.49 for CO_2 , both in blood at $37^\circ C$.

Partial pressures of respiratory gases. In a mixture of gases, the partial pressure of any one of them is calculated as follows:

$$\text{Partial pressure of X} = \text{Total pressure (mm Hg)} \times \text{Fraction occupied by X}$$

For example, the fraction of O_2 in dry air is 21%. Therefore, in dry air, at atmospheric pressure (760 mm Hg at sea level*),

$$pO_2 = 760 \times 0.21 = 160 \text{ mm Hg}$$

By convention, the composition of gas mixtures is usually quoted in terms of dry gas. Because air in the lungs is saturated with water vapor, water vapor pressure is subtracted from the total pressure in all calculations. Water vapor pressure varies with temperature only and is equal to 47 mm Hg at normal body temperature. For example, dry alveolar air is 14% O_2 . As a result, at atmospheric pressure,

$$\text{Alveolar } pO_2 = (760 - 47) \times 0.14 = 100 \text{ mm Hg}$$

Figure 5–1 shows normal values for partial pressures of O_2 and CO_2 at different sites in the respiratory and pulmonary vascular systems.

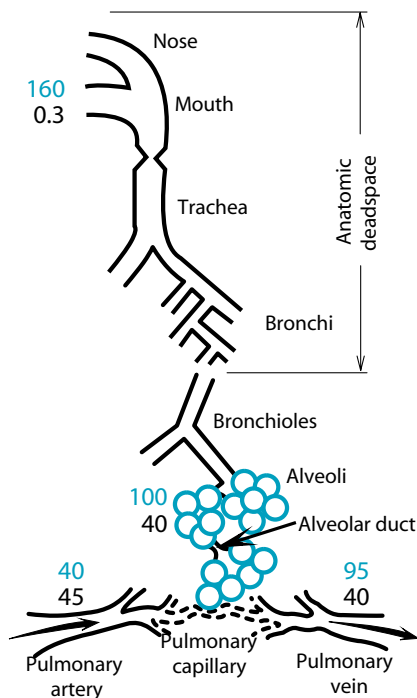


Figure 5–1 Anatomy of the airway and pulmonary gas exchange structures. The numbers indicate local partial pressures [mm Hg] of O_2 (in color) and CO_2 . Blood flows from the pulmonary veins through the heart and to the tissues. There, it gives up O_2 because tissue pO_2 ranges down to 5 mm Hg and picks up CO_2 because tissue CO_2 reaches up to 50 mm Hg.

*Atmospheric pressure decreases with altitude so that the atmospheric pressure at h km above sea level, P_h , is $P_h = P_0 \times 10^{-0.055h}$, where P_0 = atmospheric pressure at sea level.

Physics of Passive Diffusion

Gases move from regions of high partial pressure to low partial pressure, and the rate at which a gas moves through a mixture of gases is inversely proportional to the square root of its molecular weight.

Functional Anatomy of the Lungs

Within the lungs, a large number of terminal sacs, the **alveoli** and the epithelium of their enveloping capillary network, provide an exchange interface between air and blood.

Respiratory Structures

The airways. Before inspired air reaches the alveolar ducts and alveoli, it passes through the nasal cavities, pharynx, larynx, trachea, and bronchial tree (see Figure 5–1). A thin layer of mucus in these **conducting airways** helps clean, warm, and saturate inspired air with water vapor before it reaches the **exchanging airways**.

Primary lobule. A **primary lobule** is formed by each alveolar duct and its approximately 20 terminating alveoli (see Figure 5–1), each spherical alveolus measuring 100 to 300 μm in diameter. This grape-like arrangement of spherical structures offers maximum surface area for minimum volume.

Only the alveolar ventilation is available for diffusive gas exchange with pulmonary capillary blood. The barrier that lies in the diffusional path is 0.5 to 1.5 μm thick and is composed of (1) a thin layer of surface fluid, (2) a single layer of alveolar epithelial cells, (3) alveolar basement membrane, (4) parenchymal cells, (5) interstitial fluid, (6) capillary basement membrane, and (7) capillary endothelium.

The pleura. The lung moves only in response to forces transmitted from the chest wall via the pleura. The pleura are two monolayers of cells, one on the outside of the lung (visceral pleura) and one on the inner surface of the chest wall (parietal pleura). They are closely apposed, separated only by a 1- μm film of fluid that acts both as mechanical coupler and lubricant.

Vascular Structures

Pulmonary artery. Deoxygenated blood reaches the lungs through the pulmonary arteries at low hydrostatic pressure because pulmonary vascular resistance is low. A structural consequence of the lower pressures is that pulmonary arteries have thinner walls than do systemic arteries handling comparable flow.

Pulmonary microcirculation. The pulmonary microcirculation is characterized by three significant features: (1) pulmonary capillaries are large and extensively anastomosed so that each alveolus is surrounded by a dense net of microvessels; (2) pulmonary capillary hydrostatic pressure is highly dependent on posture, location within the lung, and state of physical activity; and (3) the lungs have an extensive lymphatic network that creates both a substantially negative pulmonary interstitial hydrostatic pressure (near -8 mm Hg) and an effective mechanism for clearing plasma ultrafiltrate from the tissue spaces.

Pulmonary vascular resistance. Pulmonary arterioles and venules have little smooth muscle. As a result, neuronal and humoral effects are relatively weak. Nevertheless, **hypoxic vasoconstriction** is of great functional significance in many settings. Under normoxic conditions, mechanical influences, such as the effect of gravity on intravascular distending pressure and the compressive effect of air-filled alveoli on blood vessel, exert major influences on pulmonary vascular resistance.

PULMONARY MECHANICS

The mechanical forces of the lung and chest wall are tightly coupled to each other by the surface forces in the intrapleural space, which is the thin layer of fluid that separates visceral (lung) from parietal (chest wall) pleura. As a result of this coupling, lung volume is changed when chest volume changes in response to the contraction of **respiratory muscles**.

Respiratory Muscles

The chest cavity expands vertically and cross-sectionally to cause inspiration.

Movement of the Diaphragm during Inspiration

The diaphragm is dome shaped, bulging upward into the chest cavity (Figure 5–2; dotted line). Its active contraction draws the apex of the dome toward the feet and increases chest size in the vertical direction (see Figure 5–2). Diaphragm contraction accounts for most of the inspiratory thoracic volume changes in a resting person. However, contraction of the diaphragm would pull the lower ribs inward if the rib cage, as a whole, were not pulled so as to counteract diaphragm forces.

Movement of the Rib Cage during Inspiration

While contraction of the diaphragm increases the vertical size of the chest cavity (see Figure 5–2), coordinated contraction of the external inter-

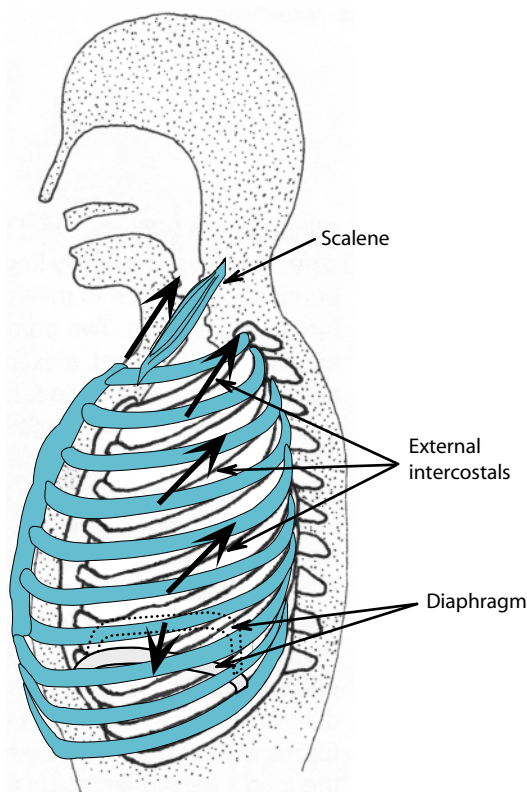


Figure 5-2 Movement of the rib cage and diaphragm during inspiration. Each rib is hinged at the vertebral column. As a result, it is lifted upward and outward by the contraction of the scalene muscles, sternocleidomastoids (*not shown*), and the external intercostals. The arrows show the direction of pull of each set of muscles. Only three sets of external intercostals are suggested, although these muscles are present between each pair of ribs.

costals, scalenes, and sternocleidomastoids causes the cross-sectional area of the chest to be increased (see Figure 5-2).

Expiration

In quiet breathing, expiration is a passive process, driven by the elastic recoil of the lungs. It is assisted at higher ventilation rates or during forceful expiration by the active contraction of internal intercostal muscles and abdominal muscles, such as the rectus abdominus.

Inspiratory muscles continue to contract, although with progressively decreasing force, during part of expiration (Figure 5-14). Their gentle opposition to elastic recoil prolongs expiration time. Expiratory air flow can

be further and voluntarily retarded by muscles that control upper airway diameter so as to permit speech and other vocalization.

Lung Volumes and Lung Capacities

The volume of air held by the maximally filled lungs can be divided into four non-overlapping **volumes** (Figure 5–3). These volumes are defined as follows:

- *Tidal Volume (V_T)*: the volume of gas inspired or expired in a single respiratory cycle. This volume can be increased or decreased by calling on inspiratory or expiratory reserve volumes.[†]
- *Inspiratory reserve volume (IRV)*: the maximum volume of gas that can be inhaled starting at the end of a normal inspiration
- *Expiratory reserve volume (ERV)*: the maximum volume of gas that can be exhaled starting from the end of a normal expiration
- *Residual volume (RV)*: the volume of gas that remains in the lungs after a maximum expiration

Measures of lung air content that include more than one volume are called **capacities**:

- *Total lung capacity (TLC)*: the total amount of gas in the lungs at the end of a maximum inspiration = the sum of RV, ERV, V_T , and IRV

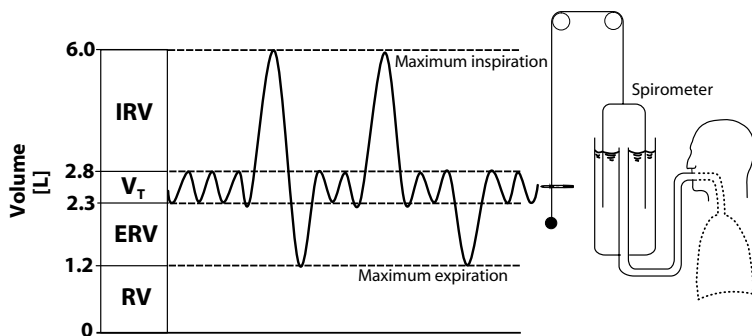


Figure 5–3 Fluctuations in lung volumes as recorded by a respirometer. Inhalation results in upward deflection. The column on the left identifies commonly defined lung volumes and indicates approximately normal values for human adults. ERV = expiratory reserve volume; IRV = inspiratory reserve volume; RV = residual volume; V_T = tidal volume.

[†]Not all of the tidal volume is available to ventilate the alveoli because some of it is held in the dead space.

- *Vital capacity (VC)*: the maximum volume of gas that can be inspired after a maximum expiration
= the sum of the ERV, V_T and IRV
- *Functional residual capacity (FRC)*: the amount of gas in the lungs at the end of a normal expiration
= the sum of the ERV and RV
- *Inspiratory capacity (IC)*: the maximum amount of gas that can be inspired starting from the FRC
= the sum of V_T and IRV
- *Forced vital capacity (FVC)*: the amount of gas that can be expelled from the lungs by expiring as forcibly as possible, after a maximum inspiration.

Changes in Pressure and Volume during the Respiratory Cycle

The mechanical aspects of respiratory function are usually described by curves showing lung volume over the respiratory range of intrapleural pressures.[‡] Two sets of curves are used to demonstrate the contributions of the different mechanical properties of the component parts.

Static pressure-volume curves are obtained under conditions of zero air flow at the moment of measurement. They are used to demonstrate (1) the contributions of elastic properties alone and (2) the balance of forces that prevents lung volume from collapsing to zero at the end of expiration. The shape of such curves is influenced by **compliance** alone. **Dynamic** pressure-volume curves are used to describe mechanical relationships pertaining to normal breathing. The shape of these curves is influenced by both compliance and **resistance** in the components of the respiratory system.

Compliance of Respiratory Structures

Compliance is a mechanical property of elastic materials. For a hollow, distensible container, it expresses the ease with which the container can be made to change its volume in response to a pressure change and is defined as follows:

$$\text{Compliance} = \frac{\text{Change in volume}}{\text{Change in distending pressure}}$$

Compliance is represented by the slope of a volume versus pressure curve for the container, such as that shown for the lungs in Figure 5–6.

[‡]Intrapleural pressure is measured in the potential space that is occupied by a thin film of fluid between the lung and the chest wall.

Pulmonary compliance is not linear but changes with lung volume. Therefore, it is often calculated at a specific lung volume or is normalized to lung volume. Such a measure is called **specific compliance**. Both **chest wall compliance** and **lung compliance** influence the overall pressure-volume behavior of the respiratory system.

Factors determining chest wall compliance. Chest wall compliance depends on chest geometry, composition of the chest wall, and mobility of abdominal contents.

Factors determining lung compliance. The anatomic shape and environment of the pulmonary air spaces offer a number of factors that will affect lung compliance. These include (1) the degree of tissue hydration and engorgement of the capillary mesh, (2) the stiffness of the parenchyma as influenced by elastin and collagen, (3) the geometry of the air spaces, and (4) surface forces at the air-fluid interface of the alveoli.

Surface forces are of special importance for healthy lung function because the alveoli are bubbles of air, suspended in a fluid medium. Steady state is maintained in such a bubble when the relationship between the transmural pressure (P) required to maintain it at a given radius (R) is directly related to the surface tension (T) of the air-fluid interface by the law of Laplace: $p = \frac{2T}{R}$. —

Surface tension.

The drive toward alveolar uniformity: Surface tension per unit of surface area is determined only by the nature of the liquid and is the same for all bubbles in water. As a result, small air bubbles require a higher distending pressure than do larger bubbles (Figure 5–4). Similarly, the pressure inside small alveoli should be higher than that inside large alveoli, and smaller alveoli should empty into larger alveoli that are connected to the same alveolar duct, making them of equal radius (Figure 5–5). This tendency toward alveolar uniformity is prevented by the **pulmonary surfactant system**.

The fluid film that lines healthy alveoli contains **pulmonary surfactant**, which is a material that is composed mostly of phospholipids.[§] It is synthesized in the endoplasmic reticulum of type II alveolar epithelial cells.^{||} Such synthesis begins late in fetal life.

Surfactant lines the inner surface of the alveolar membrane, the hydrophilic tails facing toward the air space. Surface tension is inversely proportional to the number of surfactant molecules per unit area. As the

[§]The major phospholipid component is dipalmitoyl phosphatidylcholine (DPPC).

^{||}Most of the cells of the alveolar epithelium are type I cells.

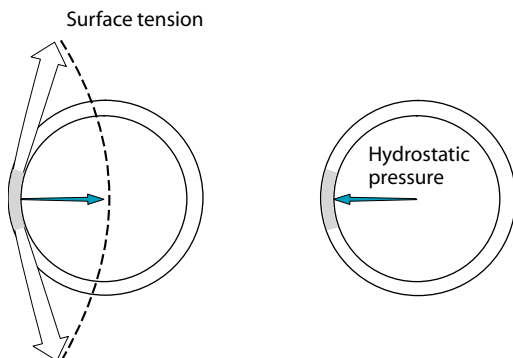


Figure 5-4 In an air bubble lined with water, surface tension creates an inwardly directed force tending to collapse the bubble. The hydrostatic pressure within the bubble opposes the collapse. At steady state, tension and pressure are related by the law of Laplace.

alveolus stretches, surfactant density decreases, and surface tension increases. As a result, surface tension is lower in small alveoli than in large alveoli; small alveoli can be maintained by the same hydrostatic pressure as large alveoli, and there is no tendency for small alveoli to empty into large alveoli.

The threat of alveolar collapse: Each alveolus is open and connected to other alveoli, and there is nothing to prevent air from escaping when surface tension shrinks any one of them; no opposing internal pressure can

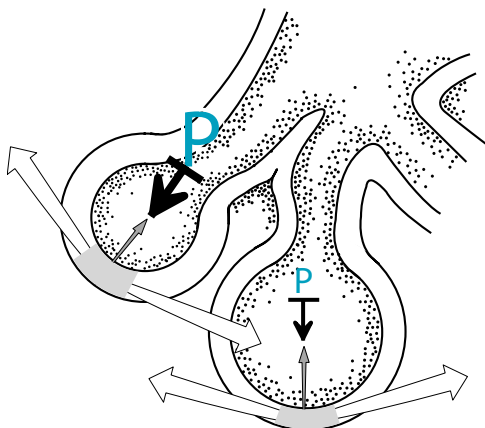


Figure 5-5 If small and large alveoli had the same surface tension per unit of surface area, then the pressure in small alveoli should be greater and smaller alveoli should collapse by emptying into larger ones.

build up, and collapse should be unavoidable. However, collapse does not usually happen, and two factors are responsible. They are (1) the consequences of *anatomic interdependence* and (2) adhesion of the lung surface to the inside of the chest wall.

Anatomic interdependence: Alveoli are anatomically interdependent in that they are bathed in a common pool of interstitial fluid. The hydrostatic pressure in this fluid space is near $-5 \text{ cm H}_2\text{O}$ at the end of expiration when alveolar pressure is zero, that is, the pressure inside the alveoli is greater than that outside the alveoli.

Negative pulmonary interstitial pressure is created when pleural adhesion to the chest wall opposes the elastic recoil that acts toward collapsing the lung.

Adhesion of the pleura: The ultimate factor preventing alveolar collapse is that the lung, as a whole, cannot collapse because of close mechanical coupling between its outer lining (the visceral pleural membrane) and the inner lining of the thorax (the parietal pleural membrane).

Resistance in Respiratory Structures

Three sources of resistance must be overcome during breathing:

1. Airway resistance (R_{AW}) is the most important resistive component, and it is most subject to increase with disease. It is calculated from the Poiseuille relationship as

$$R_{AW} = \frac{8 \times \text{Airway length} \times \text{Gas viscosity}}{\pi \times \text{Radius}^4}$$

Airway resistance increases greatly if air flow becomes turbulent, and it increases dramatically with small decreases in airway diameter.

2. Viscous resistance in the tissues of the chest wall contributes up to 20% of total resistance. This resistance component arises from friction between tissue elements of the chest wall.
3. Viscous resistance in the lungs contributes up to 15% of total resistance.

The contribution of resistance to the shape of pressure-volume curves is most readily seen by comparing the area under a dynamic pressure-volume curve with that under a static pressure-volume curve covering the same range of volume.

Static Pressure-Volume Characteristics of Respiratory Structures

The lungs have a natural tendency to collapse unless they are expanded by a negative intrapleural pressure. Similarly, the chest cavity has a natural ten-

dency to expand unless it is restrained by negative intrapleural pressure. These properties are shown by the static pressure-volume characteristics (see Figure 5–6).[#] The illustration makes it clear that the system will reach equilibrium when the recoil forces of the two structures are equal and opposite. Therefore, expiration is never to the point where all air is removed from the lungs. It normally ends at a point where the net elastic force arising from the collapsing lung is exactly balanced by the net elastic force with which the chest cavity resists further volume reduction. At that point, the chest wall and lungs assume a volume that is called **functional residual capacity** (FRC). It is near 50% of total capacity and at an intrapleural pressure of approximately -5 cm H₂O. Functional residual capacity is not always the same as end expiratory volume. The two will differ after forceful expiration when expiratory muscles have been used to reduce lung volume or in obstructive diseases when expiration ends before FRC is reached.

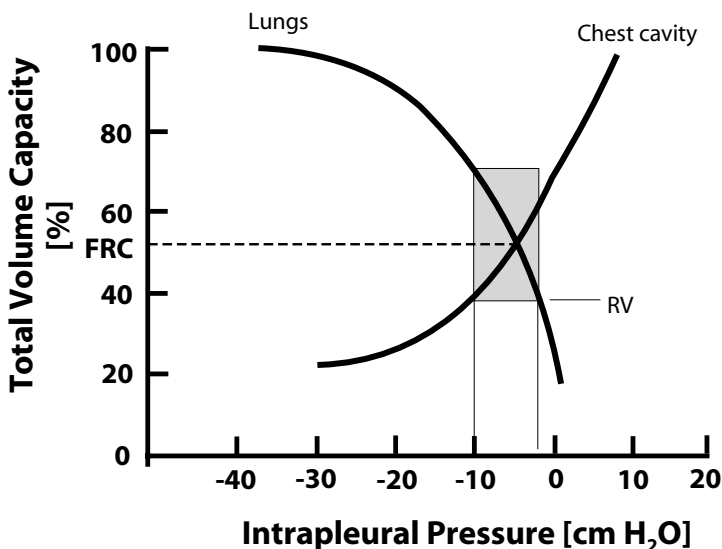


Figure 5–6 Static pressure-volume curves of the respiratory system, obtained under conditions of zero air flow at each step of intrapleural pressure. Under those conditions, the lungs and chest wall are governed by the same pressure gradient. The area within the shaded rectangle indicates the pressure-volume range of normal breathing. *Both curves normally show hysteresis, less pressure being required to maintain a given volume during deflation than during inflation. Hysteresis has been omitted for the purpose of clarity.* FRC = functional residual capacity; RV = residual volume.

[#]They are called “static” because they are measured in experimental settings where pressures are maintained until air flow stops.

Figure 5–6 also shows that (1) lung volume does not collapse to zero, even when the distending pressure is zero. The reason is that small airways collapse before the alveoli do, leaving a **residual volume**; and (2) the respiratory structures are most compliant (steepest slope) in the operating range of normal breathing.

Dynamic Pressure-Volume Characteristics of the Lung

Dynamic pressure-volume curves are obtained under conditions when air flow is not zero. Under such conditions, airway resistance causes hysteresis and a pressure-volume loop rather than a straight line. The explanation is most easily given with reference to a fixed volume such as, for example, 0.5 L above FRC in Figure 5–7:

During inspiration, intrapleural pressure f is required just to hold the lungs at that volume. Additional pressure $b-f$ is required to overcome airway resistance and cause filling of the lungs. During expiration, intrapleural

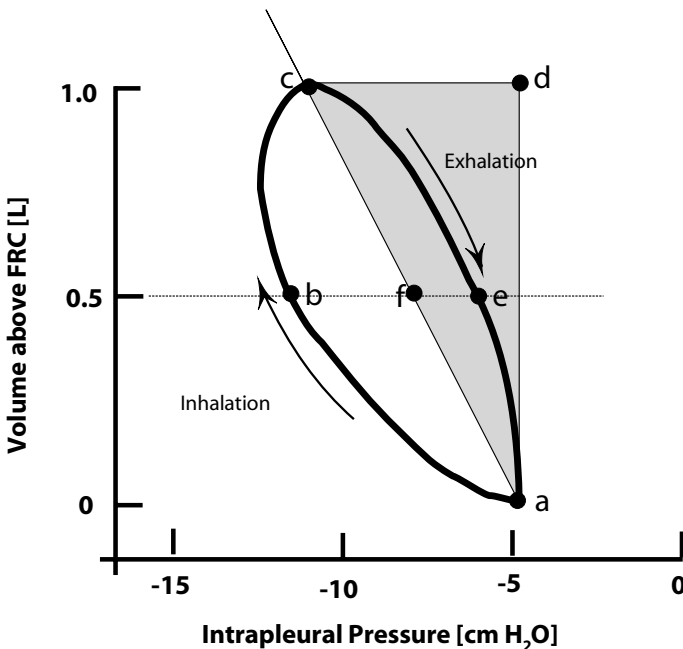


Figure 5–7 Dynamic pressure-volume characteristics of the lungs, covering only the range of quiet breathing shown by the small shaded rectangle in Figure 5–6. The line afc represents the static pressure-volume curve over the pressure range of interest. The area $abcfa$ represents the work done to overcome airway resistance. The triangular area $afcda$ represents the work done against elastic resistance. The work of expiration, area $afcea$, lies within the shaded triangle that represents elastic work, indicating that work of quiet expiration is normally done by recoil of the elastic elements.

pressure f would prevent the lungs from collapsing. However, airway resistance creates a “back-up” pressure that tends to keep the lung inflated and does not have to be provided by intrapleural forces. As a result, a smaller intrapleural pressure (e) than predicted by static conditions (f) is required.

The Work of Breathing

The area under a pressure-volume curve represents work done. Therefore, the area under a dynamic pressure-volume curve represents the **work of breathing**. Work is required both to expand the elastic components (shaded area in Figure 5–7) and overcome resistance.

Pulmonary Air Flow

Pressure gradients. Air moves into and out of the lungs in response to differences between alveolar pressure and pressure at the mouth and nose (= atmospheric pressure). Alveolar pressure fluctuations arise from changes in chest volume that are caused by activity in the muscles of respiration and are coupled to the lungs and alveoli by way of mechanical factors, such as **surface tension**.

Types of air flow. Air flow can be **laminar** or **turbulent**, depending on whether the streamlines are continuous or disturbed and broken up. Turbulent air flow requires greater driving pressure to generate a given volume flow. It can occur at branch points or constrictions. There is an empirical relationship between the two types of airflow and a dimensionless constant called the **Reynold’s number** (Re). By definition,

$$Re = \frac{\text{Flow velocity} \times \text{Conduit diameter} \times \text{Gas density}}{\text{Gas viscosity}}$$

When Re is greater than 2,000, then flow is usually turbulent.

GAS TRANSPORT AND EXCHANGE

Carriage of Oxygen

Blood oxygen content is a nonlinear function of partial pressure (Figure 5–8). It has two components: O_2 that is physically dissolved in plasma and O_2 that is carried in association with hemoglobin. Each molecule of this protein can, depending on ambient pO_2 , bind up to four molecules of O_2 in an easily reversible manner. Chemical binding of O_2 to hemoglobin reaches a maximum near 20 mL per 100 mL of blood (vol%; see Figure 5–8) at pO_2 near 150 mm Hg. Increases in O_2 content above that point are due entirely to physically dissolved O_2 . In view of the dominant importance of

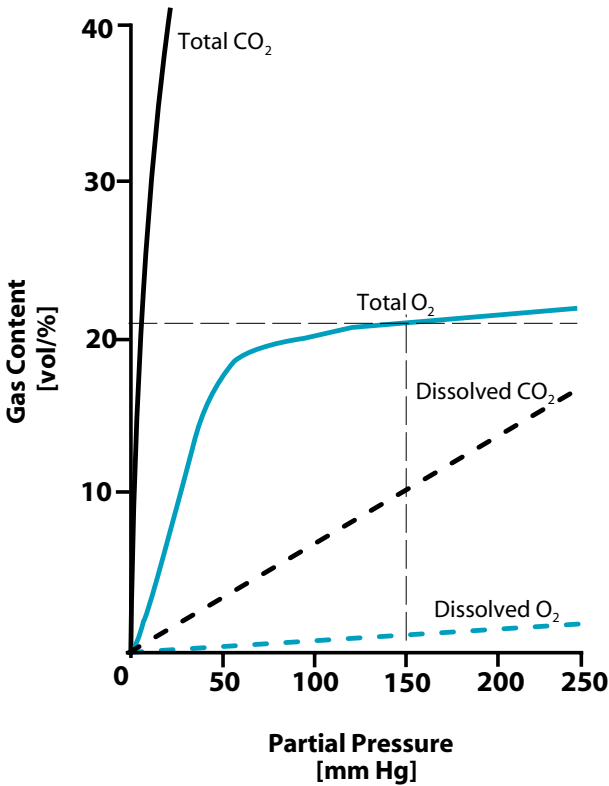


Figure 5–8 Equilibrium curves for CO_2 and O_2 in blood. The solid lines represent total content (chemically associated + physically dissolved) at a fixed concentration of the other gas. The interrupted lines show the physically dissolved portion of total content. Because of its higher solubility, more CO_2 than O_2 is carried in physically dissolved form.

hemoglobin, O_2 transport in blood is commonly shown in terms of hemoglobin saturation only.

Hemoglobin-Oxygen Dissociation Curve

In pulmonary venous blood, at a pO_2 of 100 mm Hg, O_2 binding is at 98% of its potential maximum, and the oxygen saturation of hemoglobin (SaO_2) is said to be 98% (Figure 5–9). In the tissues, on the other hand, at a pO_2 near 20 mm Hg, SaO_2 is only about 20%. This difference reveals the O_2 transport function of hemoglobin. Arterial blood with high pO_2 arrives in tissue where pO_2 is low because of aerobic metabolism in the cells of the tissue. Therefore, in the tissues, oxygen leaves oxyhemoglobin, moves down its partial pressure gradient, and enters tissue cells. It leaves nonoxygenated hemoglobin behind. In the lungs, venous blood arrives at low pO_2 and is

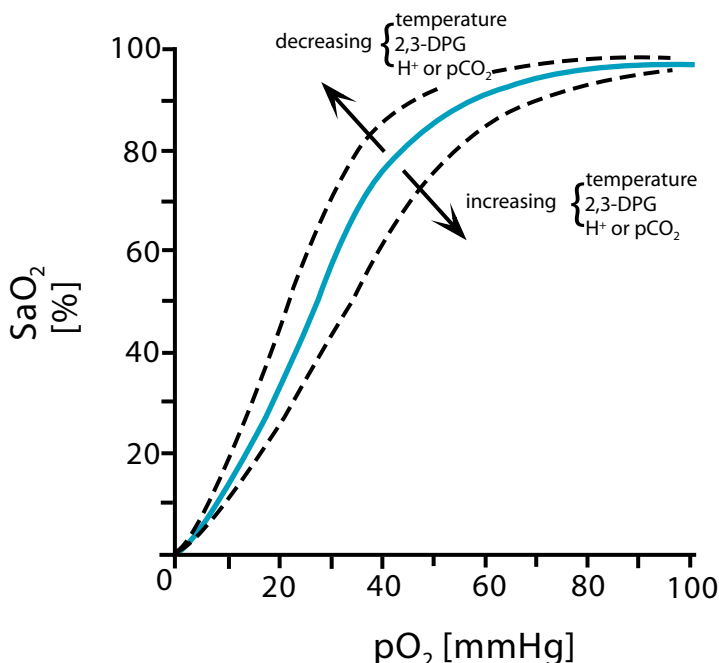


Figure 5-9 The hemoglobin-oxygen dissociation curve. The plateau at the upper end signifies a stable, near-maximal saturation, despite wide variations in alveolar pO_2 . The steep portion between 15 and 45 mm Hg results from the unloading of O_2 from oxyhemoglobin as pO_2 decreases in tissues. The effect of increasing or decreasing temperature, 2,3-DPG, or $[H^+]$ are shown as dashed lines. 2,3-DPG = 2,3-diphosphoglycerate.

exposed in the alveolar capillaries to the high pO_2 of inspired air. Oxygen moves down its partial pressure gradient and combines rapidly with hemoglobin in red cells to form oxyhemoglobin.

At any one pO_2 , the affinity of hemoglobin for O_2 is importantly affected by three factors: temperature, [2,3-DPG],** and $[H^+]^{\dagger\dagger}$ (or pCO_2).

An increase in temperature, [2,3-DPG], or $[H^+]$ (often resulting from an increase in pCO_2) will shift the curve to the right because such changes reduce the affinity of hemoglobin for O_2 . Decreases in temperature, [2,3-DPG], or $[H^+]$ (often resulting from a decrease in pCO_2) will shift the dissociation curve to the left because such changes increase hemoglobin's affinity for O_2 , thereby inhibiting O_2 release.

These shifts in the hemoglobin dissociation curve are often beneficial. For example, pCO_2 (and, therefore, $[H^+]$) is high in tissues. The resultant

**2,3-Diphosphoglycerate is an intermediary product in the conversion of glucose to pyruvate and is present in red cells at high concentration.

†† The rightward shift of the dissociation curve by increased $[H^+]$ is called the **Bohr effect**.

decrease in hemoglobin affinity for O_2 means that additional oxygen can be released from hemoglobin binding and be available for the tissue. O_2 binding effects arising from such agents as carbon monoxide or Fe^{+++} are described in Chapter 3, "Blood."

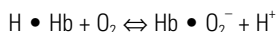
Carriage of Carbon Dioxide

Carbon dioxide, like O_2 , is carried in blood both in physical solution and chemical combination. As indicated in Figure 5–8, a given volume of blood carries more CO_2 than O_2 , both in chemically combined and physically dissolved forms.

The quantity of hemoglobin-associated CO_2 at a given pCO_2 is decreased greatly if the coexistent oxygen saturation is increased. This is known as the **Haldane effect**.

The Haldane Effect

The mechanisms of both the Haldane and Bohr effects reside in the acidity of hemoglobin in its oxygenated and deoxygenated states. The equilibrium between the two is represented by the reaction



The equation shows that (1) oxygenated hemoglobin ($Hb \bullet O_2^-$) is a stronger acid than deoxygenated hemoglobin ($H \bullet Hb$). Therefore, oxygenation of $H \bullet Hb$ will release H^+ (Figure 5–10). The released H^+ will combine with HCO_3^- and form H_2CO_3 , which dissociates and releases CO_2 from chemical binding. Increasing $[H^+]$ will shift the reaction to the left, thereby releasing O_2 from its association with hemoglobin.

Forms of Carbon Dioxide

Carbon dioxide is carried in blood in three forms: 90%^{**} is transported as HCO_3^- , about 5% is transported in chemical association with hemoglobin (carbamino hemoglobin, $Hb \bullet NH \bullet COO^-$) (Figure 5–11), and 5% is carried as dissolved gas.

Only about 0.001 of total CO_2 is carried as H_2CO_3 . HCO_3^- is the dominant CO_2 carrier because CO_2 readily combines with water to form carbonic acid, H_2CO_3 , which dissociates readily into H^+ and HCO_3^- :



^{**}Percentages refer to arterial blood. In venous blood, the relevant percentages are 60%, 35%, and 5%, respectively.

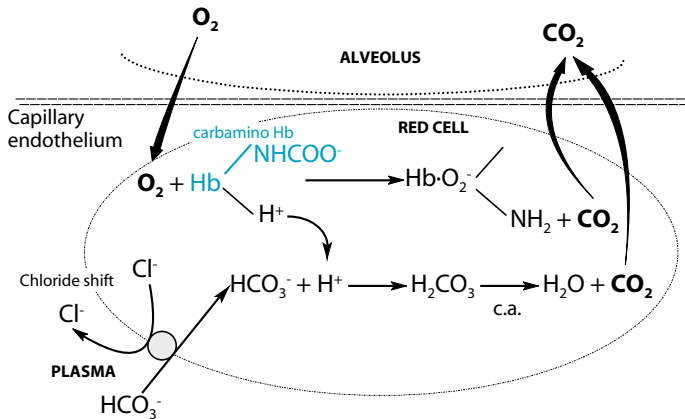


Figure 5-10 Gas exchange between an alveolus and a red blood cell. O_2 moves down its partial pressure gradient, enters capillaries, and combines rapidly with hemoglobin (Hb) in red cells to form oxyhemoglobin (HbO_2^-). In comparison with carbaminohemoglobin, oxyhemoglobin is a stronger acid and a weaker CO_2 binding agent. As a result, free H^+ and CO_2 are released from oxyhemoglobin. CO_2 diffuses down its partial pressure gradient into the alveolus to be blown off in expired air. H^+ , released from oxyhemoglobin, combines with HCO_3^- and quickly yields CO_2 because of the presence of carbonic anhydrase. As HCO_3^- is used up to form H_2CO_3 , more of it enters the red cell from plasma in exchange for Cl^- by way of the band 3 protein HCO_3^-/Cl^- exchanger. This exchange is called the chloride shift.

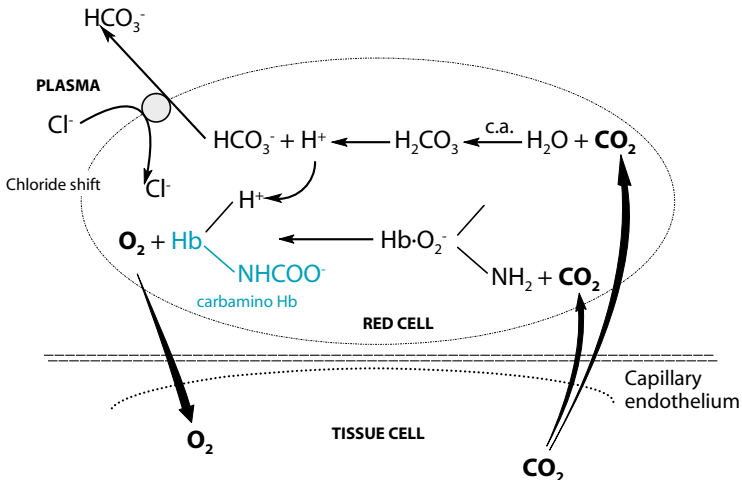


Figure 5-11 Gas exchange between tissue cells and a red blood cell. CO_2 enters tissue capillaries down its partial pressure gradient. Carbonic anhydrase (found in red cells, but not in plasma) catalyzes the formation of H_2CO_3 . H_2CO_3 dissociates to HCO_3^- and H^+ . HCO_3^- diffuses out of the red cell and is replaced by Cl^- in the chloride shift. The H^+ ions are buffered by nonoxygenated hemoglobin. CO_2 also reacts with amino groups in hemoglobin to form carbaminohemoglobin. O_2 , carried reversibly by oxyhemoglobin, moves down its partial pressure gradient, enters tissue cells, and leaves nonoxygenated hemoglobin behind. Nonoxygenated hemoglobin is then available to accept H^+ and CO_2 .

Gas Exchange

Between Air and Blood in the Lungs

Systemic venous blood, with a pO_2 near 40 mm Hg and a pCO_2 near 45 mm Hg, reaches the alveolar capillaries, where it is brought close to alveolar air with pO_2 near 100 mm Hg and a pCO_2 near 40 mm Hg. The pressure gradients cause O_2 to diffuse into the capillaries and CO_2 to diffuse out of the capillaries (see Figure 5–10). Oxygenation of hemoglobin causes H^+ to be dissociated and to combine with HCO_3^- , leading eventually to the production of CO_2 . All binding reactions are driven toward free CO_2 (see Figure 5–10). The rate-limiting steps are the chloride shift and dehydration of H_2CO_3 to form H_2O and CO_2 .

Between Cells and Blood in the Tissues

Systemic arterial blood arrives in tissue capillaries with a pO_2 near 95 mm Hg and a pCO_2 near 40 mm Hg. Cytosolic pO_2 is between 5 and 50 mm Hg and pCO_2 is slightly higher than 45 mm Hg. O_2 enters cells and CO_2 enters tissue capillaries, each down its partial pressure gradient (see Figure 5–11). Carbonic anhydrase, found in red cells but not in plasma, catalyzes the conversion of CO_2 eventually to HCO_3^- . H^+ , produced in the reaction, is bound by deoxygenated hemoglobin. CO_2 also reacts with the amino groups in hemoglobin and forms carbamino hemoglobin.

PULMONARY CIRCULATION

The pulmonary vascular bed is characterized by low perfusion pressures because it is of low resistance but accommodates nearly all of the cardiac output perfusing all the other organs. The small discrepancy from left ventricular output arises from two shunt flows that convey blood directly to the left atrium without passing through the right ventricle and the ventilatory areas of the lungs. They are (1) shunts between some bronchial and pulmonary capillaries and (2) some coronary vessels that empty directly into the chambers of the left heart.

Hypoxic Vasoconstriction

In most vascular beds, hypoxia, hypercapnia, or locally increased $[H^+]$ causes pronounced vasodilatation. However, such changes, whether presented in pulmonary arteriolar blood or in alveolar gas, will act directly on pulmonary vascular smooth muscle and produce constriction. When such constriction occurs in response to changes in alveolar gas, it is a protective mechanism in that it shunts blood away from poorly ventilated alveoli.

Similarly, reduction of blood flow to an area will cause local alveolar $p\text{CO}_2$ to decline, and this causes bronchial constriction in that area so that ventilation is diverted toward regions that are better perfused.

Effects of Gravity on Pulmonary Perfusion

Normal pulmonary arterial pressure is 25/10 mm Hg, with a mean pressure near 15 mm Hg (20 cm H_2O) above atmospheric pressure. This value is so low that the effects of gravity on local hydrostatic pressure are significant. Pulmonary arterioles, capillaries, and venules that are located in the apex, more than 10 cm above heart level, can have an intravascular hydrostatic pressure below 0 mm Hg (Figure 5–12). Vessels near the base of the lungs are, in the upright posture, situated below heart level and have higher pressure than those at the apex.

As a result of this vertical intravascular hydrostatic pressure gradient, blood flow and blood volume in certain regions of the lungs can be affected by respiratory pressure fluctuations and by postural changes. (1) In apical regions, where alveolar pressure exceeds pulmonary venous pressure, blood flow will be determined by the difference between pulmonary arterial pressure and alveolar pressure, not by the difference between arterial and venous pressures. (2) Near the base of the lungs, elevated hydrostatic pres-

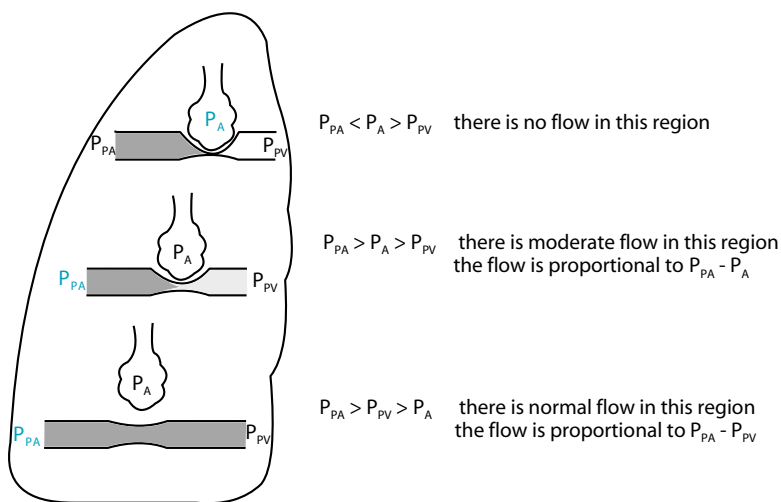


Figure 5–12 In an upright person, the apex of the lung is located several cm above the heart. Therefore, the hydrostatic pressure in pulmonary arterioles and venules (P_{PA} and P_{PV} , respectively) can be lower than alveolar pressure (P_A). This can lead to poor perfusion of the lung apex.

sure in the upright position tends to expand blood vessels and, thereby, tends to increase the local blood volume.

Matching Ventilation to Perfusion

The most significant factor determining the partial pressure of any respiratory gas in pulmonary venous and, therefore, systemic arterial blood is the ventilation/perfusion ratio of the lungs. An arterial-to-alveolar difference in pO_2 and pCO_2 can arise if there is a difference in the ratio of ventilation (\dot{V}_A) to perfusion (\dot{Q}) in any one region, even though there is complete alveolar/capillary equilibration in each of the regions.

Lung units that are overperfused in relation to their ventilation ($\dot{V}_A/\dot{Q} < 1$) will show high pCO_2 and low pO_2 in their capillary blood and contribute a disproportionately large amount of blood to the pulmonary outflow. Such units will cause a systemic elevation of pCO_2 and depression of pO_2 , just as if gas diffusion across the entire capillary/alveolar interface of the lungs were impaired.

In normal individuals, ventilation/perfusion inequalities typically bring about arterial pO_2 and pCO_2 that are 5 to 10 mm Hg lower and 2 to 4 mm Hg higher, respectively, than they are in alveolar gas. This inequality arises partly from vertical ventilation/perfusion inequalities, partly from the **dead space**, and partly from veno-arterial shunts in the bronchial and coronary vasculature.

Vertical Ventilation/Perfusion Inequalities

Both ventilation and perfusion decrease from the base toward the apex in the upright lung, but the change in ventilation with height above the heart level is much less than that in perfusion (Figure 5–13). As a result, (1) the ventilation/perfusion ratio is lower near the base of the lungs than at the apex, (2) the extent of capillary–alveolar gas diffusion is lower near the base of the lungs, and (3) pulmonary venous pO_2 is lower and pulmonary venous pCO_2 is higher near the base of the lungs. These unequal vertical gradients in ventilation and perfusion are responsible for the observation that pO_2 in pulmonary venous blood is generally lower than alveolar pO_2 .

Dead Space (Physiologic and Anatomic)

Physiologic dead space is the volume of inspired gas that does not equilibrate with blood ($\dot{V}_A/\dot{Q} = 0$). In healthy individuals, it consists mostly of **anatomic dead space**, which is the volume contained in the conducting airways, down to the level of the bronchial tree (see Figure 5–1). Inspired gas

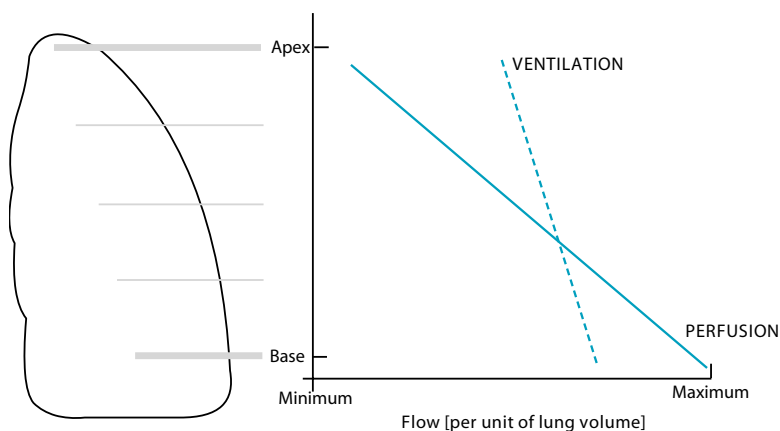


Figure 5-13 In an upright person, both ventilation and perfusion decrease toward the apex of the lung, but perfusion decreases more rapidly.

that remains in the anatomic dead space is expired without change in composition, except for added water vapor. Its volume in the resting adult is near 150 mL. Physiologic dead space can be increased by **shunting** of blood.

Shunt or Venous Admixture

Short circuiting of blood so that it bypasses the gas exchange regions of the lungs leads to admixture of venous blood to arterialized blood and a consequent decrease in arterial pO_2 . In normal individuals, the shunt amounts to a few percent of pulmonary blood flow and results in a difference of no more than 10 mm Hg between arterial and alveolar pO_2 .

NEURAL CONTROL OF RESPIRATION

The intrapleural pressure fluctuations that cause air to flow into and out of the lungs result from periodic contractions and relaxations of respiratory muscles. These muscles are innervated by motor neurons that are driven by a rhythm-generating network in the lower brainstem. The activity of the central respiratory network is adjusted both by inputs from higher nervous centers and sensory feedback from the periphery.

The control of intrathoracic volume by muscles of inspiration and expiration runs parallel to the control of upper airway dimension. The diameter of the upper airway (pharynx, larynx, trachea, and bronchial tree) determines airway resistance and is the main mechanism for controlling the rate of exhalation so that special respiratory patterns, such as coughing, sneezing, laughter, and speech, become possible.

Generation of the Respiratory Rhythm

The neural rhythm of respiration consists of periodic activation of inspiratory muscles^{§§} and expiratory muscles^{|||} (Figure 5–14). These patterns are controlled by a brainstem neural network. Three areas in the **ventral respiratory group** are of particular importance: the **nucleus ambiguus** (see Figure 4–2) and, surrounding it, the **pre-Bötzinger** and **Bötzinger complexes**. These areas are in close proximity to the cardiovascular control areas, and they consist of various populations of neurons that differ by the timing and pattern of their discharge relative to phrenic nerve activity. Discharges in the ventral respiratory group are modulated by neurons of the **dorsal respiratory group**. They are located near the nucleus tractus solitarius (see Figure 4–2) and probably receive input from the peripheral afferents.

Although the origin of the respiratory rhythm has not yet been established with certainty, it is likely to be a network of reciprocally interconnected neurons with oscillatory responses to activation from outside the network.

System Control Loops

The rate and depth of the basic respiratory rhythm are set by brainstem neurons and are modulated by other central nervous system areas and by peripheral needs.

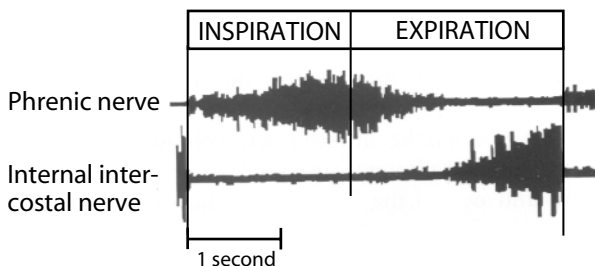


Figure 5–14 Respiratory rhythm as revealed by muscle neurograms. Phrenic nerve activity is representative of inspiratory muscle activation. It increases progressively during inspiration and decreases gradually during early expiration so that the passive expiratory collapse of thoracic volume is a gradual process. Nerves supplying expiratory muscles like the internal intercostals are normally silent during quiescent, restful breathing. When they are active at higher respiration rates or during forceful exhalation, they are active in the latter half of expiration.

^{§§}Inspiratory muscles include the diaphragm, which is innervated by the phrenic nerve, whose motor neurons are located in the ventral horns from C3 to C5, and the external intercostal muscles, whose motor neurons are located in ventral horns along the thoracic cord.

^{|||}Expiratory muscles include the internal intercostal muscles. Their motor nerves also originate from the thoracic cord.

Central Nervous System Modulation of Ventilation

Four central nervous system areas are significantly involved in adapting breathing patterns to special circumstances: (1) The **hypothalamus** adjusts breathing to whole-body needs arising from physiologic states such as exercise or sleep; (2) the **limbic forebrain** initiates breathing patterns that have emotional connotations, including surprise gasps or languorous sighs; (3) the **motor cortex** issues breathing program modifications for the purpose of generating speech and for volitional control over breathing; and (4) the **cerebellum** participates in breathing modulations associated with postural changes.

Peripheral Modulation of Ventilation

The respiratory tract from the nasal submucosa to the pulmonary interstitium is supplied with receptors that initiate a number of reflex responses, including defense reflexes.

Stretch receptors and stretch reflexes. The airways and the lung parenchyma, especially the region of the bronchial branches, contain nerve endings whose discharge frequency increases linearly with increasing lung volume. Selective stimulation of the afferents during inhalation initiates two responses: (1) inspiration is terminated, and the respiratory phase is switched to expiration; and (2) the tracheobronchial smooth muscle relaxes, and this dilates the airways. These responses are called the **Hering-Breuer reflex**. It originates in slowly adapting stretch sensors.

The Hering-Breuer reflex is easily demonstrated in animals, in which interruption of the afferent nerves leads to a characteristic change in breathing pattern toward slow, deep breathing that is thought to be regulated by chemical factors. Stretch reflexes are not evident in humans at normal tidal volume. Therefore, the switch from inspiration to expiration in normal human breathing is determined by central nervous system mechanisms alone. Stretch reflexes can become activated at inspiratory depths above 1,000 mL, which is within the range of inspiratory reserve volume (see Figure 5–3).

Chemosensors and chemo-reflexes. Chemosensitive neurons are located centrally (in the medulla) as well as peripherally (in the carotid bodies).^{##} They respond, with different sensitivities, to changes in pO_2 , pCO_2 , or $[H^+]$ of tissue fluid or blood. The importance of chemo-reflexes to respiratory function is suggested by the overall outcomes of respiratory control.

^{##}Chemosensitive cells are also located in the aortic bodies, but they appear to have no role in normal human respiratory control.

Overall outcome of respiration. The function of the respiratory system accomplishes three outcomes: (1) alveolar $p\text{CO}_2$ is held constant, (2) excess plasma $[\text{H}^+]$ is eliminated, and (3) arterial $p\text{O}_2$ is raised when it falls to dangerously low levels.

Of these three, the influence of CO_2 is paramount in the regulation of breathing. CO_2 is produced continuously in the Krebs cycle during metabolism in all cells. Additional CO_2 is formed when H^+ is produced during anaerobic metabolism.

Metabolic hyperbola. The chemical composition of alveolar gas or arterial blood is a function of metabolic CO_2 production and alveolar ventilation. At any rate of CO_2 production, alveolar $p\text{CO}_2$ decreases as alveolar ventilation increases, and the relationship between the two is described by the metabolic hyperbola (Figure 5–15).

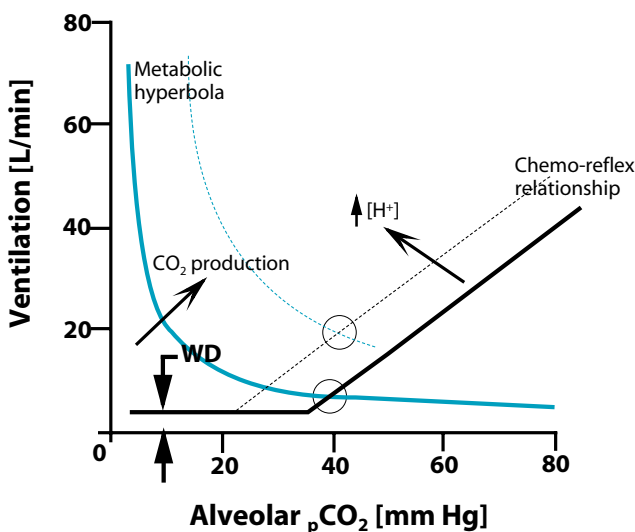


Figure 5–15 Without chemo-reflexes, the relationship between ventilation and alveolar $p\text{CO}_2$ is described by the metabolic hyperbola. When CO_2 production is constant, alveolar $p\text{CO}_2$ decreases in hyperbolic fashion with increasing ventilation. Different rates of metabolic CO_2 production will yield a family of metabolic hyperbolas, parallel-shifted to the right (*interrupted colored curve*). As a result of chemo-reflexes, ventilation increases with increasing $p\text{CO}_2$ above a threshold near 35 mm Hg (*solid black curve*). The horizontal portion of the curve is a basic ventilatory drive that is present in wakefulness only. The two relationships are simultaneously satisfied at an alveolar $p\text{CO}_2$ of 40 mm Hg during basal CO_2 production. During exercise, when there is an increase in both CO_2 production (*interrupted colored line*) and blood $[\text{H}^+]$, the new steady state is achieved at a higher ventilation, but with little change in alveolar (or arterial) $p\text{CO}_2$. WD = wakefulness drive.

Chemo-reflexes.

Central chemosensors: Chemosensitive neurons with influence over ventilation are located in the medulla, close to, but separated from, the neurons generating the respiratory rhythm. Chemosensitive neurons monitor $p\text{CO}_2$ in the cerebrospinal fluid but change their discharge frequency only after CO_2 has crossed the neuronal plasma membrane and has been hydrated and then dissociated to form H^+ in the cytosol.

Peripheral chemosensors: The sensing portion of the carotid body is granular **type I cells**, also called **glomus cells**, to which the terminal fibers of the carotid sinus nerve are attached. The granules contain catecholamines, and they are released on receptor stimulation. During normal respiration, the function of the carotid sinus appears to be that of a sensitive CO_2 detector whose sensitivity is controlled by $p\text{O}_2$:

- At normal $p\text{O}_2$, peripheral chemosensors contribute only about 10% of the overall ventilatory drive.
- If arterial $p\text{O}_2$ is raised higher than 100 mm Hg, the carotid body chemosensor is turned off.
- When $p\text{O}_2$ falls below 100 mm Hg, the CO_2 sensitivity of the carotid sensors increases progressively. Their response to $p\text{O}_2$ itself (at constant $p\text{CO}_2$) is small unless there is extreme hypoxia.

Responses to blood $p\text{CO}_2$: An increase in the rate of chemosensor discharge augments ventilation by the activation of inspiratory and expiratory brain-stem neurons. As ventilation increases, CO_2 is removed and alveolar $p\text{CO}_2$ falls in accordance with the metabolic hyperbola (see Figure 5–15). Steady state is reached when the metabolic hyperbola and the chemo-reflex relationship are both satisfied (see Figure 5–15).

Responses to blood $[\text{H}^+]$: Changes in blood acidity are additive to the $p\text{CO}_2$ chemo-reflex relationship (see Figure 5–15) and cause a parallel shift of the relationship. This changes the threshold to a lower value of $p\text{CO}_2$ but does not change the sensitivity of the reflex. For example, increased blood $[\text{H}^+]$, such as might be observed during exercise, would shift the relationship to the left (see Figure 5–15), and this leftward-shifted curve intersects the rightward-shifted metabolic hyperbola of increased CO_2 production at a steady-state $p\text{CO}_2$ that is not far from 40 mm Hg.

Ventilation and acid-base balance: When acids are produced in the body, a large fraction of them is buffered by combination of their H^+ with HCO_3^- in the body fluids to produce H_2CO_3 . H_2CO_3 , in turn, dissociates to form CO_2 and H_2O . CO_2 stimulates ventilation and, thereby, helps convert harmful free hydrogen ions (H^+) into harmless H_2O .

Responses to blood pO_2 : The ventilatory response to changing arterial pO_2 represents a defense against extreme hypoxia because at normal and constant pCO_2 , there is little increase in ventilation until pO_2 falls to near 50 mm Hg. However, as described above, arterial pO_2 modulates the sensitivity of the reflex response to pCO_2 .

Irritant receptors and defense reflexes: There is an abundance of rapidly adapting receptors throughout the airways and the lung parenchyma. They have mostly vagal afferent fibers and respond with short volleys of action potentials to stimuli, such as fast lung inflation or deflation, irritants, such as airborne powders or chemicals, bloodborne chemicals, lung congestion, or mechanical irritation of the nasal passages.

Airway defense reflexes elicit protective responses when harmful agents or stimuli are brought to the respiratory system:

- Coughing and bronchoconstriction are elicited by mechanical, chemical** or cold stimuli acting on the subepithelial laryngeal and tracheal receptors. Intrathoracic pressure of up to 300 mm Hg and tracheal air flow velocities near the speed of sound are achieved by coordinated brief inspiration, short occlusion of the glottis, and strongest possible expiration.
- Sneezing (and sniffing)** are elicited by, respectively, mechanical or chemical stimulation of receptors in the nasal submucosa.
- Initial apnea is followed by rapid, shallow breathing when pulmonary “J” receptors are stimulated. J receptors are located in the region between the capillaries and alveolar wall and are stimulated by mechanical or chemical stimuli, including pulmonary edema and lung collapse.

SPECIAL RESPIRATORY RESPONSES

Breath Holding

Voluntary breath holding can be maintained for 60 to 90 seconds and is terminated at the **breaking point** when pCO_2 has increased or pO_2 has decreased to a sufficient level. The breaking point can be delayed for as long as 140 seconds by deliberate, preparatory lowering of pCO_2 , such as during voluntary hyperventilation. This can be a dangerous practice.

Many cases of swimming pool drowning occur when divers attempt to prolong their breath-holding time by vigorous hyperventilation before they dive. During this maneuver, pCO_2 can be lowered sufficiently so that hypoxia

**Including histamine, bradykinin, prostaglandins E_2 and I_2 , and air pollutants, such as sulfur dioxide.

**Sniffing is generally brought on by pleasant fragrances and serves exploration rather than defense.

causes underwater fainting before the respiratory breaking point is reached. When it is reached, water is aspirated, and death by drowning follows quickly.

Hiccough (Hiccup)

This is caused by a spasmodic contraction of the diaphragm with simultaneous, temporary closure of the glottis.

Yawning

This respiratory act is caused in a variety of settings, the common denominator for which may be poor cerebral oxygenation. Thus, it often precedes an orthostatic faint or fainting caused by poor air quality in confined spaces. Its cause during tiredness is uncertain. Its physiologic purpose may be supranormal air intake either to increase oxygen intake or to expand partially collapsed alveoli.

Hypoxia

Hypoxia is defined as oxygen deficiency at the tissue level, and it is often subclassified according to one of four possible causes: (1) reduced arterial pO_2 (= hypoxic hypoxia), (2) reduced hemoglobin but normal arterial pO_2 (= anemic hypoxia), (3) inadequate blood flow but normal hemoglobin and arterial pO_2 (= ischemic hypoxia), and (4) compromised O_2 utilization by cells (= histotoxic hypoxia).

Hypoxic Hypoxia

Hypoxic hypoxia results when the oxygen transport systems function normally but inspired air has a low pO_2 , such as air at altitude.

At sea level, the pO_2 of alveolar air is near 150 mm Hg, and this falls to about 50 mm Hg at 9,000 m, a level that can be tolerated after acclimatization but leads to unconsciousness in unacclimatized individuals. Sudden exposure to altitudes above 3,000 m (alveolar pO_2 = 100 mm Hg) can cause **mountain sickness**. This lasts for about a week and is characterized by breathlessness, irritability, insomnia, headache, nausea, and vomiting. Severe cases include pulmonary and cerebral edema. Mountain sickness occurrence and severity appear to be directly related to cerebral edema, and they are much reduced in those who develop diuresis at altitude.^{***}

^{***}Altitude diuresis is presumably a result of increased activation of atrial stretch sensors secondary to increased venous return caused by hyperventilation-induced respiratory "pumping" (see Neural Control of Cardiovascular Function in Chapter 6).

Compensatory responses to altitude include (1) increased ventilation, (2) increased erythropoietin secretion and, consequently, increased erythrocyte production, (3) increased numbers of mitochondria, and (4) increased muscle content of myoglobin, which is a muscle protein that is capable of binding oxygen reversibly.

Anemia

A state of anemia is said to exist when the blood hemoglobin concentration falls more than 2 g/dL below the normal level (16 g/dL for males; 14 g/dL for females). The reduced O_2 transport capacity of anemia is not generally a problem at rest because of increased 2,3-DPG levels,^{§§§} which shifts the O_2 -hemoglobin dissociation curve (see Figure 5–9) to the right.

Carbon Monoxide Poisoning

Carbon monoxide avidly reacts with hemoglobin to form **carboxyhemoglobin**, which (1) is cherry red in color, (2) cannot bind oxygen, and (3) shifts the dissociation curve (see Figure 5–9) of the remaining oxyhemoglobin to the left so that less of the bound O_2 is released at tissue pO_2 . Nevertheless, arterial pO_2 and pCO_2 remain normal, and ventilation is not stimulated until a very large fraction of hemoglobin has been bound as carboxyhemoglobin.

Cyanide Poisoning

Cyanide poisoning is the most common form of histotoxic hypoxia. Cyanide inhibits cytochrome oxidase, a vital enzyme for oxidative phosphorylation.

Responses to Respiratory Abnormalities

Asphyxia

Asphyxia results when the airway is occluded. Arterial pO_2 and pCO_2 rise together, and there is violent stimulation of respiration and sympathetic nervous activity in response to central hypoxia (**Cushing response**).

^{§§§}The stimulus for increased 2,3-DPG production in anemia may be higher levels of deoxyhemoglobin and preferred binding of 2,3-DPG to deoxyhemoglobin. This causes more 1,3-DPG to be converted to 2,3-DPG and then to 3-PG rather than be converted to 3-PG directly.

Drowning

In a submerged, drowning person, the instinct not to breathe under water is so strong that it overrides chemical stimuli and inhalation is not attempted until the break point is reached at the edge of consciousness. When a breath is attempted, water is drawn into the region of the glottis. In about 10% of drowning victims, the water induces an intense laryngospasm, the airway is obstructed, and the person dies of asphyxia without water ever entering the lungs. In the remainder of victims, the glottis relaxes, and water, containing only dissolved O_2 , enters the alveoli. In fresh-water drownings, the water is quickly transferred to cells, including red cells, and causes them to swell to bursting. In saltwater drownings, the hypertonicity of seawater draws fluid out of cells and out of the capillaries.

When there is water in the lungs, insufficient oxygen is transferred, and hypoxic vasoconstriction decreases pulmonary blood flow and left heart filling. The ultimate cause of death is heart failure.

Cheyne-Stokes Respiration

This is a kind of periodic breathing characterized by periods of apnea lasting 5 to 20 seconds and separated by periods of hyperventilation, during which tidal volume at first increases and then decreases (Figure 5–16). This breathing pattern is often seen in healthy people during sleep at altitude or in several disease states. The pattern represents an instability of the respiratory control system that may be brought on by hypersensitivity to CO_2 without a change in threshold pCO_2 . In this setting, periods of hyperventilation would

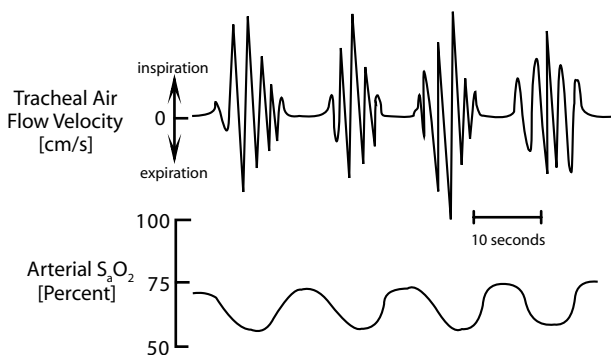


Figure 5–16 An example of Cheyne-Stokes respiration, as recorded by tracheal air flow velocity. As a result of the bouts of hyperventilation, separated by periods of apnea, hemoglobin saturation in arterial blood fluctuates as well and with a time delay.

lower $p\text{CO}_2$ below the threshold, causing apnea, until the chemoreflex is triggered again and, once triggered, responds with increased sensitivity. Cheyne-Stokes respiration is also brought on when circulation time is increased so that there is an increase in the time it takes chemical signals to reach the brain.

Oxygen Toxicity

When 80 to 100% O_2 is administered to humans for more than 8 hours, the respiratory passages become irritated, leading to sore throat and coughing. Longer exposures or exposure at higher pressure also cause noticeable lung damage, muscle twitching, dizziness, and convulsions. These toxic effects of oxygen are thought to arise from increased production of oxygen free radicals (O_2^-).

Nitrogen Narcosis

Divers breathing compressed air so as to counteract the high ambient water pressure may suffer from **nitrogen narcosis** (rapture of the deep), a condition of perceived euphoria that arises from high partial pressure of nitrogen in blood. The cause is a central nervous system effect of high $p\text{N}_2$, but the precise mechanisms are not yet known. They can be ameliorated if helium, instead of nitrogen, is mixed with oxygen. This allows diving to greater depths but increases the risk of **high-pressure nervous syndrome**, a condition that is characterized by tremors and drowsiness.

Sleep

Sleep is characterized by (1) inhibition of skeletal muscle activity (including respiratory muscles), (2) relaxation of muscles in the upper respiratory tract (tongue and epiglottis), (3) reduced sensitivity of the ventilatory response to $p\text{CO}_2$, and (4) removal of the wakefulness drive that maintains resting ventilation at a basal level near 5 L/min (see Figure 5–15). At their most benign, these changes bring about mild snoring. At their worst, they cause sleep apnea, a syndrome in which the patient repeatedly stops breathing during sleep and resumes breathing only after arousal. Such patients show daytime signs of sleep deprivation and often develop hypertension.

Exercise

Proprioceptive, psychological, and chemical factors contribute to the increased ventilation that is characteristic of exercise (Figure 5–17). When switching from rest to a steady level of exercise, ventilation increases abruptly at first and exponentially after the initial step. The abrupt increase

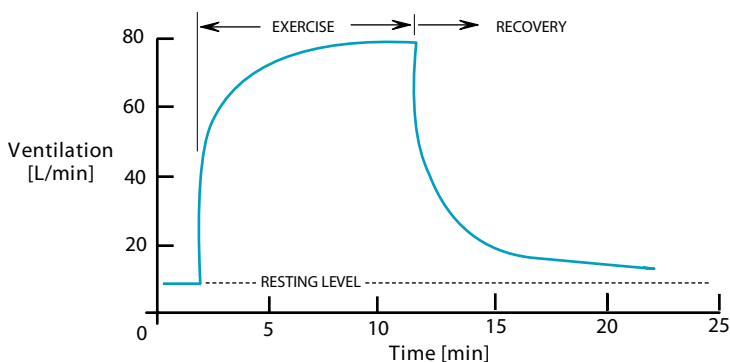


Figure 5-17 Ventilation increases rapidly to a plateau at the onset of exercise and is maintained at the elevated rate for the duration of exercise. When exercise stops, there is an initial rapid return of ventilation toward the resting level, but complete restoration of basal conditions does not occur for several minutes.

is caused by psychological and volitional factors, whereas subsequent increases are driven by the chemo-reflex response.

As exercise continues, adaptations within exercising muscle increase O_2 extraction, and increased ATP production leads to increased cellular output of CO_2 and lactic acid. The extent to which cardiorespiratory adaptations are able to meet the O_2 transport demands of exercise depends on exercise severity.

For exercise below the lactate threshold^{|||||} of about 90 watt, there is a linear increase in ventilation with exercise severity. At such exercise levels, CO_2 and H^+ stimulate ventilation, and decreased venous pO_2 increases the alveolar air–pulmonary capillary O_2 gradient. Increased diffusion and increased pulmonary blood flow (arising from increased cardiac output) lead to a linear increase of oxygen uptake from its resting value of 0.3 L/min up to 4 L/min with increasing work. In this range, the respiratory system behaves as if it responded to demands for CO_2 elimination and pCO_2 and pO_2 are regulated at or near their resting levels (see Figure 5-15).

For exercise above the lactate threshold, additional CO_2 is produced because H^+ from lactic acid is buffered by HCO_3^- , forming H_2CO_3 , which then is converted to CO_2 and H_2O . The additional CO_2 and H^+ provide a further stimulus to ventilation, and arterial pCO_2 continues to be maintained near normal, whereas arterial pO_2 increases up to about 110 mm Hg at a workload of 180 watt.

^{|||||}The lactate threshold defines a level of exercise above which there is a sustained metabolic acidemia, due mostly to lactic acid produced in anaerobic metabolism.

Cessation of exercise. After exercise ceases, ventilation does not immediately return to resting values even though arterial blood gases are at normal, resting levels. The continuing drive is provided by elevated extracellular $[H^+]$ and ceases only when $[H^+]$ is normal again. This is called **repaying the oxygen debt**.

Fatigue. The sensation of fatigue that follows heavy exercise or intense mental effort is thought to be caused by both acidosis of the cerebrospinal fluid and responses to action potentials in muscle afferents.

Fitness

How do we rate system performance? Degree of fitness is directly related to the lactate threshold or to maximum O_2 uptake ($=V_{O_{2\max}}$): (1) a fitter person is able to perform higher levels of work before there is the onset of progressive acidemia and (2) a fitter person usually also has a higher $V_{O_{2\max}}$.

In an untrained person, $V_{O_{2\max}}$ is typically near 40 mL/kg•min. This can increase to about 60 mL/kg•min during the first 6 months of training and then will not increase further in spite of continuous training and will not reach the levels that are seen in endurance athletes (near 80 mL/kg•min). $V_{O_{2\max}}$ is often predicted by means of an **Astrand work test** from heart rate changes that accompany exercise.

The Astrand fitness test. This test is performed at a work load that is below the aerobic threshold and relies on three assumptions: (1) there is a linear relationship between heart rate and work performed for any individual; (2) there exists a maximum heart rate that corresponds to maximal work, and this heart rate (though not the work performed) is the same for everyone of that age and gender; and (3) the slope of the heart rate/work load graph is the same for all members of the population.

As a consequence of these assumptions, if a subject's heart rate is measured at a selected work load, even though this work load is submaximal, the subject's maximum work capacity can be predicted from published tables and can be converted to a predicted $V_{O_{2\max}}$, which is an important measure of overall cardiopulmonary fitness.

Cardiovascular Physiology

The cardiovascular system functions primarily to transport gases, nutrients, chemical messengers, heat, and immunologic elements toward target tissues and to remove from those tissues the chemical and thermal products of their metabolism. A secondary function is periodic engorgement of certain organs to the extent that sex education has become necessary. The system consists of the heart, blood vessels, and components that regulate their functions. The transport medium is blood, and it is pumped in a continuous circuit from the left heart, through the tissues, and back to the right heart (Figure 6–1).

THE HEART

Gross Anatomy

The heart comprises two interactive muscular pumps, the right and left ventricles. They are each filled by way of an atrium and eject blood into the pulmonary artery and aorta, respectively.

Fibrous Skeleton and Muscle Fibers

The skeleton of the heart is formed by four interconnected fibrous rings (annuli) that serve as attachment points for the valve leaflets as well as the points of origin and termination of the muscle fibers that encircle each of the four cardiac chambers (Figure 6–2).

Cardiac Muscle

Microanatomy

A mature cardiac muscle cell is up to 100 μm long and 25 μm in diameter. It contains numerous myofibrils, which are chains of sarcomeres, the fundamental contractile unit (Figure 6–3). Many have two nuclei. The sarcom-

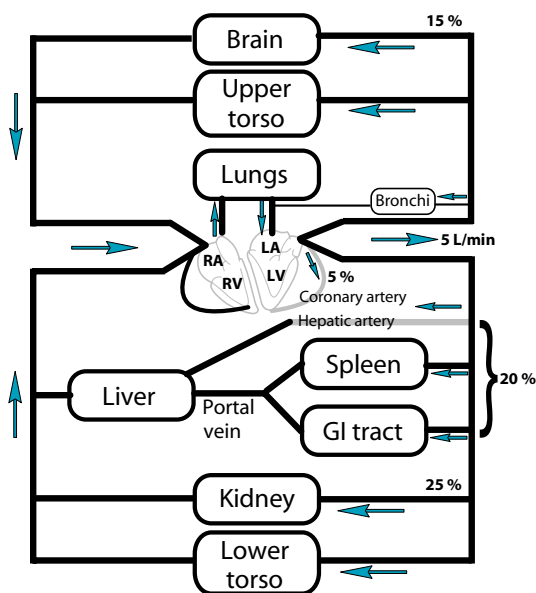


Figure 6–1 Schematic of the cardiovascular system. Resting cardiac output in humans is near 5 L/min, and its approximate distribution to different tissues is indicated.

ere length typically ranges between 1.5 and 2.2 μm , contraction to relaxation. Myocytes are coupled to one another by a net-like collagen matrix.

Differences from skeletal muscle. Cardiac muscle is striated muscle. Its contractile proteins are actin and myosin, and its regulatory proteins are tropomyosin and troponin-T, -C, and -I. Its microanatomy differs from that of skeletal muscle in that it has (1) only one or two centrally located nuclei as opposed to the several nuclei of skeletal muscle cells; (2) extensive cross connections between adjacent fibers (see Figure 6–3); (3) gap junctions between adjacent cells (gap junctions are a part of the intercalated discs) (see Figure 6–3); and (4) fewer but larger T-tubules (one per z-line).

Transverse tubular system. Ventricular myocytes have a well-developed system of sarcolemmal invaginations (T-tubules) that penetrate into the muscle fiber and course between myofibrils. They are so numerous that they constitute 40 to 50% of the surface area in ventricular myocytes. By contrast, in atrial myocytes, the T-tubules make up only 10 to 20% of the surface area. Several membrane proteins are localized preferentially in the T-tubules. Particular examples are the $3\text{Na}^+/\text{Ca}^{++}$ exchanger and L-type Ca^{++} channels.

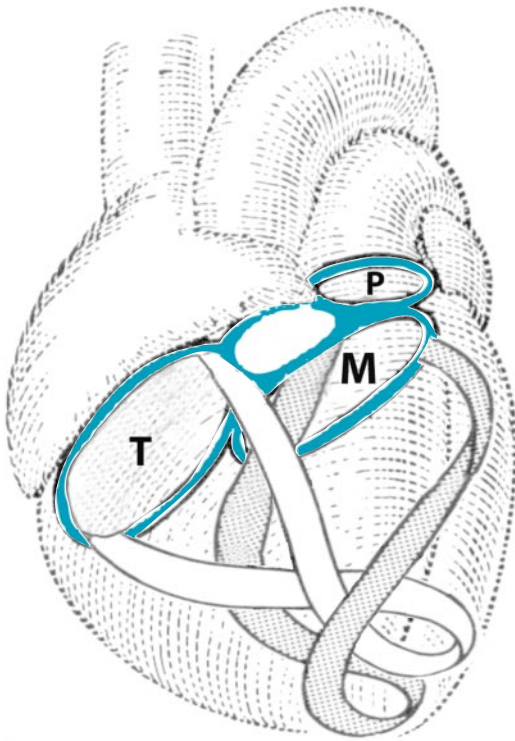


Figure 6–2 The fibrous skeleton of the heart and gross anatomy of ventricular muscle fibers. Shortening of the fibers will reduce chamber dimension and will pull the apex toward the valve rings. A = aortic; M = mitral; P = pulmonic; T = tricuspid.

Sarcoplasmic reticulum (SR). The SR is an intracellular network of membrane-lined tubules that forms a mesh around each myofibril. The SR abuts the T-tubules and sarcolemma and forms functionally important junctions at these sites. It has at least three electronmicroscopically different regions:

1. **Network SR** courses over the myofibrils and forms the connection among other SR parts and has a high content of Ca^{++} -ATPase (adenosinetriphosphatase) and phospholamban.
2. **Corbular SR** is the bulges that are found in the region of the I-band (light region adjacent to the Z-line). It has a high Ca^{++} content.
3. **Junctional SR** is found near the T-tubules, in the region of the triads. It does not make intimate contact with the T-tubules but appears to be “connected” to them by electron-dense foot processes. These are the large cytosolic domain of the SR Ca^{++} release channel (ryanodine receptor).

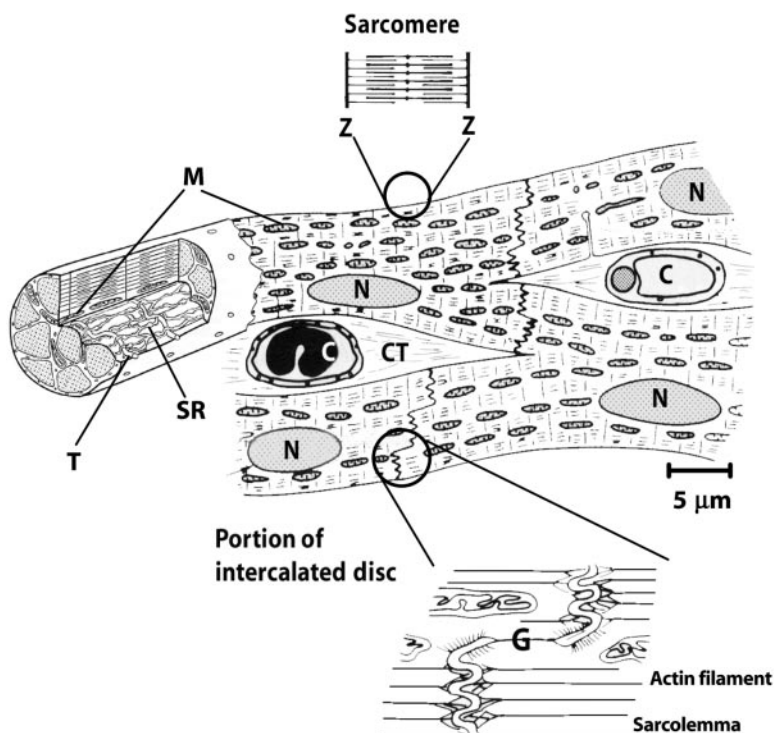


Figure 6–3 Myofibrils are formed by chains of sarcomeres and bundles of myofibrils form fibers. Extensive cross-connections between neighboring cardiac muscle fibers are the basis of the functional syncytium. There are numerous mitochondria (M), arranged like a sleeve around each myofibril. The region of abutting plasma membrane (sarcolemma) between adjacent cells is called the intercalated disc and includes gap junctions (G). C = capillary (one of them is shown with a red cell in its lumen); CT = connective tissue; N = nucleus; SR = sarcoplasmic reticulum; T = T-tubule; Z = Z-line.

The SR also has high concentrations of Ca^{++} and calsequestrin, a Ca^{++} “storage” protein with 40 to 50 Ca^{++} -binding sites per molecule.

Contractile and regulatory proteins. The components of the contractile machinery are the thick filament myosin and the thin filament G-actin, along with its associated regulatory proteins tropomyosin and troponin. The troponin molecule is a complex of three domains: (1) troponin-T binds the troponin complex to tropomyosin, (2) troponin-C binds Ca^{++} , and (3) troponin-I is an inhibitor of the actin–myosin interaction.

Heart Function

The human heart consists of a few billion myocytes, cells that are capable of creating mechanical force from chemical energy. The process is named

excitation–activation–contraction coupling. Heart function differs from skeletal muscle function in that every cardiac myocyte contracts with each heart beat. As a result, the strength of cardiac contraction is not modulated by altering the number of contracting cells but is modulated by changes in the intrinsic contractile properties of myocytes.

Cardiac Excitation

Cardiac myocytes are excitable cells and are, therefore, capable of responding to an appropriate stimulus with quick generation of an action potential. The stimulus normally originates from pacemaker cells in the sinoatrial (SA) node. An action potential that is spontaneously generated in one of these cells rapidly spreads through the **functional syncytium** and elicits action potentials in all other excitable cardiac cells. Passive transport mechanisms through ion-selective channels exert a dominant influence over short-term (0 to 300 ms) electrical behavior of cardiac cells.

Ion currents. Membrane channels that are selectively conductive for Na^+ , Ca^{++} , or K^{++} are of special importance for the contraction–relaxation cycle of cardiac muscle cells. Their conductance changes result from channel activation and inactivation on a time scale of milliseconds and in an ordered sequence that results in the action potentials described later (Figures 6–4 and 6–5). The following currents contribute most significantly:

- I_{Na} : carried by rapidly activating and inactivating, voltage-gated Na^+ channels; contains a small noninactivating component (the slow Na^+ current). Inactivated Na^+ channels become available for reactivation only after the membrane has been repolarized. Thus, the long duration of the cardiac action potential imposes a long refractory period on cardiac myocytes and prevents tetanization.
- I_f : the pacemaker current; a nonselective cation current composed mostly of Na^+ . Unlike most voltage-gated channels, which are closed at resting membrane potential and open on depolarization, the channel carrying I_f opens on hyperpolarization, and this “funny” behavior has given it the designation “f.” I_f is directly modulated by cyclic adenosine monophosphate (cAMP) and is, therefore, increased by β_1 -adrenoceptor activation.
- $I_{\text{C-T}}$: carried by voltage-gated T-type Ca^{++} channels (blocked by nickel).
- $I_{\text{C-L}}$: carried by voltage-gated L-type Ca^{++} channels (blocked by dihydropyridine).

*At least 12 different K^+ channels have so far been identified in myocytes. Their expression varies greatly in different regions of the heart, and this variation leads to regional differences in action-potential profile.

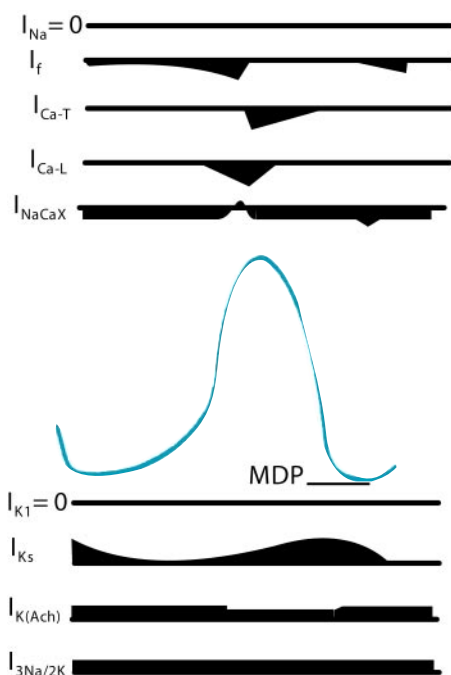


Figure 6-4 Ionic basis of the cardiac pacemaker potential. Downward deflections (traces above the action potential) represent depolarizing currents; upward deflections (traces below the action potential) represent repolarizing currents. Note the absence of I_{Na} and I_{K1} in most pacemaker cells. I_{Na} is present in Purkinje cells. Ca-T, Ca-L = T-type and L-type Ca^{++} channels, respectively; MDP = maximum diastolic potential; NaCaX = $3Na^{+}/Ca^{++}$ exchanger; $3Na/2K$ = the Na^{+} - K^{+} pump; K_1 = inwardly rectifying K^{+} channel; K_s = the slowly activating delayed rectifier K^{+} channel; $K_{(ACh)}$ = acetylcholine-sensitive K^{+} channel.

- I_{NaCaX} : carried by the $3Na^{+}/Ca^{++}$ exchanger. This exchanger operates through a sarcolemmal protein residing in the T-tubule membranes and is driven by the Na^{+} electrochemical gradient. It is electrogenic by virtue of co-transporting $3Na^{+}$ with each Ca^{++} . Its reversal potential is calculated from the equilibrium potentials of Na^{+} and Ca^{++} as $3E_{Na} - 2E_{Ca}$. E_{Na} is normally 70 to 80 mV, and E_{Ca} is near 120 mV in diastole when $[Ca^{++}]_i$ is 50 to 100 nM. These values set $E_{NaCaX} = -15$ mV. With a resting membrane potential near -80 mV, it is clear that the exchanger will operate to transfer net positive charge into the cell. As $[Ca^{++}]_i$ increases to about 1,200 nM during the action potential, E_{Ca} moves to about 80 mV and $E_{NaCaX} = +65$ mV. The plateau voltage of the action potential is generally near 0 mV. Accordingly, the exchanger tends to operate in the Ca^{++} -out mode throughout the cardiac cycle. Reversal to a Na^{+} -out/ Ca^{++} -in state depends critically on the systolic level of $[Ca^{++}]_i$.

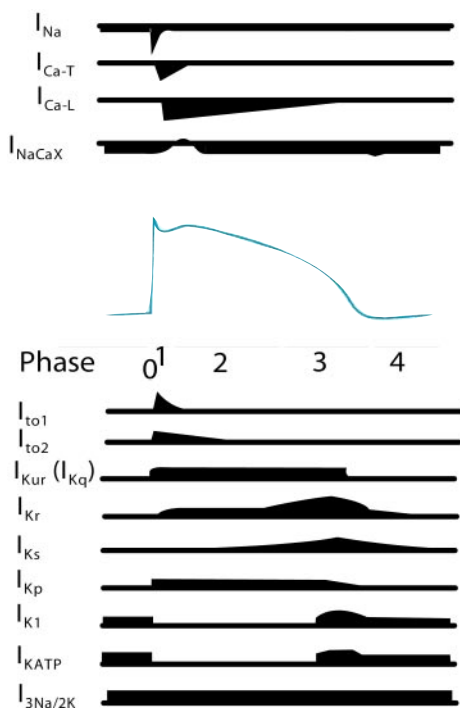


Figure 6-5 Ionic basis of the cardiac action potential. Downward deflections (traces above the action potential) represent depolarizing currents; upward deflections (traces below the action potential) represent repolarizing currents. I_{Na} = fast-acting Na^+ current; I_{Ca-T} , I_{Ca-L} = T-type and L-type Ca^{++} channels, respectively; I_{NaCaX} = $3Na^+/Ca^{++}$ exchanger; I_{to1} and I_{to2} = transient outward currents; K_1 = inwardly rectifying K^+ channel; K_p = a time-independent, H^+ -sensitive K^+ channel; K_{ATP} channels are inhibited by physiologic levels of adenosine triphosphate (ATP) and open when [ATP] decreases; $I_{3Na/2K}$ = current due to Na^+-K^+ ATPase.

It can occur under some normal circumstances and may be of importance in disease states.

- I_{to} : “to” designates “transient outward”; two components have been identified: I_{to1} is a rapidly inactivating voltage-gated K^+ channel that is blocked by 4-aminopyridine (4-AP); I_{to2} is activated by Ca^{++} and is inactivated more slowly than I_{to1} . It is not yet certain whether I_{to2} is carried by K^+ or by Cl^- .
- I_{Kur} (also called I_{Kq}), I_{Kr} and I_{Ks} : form respectively, the ultrarapid, rapid, and slow components of the delayed rectifier K^+ current; K_{ur} is blocked by quinidine; K_r is blocked by La^{3+} and the methane-sulfonilide antiarrhythmic drugs; mutations in K_s are responsible for the long QT syndrome.
- I_{Kp} : normally a small K^+ current that is highly sensitive to $[H^+]$ changes in the physiologic range. It was previously thought to be carried by Cl^- ions.

- I_{K1} : one of several inward rectifier K^+ currents. Inwardly rectifying channels are highly conductive in the inward direction when the membrane potential is negative to the K^+ equilibrium potential. They are poorly conductive in the outward direction when the membrane potential is more positive than the K^+ equilibrium potential. The channel is not voltage gated; it has only two transmembrane domains, in contrast to the six transmembrane domains that characterize voltage-gated channels.
- $I_{K(Ach)}$: a K^+ current that is carried through an inwardly rectifying channel in pacemaking tissue and atrial myocytes. The channel is directly coupled to a G protein. It mediates approximately 50% of the negative chronotropic effect of vagal stimulation.
- I_{KATP} : links membrane potential to cellular metabolic status. K_{ATP} channels are inhibited by physiologic levels of adenosine triphosphate (ATP) and open when [ATP] decreases.
- $I_{3Na/2K}$: is the outward current arising from the ubiquitous $3Na^+-2K^+$ membrane pump.

Pacemaker cells. Pacemaker cells are concentrated in the sinoatrial (SA) node, the atrioventricular (AV) node, the bundle of His, and Purkinje fibers. Sinus rhythm is normally driven by SA node cells because they are the earliest to depolarize.

Pacemaker cells differ from other myocytes in that they do not have a stable membrane potential in diastole (see Figure 6–4). After they have repolarized to the maximum diastolic potential, their membrane potential gradually depolarizes, and an action potential is generated when Ca^{++} influx increases explosively. The instability of diastolic potential arises mostly from (1) the absence of the inwardly rectifying K^+ channel, I_{K1} , the major diastolic stabilizing current; and (2) the presence of a mixed Na^+/K^+ pacemaker channel, I_f .

The slope of the diastolic potential in pacemaker cells is determined by the imbalance between I_f and $I_{K(Ach)}$, the acetylcholine-sensitive K^+ channel.

Modulation of SA-node pacemaker rate: Sinoatrial nodal cells have a high basal level of cyclic adenosine monophosphate (cAMP), and this level can be increased by β -adrenergic activation and decreased by muscarinic activation of guanylate cyclase.

Sympathetic stimulation increases intracellular cAMP. This has a direct, stimulatory effect on the pacemaker current I_f and also increases I_{Ca-L} by promoting phosphorylation of the channel. Parasympathetic stimulation slows pacemaker frequency by muscarinic mechanisms that include membrane hyperpolarization, inhibition of I_{Ca-L} as a result of kinase C–dependent inhibition of channel phosphorylation, decreased cAMP by virtue of the action of cyclic guanosine monophosphate (cGMP)-dependent phosphodiesterase, and activation of $I_{K(Ach)}$.

Myocytes. The action potential is the result of exquisitely tuned ion currents that are activated and deactivated at different intervals. Figure 6–5 shows the ion currents dominating each phase of the action potential.

Upstroke (phase 0): When a suitable stimulus depolarizes the membrane to the gating voltage for fast Na^+ channels (I_{Na}), they are activated, and the membrane potential rapidly moves toward the Na^+ equilibrium potential.

Channels carrying $I_{\text{Ca-T}}$, the transient Ca^{++} current, are activated at E_m more positive than -50 to -65mV .

At E_m more positive than -40mV , channels carrying $I_{\text{Ca-L}}$, the long-lasting Ca^{++} current, are activated and remain activated in phases 1 and 2.

The excitation propagates to adjacent myocytes at a velocity of 0.3 to 0.5 m/s through myocytes and 1 to 3 m/s through Purkinje fibers.

Early rapid repolarization (phase 1): At the peak of the upstroke, E_m reaches between $+20$ and $+40\text{ mV}$ and then undergoes rapid partial repolarization. The major contributors are (1) inactivation of $I_{\text{Ca-T}}$ and most of I_{Na} and (2) activation of I_{to} . This creates the “notch” near the peak of the action potential and determines the plateau potential and, thereby, the magnitude and time course of currents that flow during the plateau phase.

The plateau (phase 2): The plateau arises from a delicate balance between depolarizing and repolarizing currents. The major depolarizing influence is $I_{\text{Ca-L}}$, carried through channels that were opened during phase 0. Repolarizing currents arise from the K^+ currents I_{ur} , I_{r} , and I_{p} (see Figure 6–5).

Late rapid repolarization (phase 3): The plateau terminates partly because I_{r} and I_{s} increase their respective conductance and partly because $I_{\text{Ca-L}}$ decays when the L-type channels carrying it are inactivated by processes dependent on time, voltage, and intracellular $[\text{Ca}^{++}]$.

Repolarization then occurs rapidly because of the dominant influence of outward K^+ currents, mainly I_{Kr} , I_{Ks} , and I_{K1} .

As the membrane potential approaches its resting value, K^+ currents diminish as the electrochemical gradient for K^+ decreases and the $3\text{Na}^+-2\text{K}^+$ pump current gains in relative importance.

Diastole (phase 4): Nonpacemaker cells maintain a stable resting membrane potential because of an exact balance between depolarizing and repolarizing currents. The significant depolarizing currents are I_{NaCaX} and a Na^+ leakage current because the electrochemical gradient for Na^+ is steep and the Na^+ channels do not inactivate completely. The significant repolarizing currents are I_{K1} and $I_{3\text{Na}/2\text{K}}$, the current resulting from active 3Na^+ , 2K^+ pumping (capable of taking E_m down to -150 mV). I_{KATP} becomes significant only when cytosolic $[\text{ATP}]$ is low.

The conducting system of the heart. The SA node is electrically coupled by way of gap junctions to a specialized conduction system that consists of the AV node, bundle of His, and Purkinje fibers. This system, in turn, is coupled to myocytes by gap junctions and, therefore, rapidly conducts electrical activity to all parts of the heart and ensures that large numbers of cells depolarize in synchrony. The spread of depolarization along relatively fixed, predetermined paths ensures that the orientation of the electric field with respect to the body surface changes little from beat to beat.

Generation of the electrocardiogram. Whenever a sufficiently large number of cardiac cells undergo synchronized depolarization and repolarization, the resulting electrical activity can be detected as potential differences between any two points on the body surface. This results in bipolar lead electrocardiograms (ECGs), such as leads I, II, III, and others, as dictated by specific needs.

It is also conventional to record ECGs at several surface points, not with reference to one other surface point but with reference to a point that is derived electronically by the recording apparatus from voltages measured at two or three other surface points. This results in **unipolar ECGs**. (Leads aV_R , aV_L , aV_F and precordial leads V_1 to V_6 are typical unipolar leads.)

Electrocardiogram traces show deflections that are typically identified as “waves” labeled P, Q, R, S, and T. As shown in Figure 6–6, P corresponds to atrial depolarization, Q to very early septal depolarization, R to ventricular depolarization, and S to late ventricular depolarization. T is inscribed by ventricular repolarization.

Cardiac vectors. The relationship between instantaneous cardiac electrophysiologic events and ECG traces is best understood in terms of **cardiac vectors** (some prefer the term “electrical dipoles”) and their projections onto a geometric line that connects the end points of individual leads (see Figure 6–6).

Depolarization vector: As each cell depolarizes, its membrane potential changes from a normally negative value to a slightly positive value. Hence, the process of cardiac depolarization can be imagined as a wave of positivity sweeping over the tissue and can, with the help of the following conventions, be represented by a **depolarization vector**:

Depolarization is represented by an arrow that is identified with a “+” sign at its head. The direction of the arrow is the same as the direction in which the depolarization wave moves through the tissue. The length of the arrow is directly proportional to the number of cardiac cells that are depolarizing at that instant.

If a series of depolarization vectors is drawn, each representing the spatially averaged cardiac electrical activity at that instant, depolarization of the

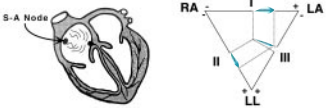
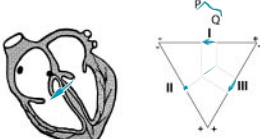
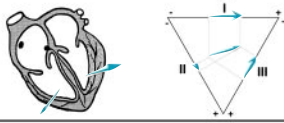
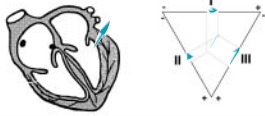
Time (ms)	Electrophysiologic Event	Vector Representation and ECG Lead Projection	Corresponding ECG Deflection
0–70	Action potentials that were spontaneously generated by the dominant pacemaker (the SA node) spread through atrial tissue		P-wave <ul style="list-style-type: none"> upward deflection in lead I smaller upward deflection in lead II upward, biphasic, or downward deflection in lead III
70–150	AV node delay		P–R segment <ul style="list-style-type: none"> normally isoelectric measured from the end of the P-wave to the beginning of the QRS complex. (Note that the P–R segment is not the same as the P–R interval . The P–R interval is defined as the interval from the onset of the P-wave to the beginning of the QRS complex.)
150	Beginning of ventricular depolarization This normally occurs at a point high in the interventricular septum		Q-wave <ul style="list-style-type: none"> defined as the first downward deflection preceding the R-wave. present in lead I small or absent in lead II may be absent in lead III because the Q vector would produce an upward deflection in lead III
155–165	Depolarization of both ventricles		R-wave <ul style="list-style-type: none"> large upward deflection in each of leads I, II, and III
180–200	Depolarization of last portions of the ventricles and of the septum tip		S-wave <ul style="list-style-type: none"> defined as the first downward deflection following R downward deflection in leads I, II, and III
250–600	Repolarization of the ventricles		T-wave <ul style="list-style-type: none"> Upward deflection in leads I, II, and III

Figure 6–6 Electrophysiologic events in a complete cardiac cycle. Vector representations of each event and the corresponding deflection in the frontal-plane, scalar ECG are also shown.

atria, for example, will be represented as a rotating arrow of variable length. Furthermore, all the depolarization vectors occurring during atrial depolarization can be averaged to yield a time- and space-averaged **P vector** (see Figure 6–6).

Repolarization vector: Repolarization events, such as the T-wave of the ECG, can be similarly derived by the application of the concept of a repolarization vector. Repolarization is represented by an arrow that is identified with a “-” sign at its head. The direction of the arrow is the same as the direction in which the repolarization wave moves through the tissue and returns cell membrane potentials to their negative, resting value.

The usefulness of the vector concept is that it allows us to derive whether a given cardiac electrical event will appear in any one lead as an upward or downward deflection or yield no deflection at all. The first step in the determination is to draw the right-angle projection of the vector onto the line that connects the end points of the lead of interest (see Figure 6-6).

An upward deflection will be observed in the lead if the head of a depolarization vector (+) points toward the “+” end of the lead or the head of a repolarization vector (-) points to the “-” end of the lead. The opposite alignments of projection and lead lines will result in downward deflections.

If a cardiac vector points to a lead line at right angles, there will be no deflection for that event in that lead (for example, there is often no Q wave in lead II) (see Figure 6-6).

Mechanical Activity of the Heart

Excitation-activation-contraction coupling. The events of excitation-activation-contraction coupling link the electrical activities of the myocyte to the force-generating actin-myosin reaction by which pressure is developed. Each cycle of cardiac mechanical activity is initiated when the concentration of intracellular ionized calcium rises from its resting value of 50 to 100 nM to a peak of about 1,200 nM.

Sources of Ca^{++} .

Voltage-activated channels. Most of the calcium that enters the myocyte at the start of an action potential is carried by $\text{I}_{\text{Ca-L}}$ (Figure 6-7). It provides no more than 10% of the total Ca^{++} needed for a maximal contraction but performs the crucial function of providing the trigger that releases calcium from intracellular, SR stores. The magnitude of $\text{I}_{\text{Ca-L}}$ is a significant regulator of SR Ca^{++} release and correlates closely with contraction strength.

Sarcoplasmic reticulum. This membrane-lined structure is filled with a Ca^{++} -rich fluid and supplies most of the Ca^{++} that binds to troponin in each heart beat. The primary release mechanism is **calcium-triggered calcium release**. It involves both L-type Ca^{++} channels in the sarcolemma of the T-tubules and a Ca^{++} -release channel in the abutting SR.

The large cytosolic domain of each SR Ca^{++} release channel (ryanodine receptor) is closely apposed to an L-type Ca^{++} channel (dihydropyridine

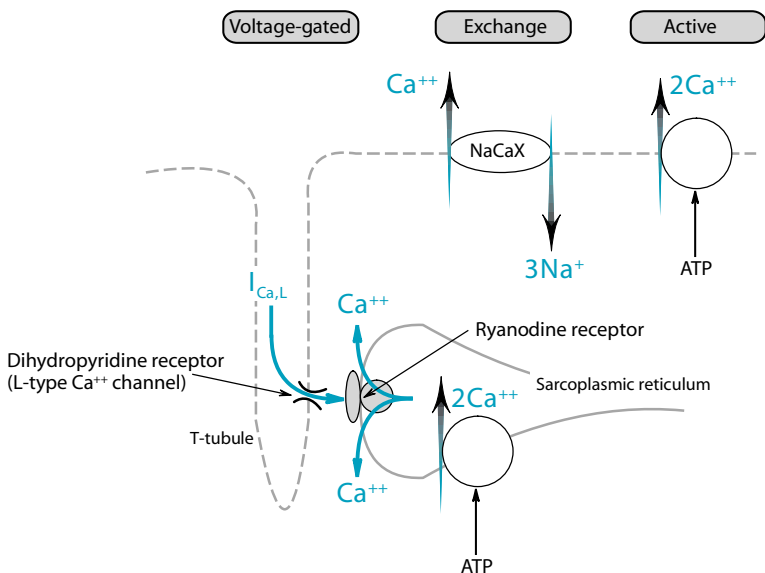


Figure 6-7 There are four major routes for Ca^{++} handling in cardiac muscle. The dominant voltage-gated channel is the L-type channel, which is also called the dihydropyridine receptor. The ryanodine receptor is the release channel in the sarcoplasmic reticulum. The $3\text{Na}^{+} - \text{Ca}^{++}$ exchanger (NaCaX) operates mostly in the Ca^{++} -out mode. Active pumps are found both in the sarcolemma and the sarcoplasmic reticulum. ATP = adenosine triphosphate; $I_{\text{Ca,L}}$ = Ca^{++} current through the L-type channel; NaCaX = sodium-calcium exchanger.

receptor) in the T-tubule sarcolemma (see Figure 6-7). One or more release channels are opened and cause a localized Ca^{++} spark when the Ca^{++} binding site in their respective cytosolic domain is activated by trigger Ca^{++} from a single apposed voltage-gated L-type channel.

In a single contraction, the sarcoplasmic reticulum is of major importance as a source of Ca^{++} . However, Ca^{++} transport mechanisms across the cell surface membrane are of great importance over any interval that contains more than one contraction-relaxation cycle because these membrane-transport mechanisms build up the intracellular stores.

Of equal importance are mechanisms such as sodium-calcium exchange (NaCaX), by which Ca^{++} is normally lost from the cytosol.

Sodium-calcium exchange. NaCaX is of importance because of its role in the action of cardiac glycosides to improve cardiac function in failure states. Changes in Ca^{++} extrusion by NaCaX may also underly the **Bowditch effect**, a phenomenon whereby cardiac performance increases with increasing heart rate.

As described above (under Ion Currents), NaCaX normally operates in the Na^+ -in/ Ca^{++} -out mode throughout the cardiac cycle. However, when there are changes in the equilibrium potential for Na^+ (for example, during tachycardia) or in the resting membrane potential, the difference between E_{NaCaX} and E_{REST} can become much smaller in diastole and might reverse in systole. The effect of this would be reduced Ca^{++} extrusion in diastole and might be inward Ca^{++} transport in systole.

Uptake and removal of Ca^{++} . Ca^{++} removal is required for relaxation. It is mostly an active process that resides in ATP-dependent Ca^{++} pumps and partly a passive process residing in NaCaX. Ca^{++} pumps are located in both the sarcolemma and the membrane that lines the SR. They differ slightly in size and mostly in the mechanisms by which they are controlled.

Sarcolemmal Ca^{++} pump. Sarcoplasmic reticulum Ca^{++} uptake is fast enough to account for the observed rate of relaxation in the healthy myocardium. Concurrent passive movements of Cl^- and phosphates maintain electroneutrality across the SR membrane. The pump is normally inhibited by high $[\text{Ca}^{++}]$ within the SR and by phospholamban. Phospholamban inhibition is removed and both Ca^{++} sensitivity and rate of Ca^{++} transport are increased when phospholamban is phosphorylated by either cAMP or Ca^{++} -calmodulin-dependent protein kinase. As a result, both sympathetic activation and elevated cytosolic $[\text{Ca}^{++}]$ will stimulate SR Ca^{++} uptake and, thereby, promote myocardial relaxation (lusitropy). Normally, cytosolic $[\text{Ca}^{++}]$ is the more important determinant.

Phosphorylation of phospholamban increases the Ca^{++} content of the SR and, thus, favors Ca^{++} retention within the myocyte over Ca^{++} efflux across the plasmalemma. This enhances cardiac contractility.

A number of phosphatases can dephosphorylate phospholamban. Ca^{++} that has been taken up into the SR is mostly stored in the free, ionized form. Some of it is bound to a number of Ca^{++} -binding proteins, the most important of which is **calsequestrin**.

Plasmalemmal Ca^{++} pump. This pump is larger than the SR pump because it incorporates within its C-terminal portion the sequences that have formed the separate regulatory protein, phospholamban, in the SR Ca^{++} pump.

Active plasmalemmal efflux is not stimulated by cAMP. It is normally inhibited by the C-terminal portion of the transporter and is disinhibited when a Ca^{++} -calmodulin complex binds directly to the C-terminal end. This provides a feedback mechanism by which elevated $[\text{Ca}^{++}]_i$ stimulates Ca^{++} efflux.

Cytosolic $[Ca^{++}]$ and force development. In the resting, diastolic state, cytosolic $[Ca^{++}]$ is near 100 nM and, as described more fully in Chapter 2, the physical conformation of troponin–tropomyosin either blocks the actin–myosin cross-bridge formation or permits only weakly attached, non–force-generating cross-bridges. In this state, cross-bridge cycling and force generation are inhibited.

When cytosolic $[Ca^{++}]$ rises from its resting value to nearly 1,000 nM, interaction of free intracellular Ca^{++} with the Ca^{++} -specific binding site on troponin-C initiates the cascade in which protein constituents undergo changes of conformation and state. These changes release steric hindrance and switch weakly bound cross-bridges to a state from which they can generate force provided that ATP is present and can be hydrolyzed to provide energy. (See Chapter 2 for more details.) Mechanical work is performed when neighboring Z-lines are pulled toward each other as described by the **sliding filament** model.

Cardiac muscle metabolism.

Adenosine triphosphate synthesis. Myocytes require ATP and generate it by two distinct processes: (1) **glycolysis** in the cytosol and (2) **oxidative phosphorylation** in the mitochondria. Whereas fetal and neonatal hearts depend mostly on glycolysis, the adult, healthy, normoxic heart depends mostly on a nonglycolytic pathway that occurs inside the mitochondria and begins with acetyl coenzyme A (acetyl CoA) and includes the Krebs cycle, electron transport chain, and oxidative phosphorylation.

Glycolysis converts glucose to two molecules of pyruvate and yields two molecules of ATP. In the well-oxygenated heart, 34 additional ATPs can be extracted by the nonglycolytic path after conversion of both pyruvates to acetyl CoA (catalyzed by the **pyruvate dehydrogenase complex** inside the mitochondria). Between 60 and 70% of the adult myocardial energy requirement is met by the metabolism of free fatty acids to acetyl CoA and the subsequent formation of ATP by the nonglycolytic path. There are five significant steps (Figure 6–8):

1. Fatty acids enter the myocardial cell by saturable, carrier-mediated processes. Catalyzed by **acyl CoA synthetase**, they become activated to **fatty acyl CoA**.
2. Fatty acyl CoA is shuttled across the mitochondrial membrane by reversible coupling to **carnitine**.
3. Once fatty acyl CoA is inside the mitochondrion, it undergoes **beta-oxidation** at the inner surface of the mitochondrial membrane. This splits off the two-carbon fragment **acetyl CoA**. The remaining fatty acyl CoA, shortened by two carbons, re-enters the cycle to split off two more carbons in the form of acetyl CoA and so on. Acetyl CoA is subsequently used in the Krebs cycle.

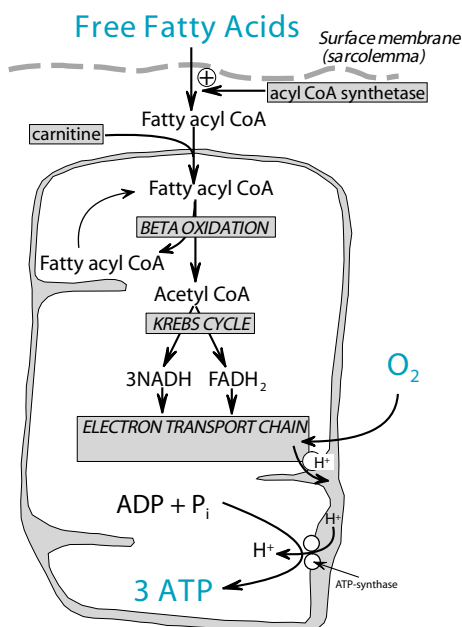


Figure 6–8 Free fatty acids enter mitochondria through the carnitine shuttle mechanism and undergo beta-oxidation to form acetyl coenzyme A, which enters the Krebs cycle to produce the reduced coenzymes NADH and FADH₂. These enter the electron transport chain, which uses O₂ and leads to H⁺, which are pumped into the space between the inner and outer mitochondrial membranes. ATP is synthesized when H⁺ flow back into the mitochondrial matrix through ATP synthase. ADP = adenosine diphosphate; ATP = adenosine triphosphate; FADH₂ = reduced flavin adenine dinucleotide; NADH = reduced nicotinamide adenine dinucleotide.

4. For the synthesis of ATP, the significant products of a complete turn of the Krebs cycle are four reduced coenzymes (three NADH and one FADH₂).

If H is regarded as a hydrogen ion (H⁺) and an electron (e⁻), the reduced coenzymes become [(NAD-e)⁻ + H⁺] and [(FAD-2e)²⁻ + 2H⁺], and it is readily seen that they are energy-rich molecules because electrons are highly reactive.

5. In the electron transport chain and the process of oxidative phosphorylation, the electrons of [(NAD-e)⁻ + H⁺] and [(FAD-2e)²⁻ + 2H⁺] are donated to molecular oxygen. The process is associated with H⁺ pumping from the mitochondrial matrix, across the inner membrane into the space between the inner and outer mitochondrial membranes. This creates an H⁺ gradient, a charge gradient, and free energy. Adenosine triphosphate is synthesized when H⁺ ions flow back into the mitochondrial matrix through membrane-bound **ATP synthase** (F₁F₀-ATPase).

Sustained increase in cardiac work entails increased rate of ATP utilization and requires an increase in the rate of ATP production. In the healthy heart, the linkage between the two is provided by coronary flow as follows: successive dephosphorylation of ATP produces first ADP and then adenosine monophosphate (AMP) (see Figure 6–28). In turn, AMP is broken down to **adenosine** or **IMP (imidazole monophosphate)**, depending on whether the enzyme 5′ nucleotidase or AMP deaminase predominates. Imidazole monophosphate stays within the cell and either enters one of the salvage pathways for the reclaiming of AMP or is degraded, eventually forming uric acid. Low cytosolic [ATP] or high [P_i] favor 5′ nucleotidase and subsequent adenosine production. Adenosine can diffuse out of the myocyte, act on coronary vascular A_2 receptors, and lead to coronary vasodilatation and increased coronary blood flow. This supplies the O_2 needed for oxidative phosphorylation.

Oxygen consumption. The O_2 consumption of the “resting” heart is about 8 mL/100g•min. Approximately 25% of that is used for basic metabolic processes, and the remainder provides energy for contraction in the following rank order: (1) development of wall tension, (2) heart rate, and (3) velocity of fiber shortening. As a result of the greater O_2 cost of tension development, cardiac O_2 consumption will increase more when there is an increase in cardiac work by increasing pressure, as opposed to increasing cardiac work by increasing cardiac output (by heart rate or stroke volume).

The heart as a pump. The job of the heart is to transfer the stroke volume from the venous side to the arterial side and to match the volume transfer rate, which is equal to the cardiac output, to the oxygen needs of the entire body. The transfer is accomplished by sequential generation of wall tension in each of the four chambers. The resulting increase in chamber pressure displaces a volume in a direction that is permitted by **valves** controlling chamber inflow and outflow.

Mitral and tricuspid valves prevent flow from ventricle to respective atrium, aortic and pulmonic valves permit flow from ventricle to aorta and pulmonary artery, respectively.

The cardiac cycle. In healthy individuals, the contraction–relaxation cycle of the heart is repeated as little as 35 times per minute in extremely fit athletes at rest to as often as 200+ times per minute when those athletes exercise at maximum capacity. The resting heart rate of an adult is typically near 60 per minute, and Figure 6–9 shows the hemodynamic changes on the left side of the heart over the duration of one beat. These changes occur in the same sequence as the electrophysiologic changes (see Figure 6–6) and are considered in three sequential phases in Figure 6–9: (1) atrial contraction, (2) ventricular contraction, and (3) ventricular filling.

Left atrial contraction. Atrial pressure rises (“a” wave) when atrial muscle contracts. The atrial–ventricular pressure gradient drives blood to the left ventricle. As a result, left ventricular volume increases toward the level of left ventricular end-diastolic volume (LVEDV), and left ventricular pressure rises in parallel with atrial pressure.

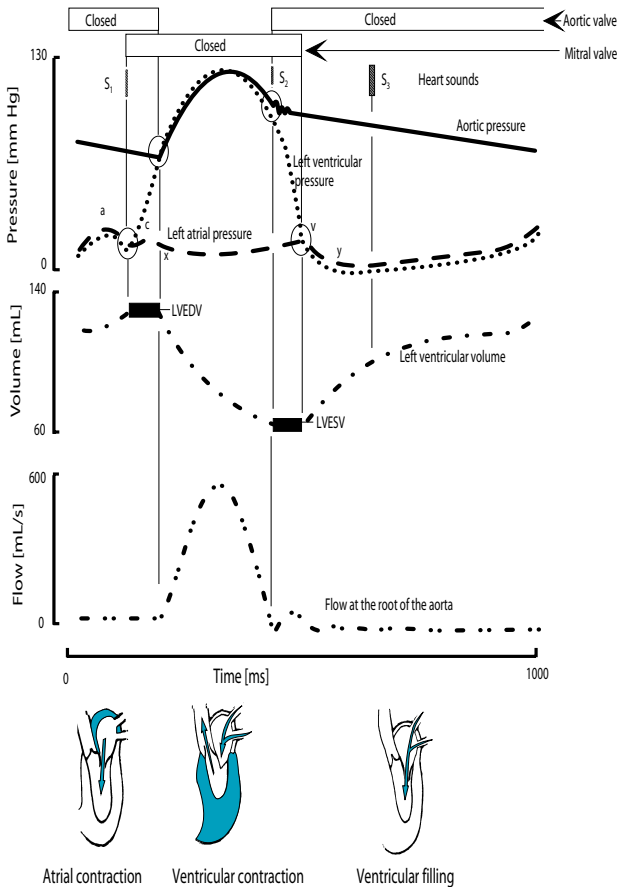


Figure 6-9 Temporal changes in selected pressures, chamber volumes, and flow on the left side of the heart in one cardiac cycle at a heart rate of 60 min⁻¹. At this rate, systole and diastole occupy approximately 340 and 660 ms, respectively. a = wave of pressure associated with atrial contraction; c = increase in atrial pressure caused by upward bulging of mitral leaflets before papillary muscles stabilize them; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; S₁, S₂, and S₃ = first, second, and third heart sounds; x = descent in pressure as atrial volume increases when the valve ring is pulled toward the apex of the heart by ventricular contraction; v = maximal atrial pressure during atrial filling; y = descent in atrial pressure caused by rapid ventricular relaxation.

Left ventricular contraction. At the beginning of ventricular contraction, the aortic valve is still closed because aortic pressure is higher than left ventricular pressure. As the ventricle begins to contract, ventricular pressure rises above atrial pressure and the mitral valve closes, producing the first heart sound (S_1). During the next few milliseconds, the ventricle continues to contract, but its volume cannot change because of the closed valves. This is the period of **isovolumetric contraction**. During this time, some left ventricular changes are mechanically coupled to the left atrium, and they result in the “c” wave and the “x” descent of the atrial pressure trace.

When ventricular pressure just exceeds aortic pressure, the aortic valve opens, and ventricular volume decreases rapidly from LVEDV toward LVESV (see Figure 6–9), and aortic flow increases as the stroke volume is ejected.

Ventricular pressure, aortic pressure, and aortic flow begin to fall when the ventricle begins to relax.

Throughout the duration of ventricular contraction and initial ventricular relaxation, the atrium fills by inflow from the pulmonary veins. This causes atrial pressure to rise after the “x” descent.

As the ventricle relaxes, ventricular pressure soon falls below aortic pressure because the ventricle relaxes rapidly, while blood inertance and blood vessel compliance retard the pressure decline in the aorta.

During this period of reduced ejection, blood continues to flow from the ventricle in the direction of the energy gradient (not the pressure gradient!) until the aortic valve closes, creating the second heart sound (S_2) (see Figure 6–9).

S_2 marks the beginning of the period of isovolumetric relaxation. After S_2 , aortic and ventricular pressures diverge markedly as the ventricle relaxes at a high rate that is determined by the **lusitropic state** of the ventricle. This state is set partly by the rate of Ca^{++} pumping into the SR and partly by the rate of cross-bridge detachment and inactivation. The latter are determined by dissociation of inorganic phosphate from the cross-bridges and by ATP binding to the myosin head. In humans, the rate and extent of isovolumetric relaxation are inversely related to LVESV; the smaller the volume, the greater are the rate and extent of isovolumetric pressure fall.

Left ventricular filling. The mitral valve opens when the falling ventricular pressure intersects the rising atrial pressure (“v” wave). Subsequent ventricular filling shows an early, rapid phase followed by a phase of more gradual filling (**diastasis**).

When the mitral valve opens, ventricular volume increases rapidly from LVESV in response to a gradient created between the full atrium and the rapidly relaxing ventricle. The rapidity of ventricular relaxation is evident from the descent in ventricular pressure (“y” descent in atrial pressure), even while ventricular volume increases (see Figure 6–9). At normal rest-

ing heart rate, this phase lasts about 140 ms, and most ventricular filling occurs in this phase. In addition, increased heart rate does not significantly impair diastolic ventricular filling until the diastolic interval becomes short enough to encroach on the period of rapid filling. This is normally near 180 beats per minute.

Heart sounds. The first and second heart sounds (S_1 and S_2) (see Figure 6–9) each contain components arising from the left and right sides of the heart. Under some circumstances, each sound may, therefore, be “split” into separate components (mitral and tricuspid for S_1 , aortic and pulmonic for S_2). The mitral component normally precedes the tricuspid component in S_1 , and the aortic component normally precedes the pulmonic component in S_2 .

S_3 , when it is present in young humans or in the more elderly in some pathologic conditions, occurs at the end of the period of rapid ventricular filling.

Pressure-volume loop of the left ventricle. Figure 6–9 shows the cardiac cycle against time. As a result of the thermodynamic consideration that a part of the external work of the heart is the product of chamber pressure and volume, left ventricular function is often described by plotting for each cardiac cycle its instantaneous pressure against its instantaneous volume. The cyclic nature of the phenomenon results in the inscription of a closed loop (Figure 6–10). The starting point is generally taken to be the end of diastole (point “1” in Figure 6–10).

Determinants of cardiac performance. The term performance describes the quality of cardiac function. It involves properties of both contraction (**inotropy**) and relaxation (**lusitropy**).

Cellular determinants. The human heart is required to eject blood against a wide range of aortic pressures and to provide an equally wide range of cardiac output in order to meet the oxygen demands that are imposed by the full range of activities. The devices that are commonly used by skeletal muscle to alter its performance (namely, recruitment of cells or motor units and temporal summation [tetanic contraction]) are not available as regulatory devices in cardiac muscle. As a result, the control of cardiac function occurs at the level of each myocyte.

- Cardiac performance is determined by both the total number of force-generating cross-bridges and the rate of cross-bridge cycling.
- During basal, resting conditions, only about 25 to 30% of all potential cross-bridges participate in force-generating interactions with the thin filament in any one heart beat. The number can be increased by increasing cytosolic $[Ca^{++}]$ and by decreasing interfilament spacing. At any

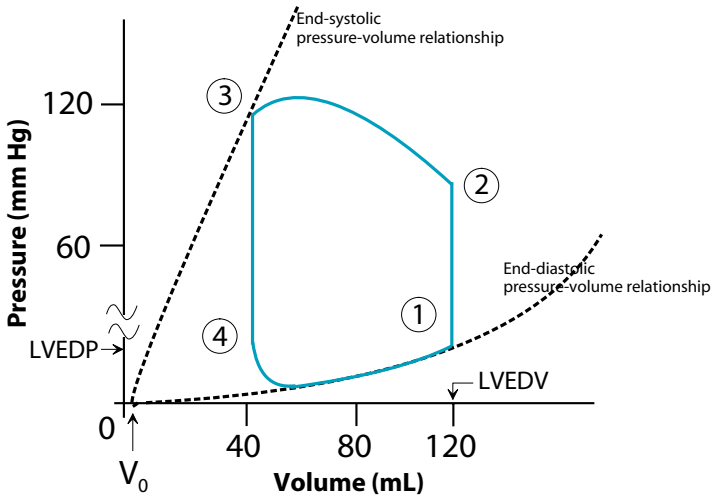


Figure 6-10 Pressure-volume loop of the human left ventricle. Systole begins at point “1” on the diastolic P-V line when volume = left ventricular end-diastolic volume (LVEDV) and pressure = left ventricular end-diastolic pressure (LVEDP). Pressure rises steeply without a change in volume during the period of isovolumetric contraction until the aortic valve opens at point “2” and ejection begins. Point “1” is a measure of preload, and point “2” is a measure of afterload. When systole ends (point “3”), ventricular pressure and volume come to lie on the systolic pressure-volume relationship. The aortic valve closes at that point and pressure falls without a change in volume during the period of isovolumetric relaxation. When the mitral valve opens at point “4,” diastolic filling of the ventricle begins. V_0 = unstressed volume (normally near 5 mL).

given initial sarcomere length, the amount of Ca^{++} released into the cytosol is the primary determinant of contractile force.

- The primary source of Ca^{++} is the SR, and the primary determinant of SR Ca^{++} release is the amount of Ca^{++} entering via $I_{\text{Ca-L}}$ during each action potential.
- The rate of cross-bridge cycling is influenced in the long term by isoform switching of myosin heavy and light chains and in the short term by myosin light chain phosphorylation and dephosphorylation.

Functional determinants. Three factors determine cardiac performance: (1) increased sarcomere stretch before actomyosin activation (**preload**) increases performance, (2) increased wall tension (**afterload**) decreases performance, and (3) increased efficacy of actomyosin interaction (**contractility**) increases performance.

Preload: Changes in diastolic fiber length change cardiac performance according to the **Starling-Frank law** of the heart. This is also called the **length-tension relationship**. It states that until an optimal sarcomere

length is reached, increasing sarcomere length will increase ventricular performance in the next several heart beats.

In resting humans, preload effects help adapt cardiac performance to postural changes and match left-sided heart output to right-sided heart output during respiratory changes in venous return. During exercise, preload is increased by the pumping action of muscles and respiratory movements and the increase augments cardiac output. Preload becomes an increasingly important mechanism for increasing cardiac output in the elderly because the effectiveness of autonomic modulation of cardiac performance decreases with advancing age.

Cellular basis of the preload mechanism: It is often stated that the increase in cardiac performance with increased diastolic stretch results from a more optimal alignment of myosin heads with their binding sites on the actin filament and consequent formation of more actomyosin cross-bridges. This is not supported by measurements. The following three cellular consequences of sarcomere stretch are now thought to be responsible: (1) increased Ca^{++} release from the SR, which may arise from activation of stretch-sensitive ion channels; (2) increased Ca^{++} sensitivity of troponin-C so that a greater force is developed at any one $[\text{Ca}^{++}]_i$; and (3) decreased lateral distance between adjacent thick and thin filaments and commensurate increase in the rate of cross-bridge transition from weak binding states to strong, force-generating states (Figure 6–11).

Hemodynamic determinants of preload: Three factors determine the degree of ventricular filling in diastole: (1) filling pressure, which is the difference between atrial pressure and ventricular pressure; (2) ventricular compliance, which is a measure of the ease with which the ventricle expands while it accepts diastolic inflow; it is affected by the properties of cardiac muscle itself or by factors that alter conditions in the pericardial space; and (3) the duration of the diastolic interval, which is inversely related to heart rate. Significant reductions in this interval occur at heart rates in excess of 180 min^{-1} , and such rates can be associated with compromised ventricular diastolic filling.

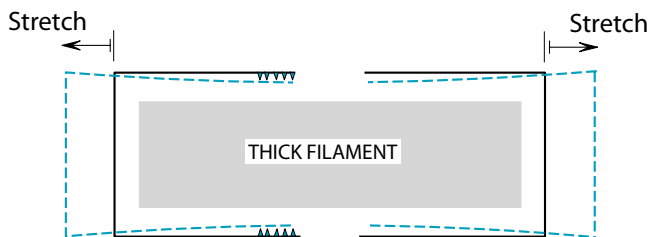


Figure 6–11 Longitudinal stretch reduces the spacing between thick and thin filaments.

Afterload: Conceptually, the afterload of a muscle is the load placed on it *after* it has begun to contract. Therefore, the afterload of the heart is sometimes thought of as the aortic pressure because that is what the left ventricle “sees” after the aortic valve has opened. It is more helpful to think of afterload as ventricular wall tension. This formulation emphasizes the mechanisms by which increases in intrathoracic pressure or in wall thickness help to reduce ventricular afterload.

Ventricular wall tension is related to transmural pressure, chamber radius, and ventricle wall thickness by the law of Laplace:

$$\text{Wall tension} = \frac{\text{Transmural pressure} \times \text{Chamber radius}}{2 \times \text{Wall thickness}}$$

Increased afterload decreases cardiac performance. However, the healthy heart is able to increase its contractility in the face of increased afterload. This is sometimes called the **Anrep effect**. It is believed to be caused by metabolic factors, secondary to subendocardial diastolic hyperemia in reaction to greater systolic compression of the coronary vasculature.

Contractility: Contractility refers to any factor influencing myocardial performance when preload and afterload are not changed. In the whole heart, increased contractility is associated with increased rate of isovolumetric pressure rise, more rapid rate of isovolumetric relaxation, shorter duration of systole, greater extent of systolic fiber shortening, greater stroke volume, higher ejection fraction, decreased end-systolic volume, and a steeper end-systolic pressure-volume relationship in the pressure-volume loop of the ventricle (Figure 6–12).

Cellular basis of contractility: Short-term changes in contractility arise predominantly from changes in Ca^{++} dynamics that affect cytosolic concentration $[\text{Ca}^{++}]_i$.

Increased $[\text{Ca}^{++}]_i$ increases (1) the total number of actomyosin cross-bridges that are formed during the excitation–activation phase and (2) the rates of protein phosphorylation that drive the activation–contraction phase.

$[\text{Ca}^{++}]_i$ can be increased (1) by increasing systolic entry of Ca^{++} , such as occurs after β_1 -adrenoreceptor activation (see Regulation of Cardiac Contractility), or (2) by decreasing Ca^{++} removal in diastole. The latter is the basis of the **Bowditch effect** (treppe phenomenon), which is the observation that systolic ventricular pressure can be increased by increases in heart rate. The explanation is that tachycardia leads to progressive increase in $[\text{Na}^+]_i$ and decrease in $[\text{K}^+]_i$ as the $\text{Na}^+\text{-K}^+$ pump is unable to maintain normal levels in the shortened diastolic interval. The consequent changes in resting membrane potential (less negative) and NaCaX reversal potential (more negative) cause decreased Ca^{++} egress by the exchanger.

Long-term changes in contractility arise from changes in the properties of the myosin molecule. The myosin molecule consists of two heavy chains

(MHC), each of them associated with one essential and one regulatory light chain (MLC). There are multiple fast and slow isoforms of both MHC and MLC, and they can differ markedly in the rate at which they convert chemical energy into work. The differences reside in reaction kinetics (rate constants for attachment and detachment, maximum shortening velocity, and rate of ATP consumption) but not in the amplitude of the elementary force and displacement events.

The expression of MHC and MLC genes is controlled by factors that include loading conditions and hormones such as thyroid hormone.

Assessment of cardiac contractility: Cardiac performance can be assessed relatively easily by measuring such indices as cardiac output or stroke volume. Measurement of the basic contractile ability (= contractility) is more difficult, and a variety of approaches are used in clinical studies.

1. Ejection indices: These are based on the effectiveness of left ventricular ejection and include aortic flow velocity, acceleration of blood in the aorta, and left ventricular ejection fraction.
2. Ventricular dimensions and their rate of change: Angiography, echocardiography, radionuclide ventriculography, and computed tomography each permit estimates of ventricular dimensions and their rates of change.
3. dP/dt : The maximum rate of change of ventricular or aortic pressure, dP/dt_{\max} , is one of the more common indices of contractility. Its most significant shortcoming is its dependence on preload, afterload, and heart rate.
4. Systolic time intervals: These indices express the relative duration of ventricular systole and diastole. Two of the more common indices are PVP and PEP/LVET.[†]
5. Pressure-volume curves: The effects of preload and afterload on cardiac performance (work) are readily shown with the help of pressure-volume loops (Figure 6–12). The loops are also helpful in assessing the contractile state of the heart (contractility) because of the observation that the end-systolic points of the P-V loops of a given ventricle, *at a constant contractility*, fall on the end-systolic P-V relationship, no matter what the initial LVEDV or the aortic diastolic pressure happens to be. As a result, contractility can be assessed as the slope of the line connecting the end-systolic pressure-volume points of several loops obtained at different preloads or afterloads in a denervated heart.

[†]PVP = time to peak ventricular pressure (measured from the first heart sound to peak aortic (or ventricular) pressure; PEP = pre-ejection period (measured from onset of QRS complex to beginning of aortic pressure rise); LVET = left ventricular ejection time (measured from the beginning of aortic pressure rise to the second heart sound).

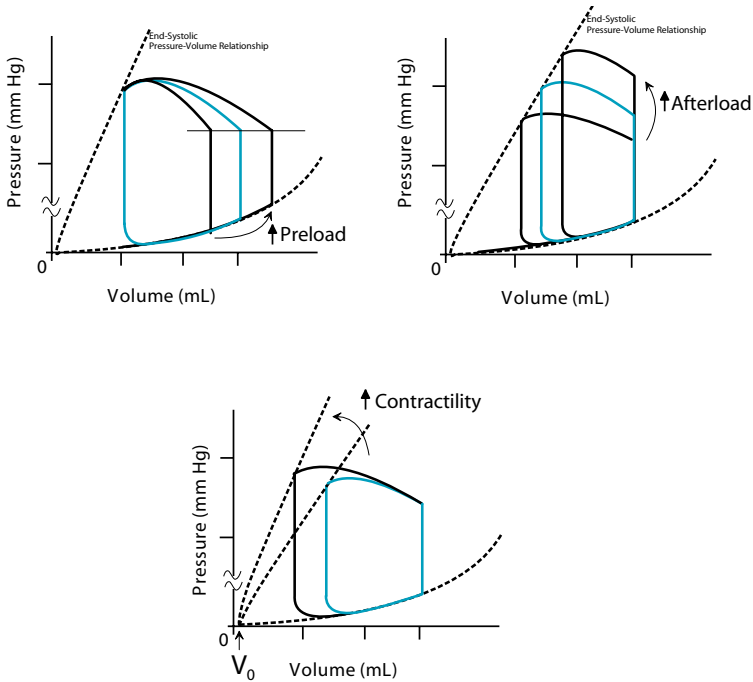


Figure 6-12 Effects of increased preload alone, increased afterload alone, or increased contractility alone on cardiac performance (work). Increases in contractility cause the end-systolic P-V relationship to be steeper but do not change V_0 , the unstressed volume.

BLOOD VESSELS AND LYMPHATICS

Vessel Wall Structure

Blood vessels contain only two cell types: endothelial cells and smooth muscle cells. In addition to these cells, there are collagen, elastin, and proteoglycans. All these components are arranged in layers, called **tunicae** (Figure 6-13).

Adventitia

The outermost layer of the vascular wall consists of dense fibroelastic tissue in most vessels. This layer also contains the nutrient blood vessels, lymphatics, and nerves. Some of the nerves are sensory or motor nerves for the blood vessel; many are nerve trunks that innervate the organ served by that blood vessel. The adventitia is relatively thin in elastic arteries and thicker in muscular arteries, where it may form half the vascular wall; it forms an indistinct,

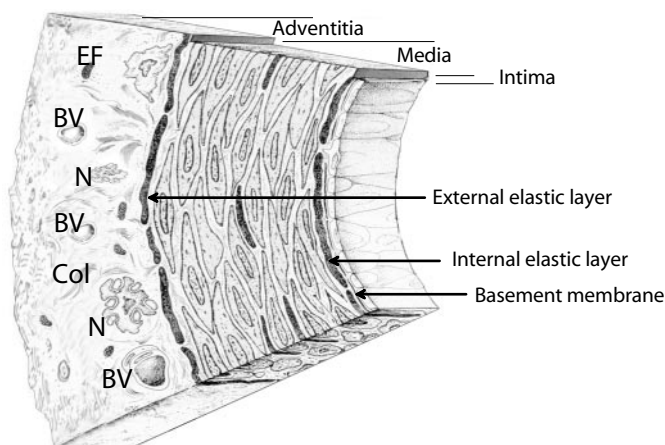


Figure 6-13 Layered arrangement of blood vessel wall into adventitia, media, and intima. EF = longitudinal elastic fiber; BV = blood vessel (vasa vasorum); N = nerve; Col = collagen bundles.

narrow sleeve in arterioles and venules. In medium-sized and large veins, it may form up to 75% of the wall thickness. Furthermore, in such vessels, firm collagenous attachments between adventitia and surrounding connective tissue allow the caliber of these veins to be changed by tissue deformation.

Media

The middle layer contains smooth muscle cells, arranged helically between a number of concentrically arranged elastic sheets. Thin elastic fibrils interconnect the elastic sheets, and the entire layer is embedded in a viscous, gelatinous ground substance of mucopolysaccharides. The tunica media is up to 500 μm thick in the aorta, 20 to 50 μm in medium-sized veins, two to three layers of smooth muscle cells in arterioles, and one to two such layers in venules.

Intima

The intimal layer is in contact with flowing blood. In most vessels, it consists of a layer of endothelial cells and the basement membrane surrounding them. Large elastic arteries also contain a subendothelial layer of collagen bundles, elastic fibrils, and some smooth muscle cells. The endothelium is thin (200 to 500 nm) and forms a selective barrier against plasma lipids and lipoproteins. It also secretes vasoactive substances and participates in thrombotic and antithrombotic activities.

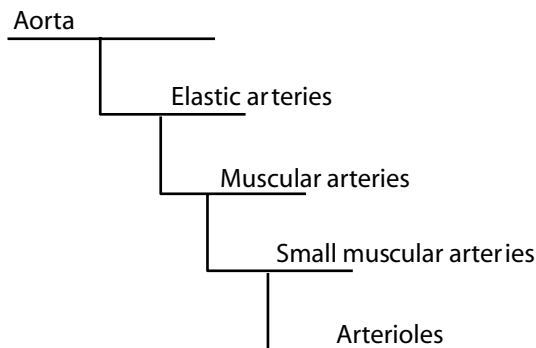


Figure 6–14 Arterial vessels branch successively to become arterioles eventually.

Architecture of the Peripheral Circulation

From the aorta, the blood is distributed to individual vascular beds through a system of successively branching elastic arteries, muscular arteries, small arteries, arterioles, and metarterioles (Figure 6–14).

The arterioles are the origin of the microcirculatory units (Figure 6–15) that provide the interface between blood and the cells of tissues.

Blood returns from the capillaries to the right atrium of the heart through a confluent network of venules and increasingly larger veins and lastly the inferior and superior venae cavae.

Arteries

Elastic arteries, such as the aorta, brachiocephalic trunk, and subclavian artery, store energy for flow in diastole. Their medial layer contains sheets of smooth muscle and many elastic layers. They are not under nervous control.

Muscular arteries, such as the brachial, femoral, and celiac arteries, have few or no elastic layers, and these layers are highly fenestrated. The smooth muscle is arranged in concentric layers, and there may be up to 30 of these layers. For the most part, the muscle arrangement is helical, but in some arteries (for example, coronary and renal), lengthwise bundles are found near the intima–media interface.

Small muscular arteries distribute blood flow *within* organs, as opposed to larger muscular arteries, which distribute blood *to* organs.

Arterioles

These are small vessels with an internal diameter of about 30 μm . They have an endothelial lining, surrounded by one or two layers of smooth muscle

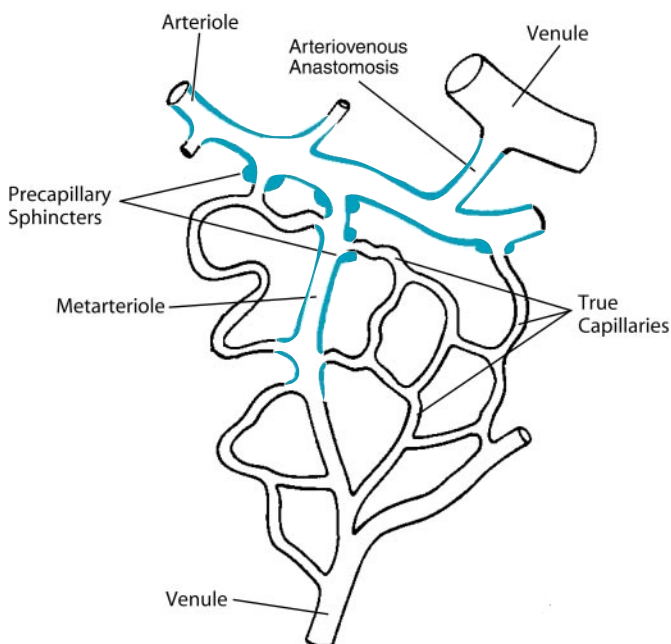


Figure 6–15 A typical microcirculatory unit consists of an arteriole, a metarteriole, several capillaries, and a venule. Tissues, such as skin, which sometimes require blood flow far in excess of local nutritional needs, also have arteriovenous anastomoses that permit bypass of the capillary vessels. The presence of vascular smooth muscle is indicated in color.

cells. No elastic layers are evident. Nearly 50% of the wall is smooth muscle, and this increases to nearly 70% in the precapillary sphincter regions. The functions of arterioles are (1) to provide and regulate peripheral vascular resistance, (2) to control flow within organs, and (3) to regulate capillary hydrostatic pressure.

Microcirculatory Unit

The components of a typical microcirculatory unit are shown in Figure 6–15. They differ in diameter, smooth muscle content, and function.

Metarterioles. These vessels are a little smaller than arterioles, form the origin of true capillaries, and have a smooth muscle covering that becomes sparser along the length of the metarteriole until it disappears altogether near the venular end, where the metarteriole assumes all the structural characteristics of a capillary exchange vessel. When the precapillary

sphincters are closed, the metarteriole forms the connection between arteriole and venule, and it is likely that the basal exchange function of most resting tissues is adequately met by the capillary-like venular end of metarterioles. When the tissue is not at rest and requires higher rates of perfusion, capillaries are recruited by relaxing precapillary sphincters at the metarteriole–capillary junction.

Capillaries. These thin-walled vessels consist of endothelium supported by very sparse smooth muscle cells, called pericytes. The capillary wall consists of overlapping endothelial cells, and the overlap incorporates a tight junction. Capillaries are surrounded by the basement membrane (see Figure 7–4). The luminal side of the cells is covered by the **glycocalyx**, which extends also into the region of overlap between adjacent cells (see Figure 7–4). As a result, capillary permeability to macromolecules is determined partly by the narrowness of the physical approximation between endothelial cells (8 to 10 nm) and partly by the extent of the glycocalyx “cloud” that encroaches into the junctional space. The normal thickness of this cloud is 100 to 500 nm, and its shape and integrity are influenced by plasma constituents, such as **albumin** and **orosomucoid** (α_1 -acid glycoprotein), because these proteins influence the permeability of the capillary wall. Capillaries in different organs differ in the structure of their endothelium. Four basic types can be identified.

1. Continuous epithelium. Most capillaries are formed by **continuous epithelium** in which the cells are thin (about 200 nm). Neighboring cells are separated by tight junctions that, nevertheless, permit transport of water and small solutes.

2. Fenestrated epithelium. Capillaries in the gastrointestinal (GI) mucosa, the kidney, and secretory glands are formed by **fenestrated epithelium**. It differs from continuous epithelium in that its basement membrane is not continuous and its cells are thinner (about 50 nm) and are penetrated by **fenestrae** that cut right across the endothelium. The fenestrae are circular, about 50 nm in diameter, are covered by a thin membrane, lack a lipid bilayer, and are very negatively charged. Their presence increases capillary permeability to water and small solutes without altering the permeability to macromolecules.

3. Discontinuous epithelium. Capillaries in the liver, spleen, and bone marrow are formed by **discontinuous epithelium**, in which the basement membrane is incomplete, and the junctions between endothelial cells are so large that they offer virtually no restriction to the passage of plasma proteins.

4. Tight-junction epithelium. Capillaries in most regions of the brain have epithelium that is sealed so tightly that even solutes as small as ions are severely restricted from passing across the capillary wall (the **blood–brain barrier**). Such capillaries allow the transport of lipid-soluble substances directly through the cell and of other substances only if there is a specific transport mechanism present in the cell membrane.

Venules and small veins. Venules function mainly to buffer changes in blood volume. They are only slightly larger than capillaries. In addition to endothelium, they have a thin medial layer that lacks distinct elastic laminae, although some delicate elastic fibrils are present in the small veins.

Medium-sized and large veins. In these vessels, there is often no clear demarcation between the three layers. The media are thin, and there are few smooth muscle cells. In many of the larger veins, the smooth muscle is arranged longitudinally rather than concentrically. The walls of large veins do not show the elastic layers that characterize elastic arteries. On the other hand, the connective tissue components are relatively more abundant.

Many veins, particularly those in the extremities, have valves. These are formed by folds in the **tunica intima**.

The venous system in human lower extremities is only marginally adapted to its function. In many people, the surface veins of the legs become tortuous, dilated, and scarred. The valves become thickened and ineffective. Blood is trapped in these veins, and the condition is called **varicose veins**.

Lymphatics. The lymphatic circulation parallels in function the capillary and venous circulation and consists of **initial lymphatics**, **collecting lymphatics**, and **central ducts**.

Initial lymphatics. These vessels, like capillaries, consist of overlapping endothelial cells only. They differ from capillaries in that the overlapping endothelial cells have no tight junctions, and their basement membrane is (1) discontinuous and (2) attached by anchoring filaments to the surrounding tissue cells (Figure 6–16). These filaments translate tissue deformation into opening or closing of the endothelial overlap cleft. This contributes to lymph acquisition and transport toward the center.

In most organs, the initial lymphatics are located in the adventitia of arteries and arterioles. They are hardly ever found in the region of the capillaries.

Collecting lymphatics. These are larger vessels (~150 to 600 μm), further downstream. They are chains of spontaneously contractile (10/min) **lym-**

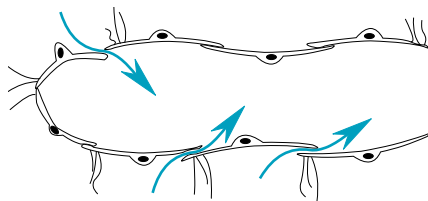


Figure 6–16 The basement membrane of initial lymphatics is attached to surrounding matrix elements by means of anchoring filaments. When the tissue moves, then the filaments translate such motion into opening and closing of endothelial gaps to control lymph entry.

phangions, with valves at intervals of 6 to 20 mm. Valves allow lymphangion contraction to propel lymph downstream into the next lymphangion, toward the central ducts.

Lymph nodes. Lymph nodes are positioned so that each collecting lymphatic drains into one of them. The nodes filter incoming lymph, phagocytose bacteria, and add differentiated lymphocytes to the effluent.

Central ducts. Typically, in humans, the lymphatics of the right upper body drain into the **right lymphatic duct** that inserts into the junction of the right subclavian and right jugular veins while the left upper body and all of the lower body drain into the **thoracic duct** that empties into the junction of the left subclavian and left jugular veins. In the two central ducts, the walls are thicker and the valve spacing is greater than in collecting lymphatics. In addition, their media and adventitia contain elastic fibers and nerves.

Cellular Physiology of Blood Vessels

Blood vessels contain only two cell types: smooth muscle cells and endothelial cells.

Vascular smooth muscle. Vascular smooth muscle (VSM) cells encircle blood vessels in a helical fashion. Individual cells make extensive electrical and metabolic contact with neighboring cells by **gap junctions** so that localized ionic events can readily spread along a blood vessel. The molecular basis of their contractile function is described in Chapter 2. It resembles striated muscle in that (1) Ca^{++} is required to initiate reversible actin–myosin interactions and (2) hydrolysis of ATP provides energy for the cross-bridge power stroke.

Vascular smooth muscle differs from striated muscle in that it contains no troponin. In it, **calmodulin** plays the role of cytosolic Ca^{++} receptor.

The plasma membrane of VSM contains a large variety of receptors whose activation influences vascular tone by one of two mechanisms described in Chapter 2: (1) alteration of the concentration of free, ionized calcium in the cytosol ($[Ca^{++}]_i$) or (2) alteration of Ca^{++} sensitivity.

Endothelium. The seven major functions of the endothelium are summarized in Table 6–1.

Endothelium as a selectively permeable membrane. Molecules larger than albumin generally do not move across the epithelium by passive transport without hindrance. This allows plasma proteins to exert an osmotic force across the capillary wall. Passive transport can also occur by way of **pinocytotic vesicles** (60 to 70 nm diameter). They are formed at specialized regions of the endothelial cell plasma membrane (**clathrin-coated pits**), enclose a region of cytosol, move passively, down a concentration gradient, attach themselves to a distal site, open, and empty their contents into the interstitial space.

Interactions of endothelium with blood.

Interactions with platelets: The endothelium normally prevents adhesion of platelets. Many factors are involved. Chief among them are (1) a high concentration of negative charges associated with chondroitin sulfate and heparan sulfate, both bound to the glycocalyx, and (2) the local concentration of

Table 6–1

Endothelial Functions

Function	Detail
Selectively permeable barrier	Proteins do not penetrate
Produces antithrombic agents	<ul style="list-style-type: none"> • Prostacyclin (PGI_2) • Binds coagulation inhibitors
Produces coagulation agents	Plasminogen factor
Transport of lipoproteins	LDL receptors
Produces inflammatory mediators	IL-1; VCAM, ICAM, selectins
Produces growth factors	VEGF; cell colony stimulating factor; insulin-like growth factor; fibroblast growth factor
Synthesizes vasorelaxing agents	NO; CNP; PGI_2 ; EDHF
Synthesizes vasoconstrictor agents	Endothelins; Ang-II; PGH_2 ; TXA_2

Ang-II = angiotensin-II; CNP = C-type natriuretic peptide; EDHF = endothelium-derived hyperpolarizing factor; ICAM = intercellular cell adhesion molecule; IL-1 = interleukin-1; LDL = low-density lipoprotein; NO = nitric oxide; PGH_2 = prostaglandin H_2 ; PGI_2 = prostacyclin; TXA_2 = thromboxane- A_2 ; VCAM = vascular cell adhesion molecule; VEGF = vascular endothelial growth factor.

prostacyclin (PGI_2) and nitric oxide (NO). Both are synthesized in endothelial cells and inhibit platelet aggregation by reducing $[\text{Ca}^{++}]$ within platelets. Prostacyclin₂ does it by increasing cAMP, and NO does it by increasing cGMP.

The endothelium also produces several agents that promote platelet activation. They include **platelet activating factor (PAF)**, **thrombospondin**, **fibronectin**, and **von Willebrand's factor**. However, these factors are normally localized on the abluminal side of the endothelium so that the antithrombotic interaction dominates.

Interactions with leukocytes: The general pattern of interactions between endothelial cells and leukocytes is that appropriate triggers can cause the formation of specific adhesion molecules and the adhesion mechanisms ultimately result in the migration of leukocytes through the endothelial barrier (**diapedesis**) toward the interstitium. During these processes, monocytes also differentiate into macrophages.

Role of the endothelium in immune and inflammatory reactions. These consist of interactions with leukocytes as described above. In addition, inflammatory mediators can trigger a rearrangement of the cytoskeleton in endothelial cells. This changes cell shape and the overlap between adjacent cells and is the cause of increased vascular permeability, local edema, or a runny nose. Histamine, acting through the H_1 receptor, phospholipase C pathway, is a prominent example of such a trigger.

Endothelial role in lipid metabolism. Lipoproteins continuously permeate the walls of arteries. Most exit the vessel wall by way of lymphatics and are ultimately returned to the blood; some are used for local metabolic needs, and a fraction is taken into endothelial cells by specific receptors. **Low-density lipoprotein (LDL)** is of particular interest because of the positive correlation between plasma levels of LDL and the development of atherosclerosis.

Low-density lipoprotein is taken up by endothelial cells by way of the LDL receptor and undergoes a variety of modifications including oxidation. Oxidized LDL induces monocyte adhesion to the endothelium. The monocytes then respond to chemotactic proteins and migrate into the subendothelial space. There they become engorged with lipids and form **foam cells**. Collections of foam cells form the **fatty streak**, the earliest lesion of atherosclerosis. Foam cells produce a host of growth factors that promote foam cell proliferation as well as recruitment of smooth muscle cells from the media. Such proliferation expands the intima and thins the endothelium, eventually causing it to retract or dysfunction in such a way as to expose the underlying foam cells to blood and add platelet activation to the cascading events of atherosclerosis.

Endothelium-derived growth factors. Endothelial cells produce some growth factors, but of far greater importance is the presence of receptors for growth factors. Activation of such receptors governs repair of damaged blood vessels and formation of new blood vessels (**angiogenesis**).

Endothelium-derived vasoactive substances. Endothelial cells produce both vasodilator and vasoconstrictor agents.

Vasodilator products: Four important dilating factors are synthesized and released by the endothelium. In order of importance, they are (1) nitric oxide (NO), (2) C-type natriuretic peptide (CNP), (3) endothelium-derived hyperpolarizing factor (EDHF), and (4) prostacyclin (PGI₂).

1. Nitric oxide: NO is a continuous regulator of resistance vessels and, hence, of arterial blood pressure. Nitric oxide is a labile gas, synthesized from the terminal guanidino nitrogen atom(s) of the amino acid L-arginine (Figure 6–17). The stimulus for the formation of NO can be flow-induced shear stress or a variety of receptor-coupled agonists that operate through the phospholipase C path (Figure 6–18). The effector mechanism by which NO causes vascular smooth muscle relaxation involves stimulation of a soluble guanylyl cyclase in vascular smooth muscle and a consequent increase in cGMP levels.

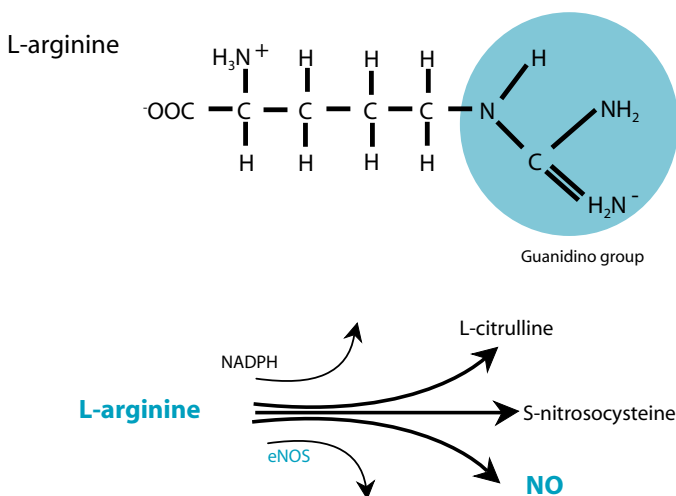


Figure 6–17 Synthesis of nitric oxide (NO) in vascular endothelial cells from L-arginine is catalysed by endothelial NO synthetase (eNOS). S-nitrosocysteine and L-citrulline are synthesized in the same reaction. Inducible NOS (iNOS) can also be used as a catalyst for this reaction. Under some conditions, the action of iNOS on L-arginine can produce superoxide radicals instead of NO.

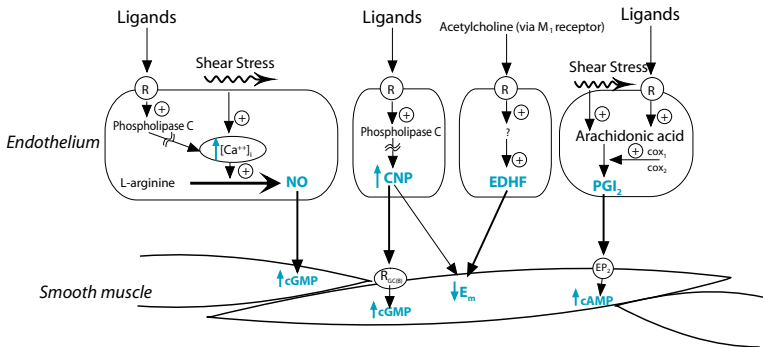


Figure 6–18 Synthesis of the endothelium-derived vasodilator factors, NO, CNP, EDHF, and PGI_2 . Their cellular mechanisms of relaxation involve increased levels of second messengers or hyperpolarization. cox_1 , cox_2 = cyclooxygenase 1 and 2, respectively; PKC = protein kinase-C; $\text{R}_{\text{GC(B)}}$ = B-type guanylate cyclase-linked receptor; NO = nitric oxide; CNP = C-type natriuretic peptide; EDHF = endothelium-derived hyperpolarizing factor; PGI_2 = prostaglandin I_2 .

2. C-type natriuretic peptide : CNP resembles ANP and BNP structurally but has no natriuretic action. It is synthesized at a basal rate in the brain, kidney, intestine, and endothelium. Its rate of release is further stimulated by agents that elevate protein kinase C, an intermediate in the phospholipase C signaling path. It causes vasodilatation by two separate mechanisms: (1) activation of the guanylate cyclase B-type receptor ($\text{R}_{\text{GC(B)}}$), leading to increased intracellular cGMP (see Figure 6–18), and (2) activation of large-conduction, Ca^{++} -activated K^+ channels, leading to membrane hyperpolarization.
3. Endothelium-derived hyperpolarizing factor: EDHF is a diffusible substance of presently uncertain chemical nature. It is a short-lived product of M_1 muscarinic receptor activation by acetylcholine, and there are two proposals for its identity: (1) **epoxyecosatrienoic acid** (EET), an intermediate in the cyclooxygenase pathway of arachidonic acid metabolism, or (2) the Ach-sensitive K^+ current that is also observed in cardiac pacemaker cells.

Endothelium-derived hyperpolarizing factor hyperpolarizes membrane potential. This desensitizes smooth muscle to constrictor influences.

4. Prostacyclin: PGI_2 is a major intermediary product in the metabolism of arachidonic acid by cyclooxygenase. It is rapidly converted to prostaglandin $\text{F}_{1\alpha}$, which has no biologic activity. Prostacyclin, however, is both an inhibitor of platelet aggregation and a vasodilator.

Vasoconstrictor products: The vascular endothelium also produces smooth muscle–constricting factors under certain circumstances. Such production varies greatly among species and also among different vascular beds within

a given species. The major contracting factors are (1) endothelin, (2) angiotensin II, (3) prostaglandin H_2 (PGH_2), (4) thromboxane (TXA_2), and (5) endothelium-derived contracting factor (EDCF).

Endothelin: This 21-amino acid peptide exists in three forms, endothelin 1, 2, and 3. They differ from one another by only a few amino acids. Endothelial cells produce only endothelin 1 and release it preferentially toward the abluminal side (Figure 6–19).[‡] Its vasoconstrictor actions are powerful and long-lasting. It operates through the ET_A receptor. Although it is normally a regulator of local function, endothelin is crucially involved in the development of atherosclerosis, where the macrophage becomes a huge source of endothelin and causes significant elevations of the peptide in circulating plasma.

Angiotensin II: Angiotensin II is produced locally because the angiotensin converting enzyme (ACE) is located in endothelial cells (see Figure 6–19). Thus, vascular endothelial tissue, by virtue of its wide distribution in the body, is the major site of conversion of angiotensin I to angiotensin II, and most circulating angiotensin II is spill-over from that which is locally

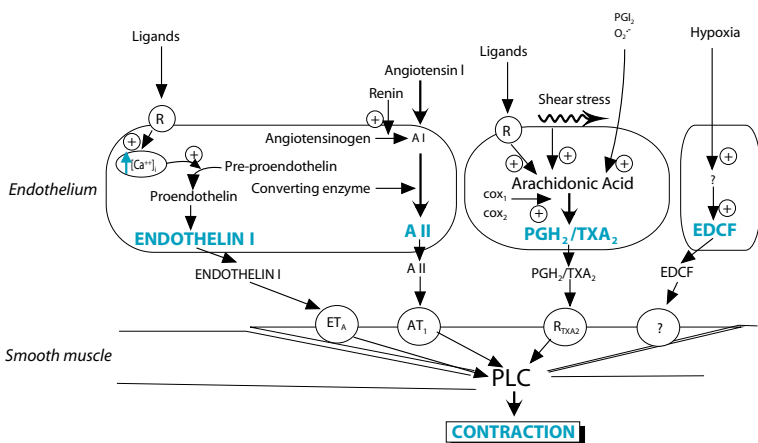


Figure 6–19 Synthesis of the endothelium-derived vasoconstrictor agents, endothelin, angiotensin II (A II), PGH_2 , TXA_2 , and EDCF. COX_1 , COX_2 = cyclooxygenase 1 and 2, respectively; PLC = phospholipase C activation; ET_A = endothelin A receptor; AT_1 = angiotensin type 1 receptor; R_{TXA_2} = thromboxane A_2 receptor; PGH_2 = prostaglandin H_2 ; TXA_2 = thromboxane A_2 ; EDCF = endothelium-derived contracting factor.

[‡]Endothelin 2 and 3 are synthesized in a variety of tissues, including the intestine, lung, spleen, and pancreas. The recent demonstration that the endothelin knockout is lethal has led to the discovery of its importance to the development of the neural network in the distal colon. Its absence during development causes Hirschsprung's disease.

formed rather than the product of freely circulating ACE acting on freely circulating angiotensin I.

Prostaglandin H_2 (PGH_2) and thromboxane A_2 (TXA_2): PGH_2 and TXA_2 are produced in small amounts in blood vessels when cyclooxygenase is activated by mechanical or a variety of chemical stimuli (see Figure 6–19). Prostaglandin H_2 has a short half-life because it is rapidly converted to one of PGD_2 , PGE_2 , or TXA_2 , depending on local concentrations of enzymes. Endothelial cells contain thromboxane A synthetase, the enzyme that forms TXA_2 from PGH_2 ; both bind the TXA_2 receptor and lead to vascular smooth muscle constriction by way of the phospholipase C pathway. Thromboxane A_2 is rapidly transformed to the biologically inactive TXB_2 .

Endothelium-derived contracting factor: EDCF is a substance of still unidentified chemical nature. It is released from endothelial cells in response to hypoxia, and such release requires activation of voltage-gated Ca^{++} channels.

DYNAMICS OF THE PERIPHERAL CIRCULATION

The peripheral circulation has three specific functions: (1) it distributes steady, uninterrupted flow to the capillary bed, even though heart action is pulsatile; (2) it distributes blood flow preferentially to tissues that have higher metabolic activity; and (3) it provides to the heart a return of peripheral blood (venous return) that is adequate for sustaining the cardiac output demanded by the tissues.

The pulsations of aortic pressure are smoothed out by the elastic and viscoelastic properties that characterize collagen and relaxed smooth muscle of the arterial vasculature. They allow the vessels to be stretched radially in systole so that their recoil provides a force for maintaining flow in diastole. The mechanisms that permit preferential distribution of blood flow depend equally on the arrangement of most blood vessels as a parallel network, on maintenance of a central distribution blood pressure, and on mechanisms for local regulation of resistance.

Resistance to Blood Flow

Flow resistance in blood vessels arises from friction of blood at the vessel walls and friction among neighboring layers of blood in regions where high flow velocity causes local turbulence.

Resistance in Single Blood Vessels (Poiseuille's Law)

The hydraulic resistance offered by a tube of uniform diameter, conveying a fluid of constant viscosity, is given by the **Hagen-Poiseuille law**:

$$\text{Resistance} \propto \frac{\text{Viscosity of the fluid} \times \text{Length of tube}}{\text{Diameter}^4}$$

It shows that blood vessel diameter has a major and inverse influence on vascular resistance. The most significant determinant of blood viscosity is the hematocrit. The higher the hematocrit, the greater is the viscosity.

The amount of energy that is required to cause flow through a tube of a certain hydraulic resistance is most readily measured as the difference between pressure at the inflow end and the outflow end (ΔP):

$$\Delta P = \text{Resistance} \times \text{Flow}$$

Resistance in Vascular Beds

Vascular beds consist of several blood vessels arranged either in series (Figure 6–20A) or in parallel (Figure 6–20B).

Blood vessels in series. Vessels are arranged in series if all the entering flow must pass sequentially through each vessel in order to leave the series network. Fine adjustments of resistance in a series network require that individual vessel diameters be adjusted precisely. Flow through the network is zero if any one of the vessels is blocked.

Blood vessels in parallel. Vessels are arranged in parallel if the flow entering such a network can pass through one or more of several alternative routes in order to leave the parallel network. Fine adjustments of resistance can be achieved by relatively coarse binary control mechanisms that either open or close individual blood vessels within the network. As a result, vascular beds that show a parallel arrangement of vessels can change their resistance by **vasomotion** (total closing or total opening of selected blood vessels). Opening of previously closed blood vessels is called **recruitment**.

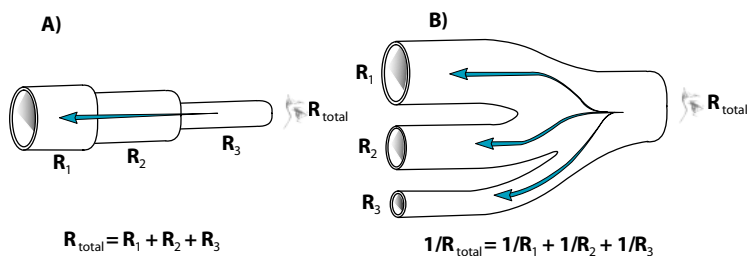


Figure 6–20 Common arrangements of blood vessels in a vascular bed. *A*, Blood vessels arranged in series. *B*, Blood vessels arranged in parallel.

Increased resistance in any one vessel decreases the flow in that vessel and decreases the flow through all vessels combined, unless the driving pressure increases. However, the vessels with unchanged resistance will receive a larger proportion of the total flow.

Figure 6–1 shows that most vascular beds are arranged in parallel and receive flow from the aorta. Increased flow resistance in one vascular bed will cause blood flow to be redistributed to other vascular beds. Decreased flow resistance in one vascular bed will preferentially draw flow toward that bed.

Pulsatile Flow and Vascular Impedance

The pulsatile nature of heart action, distensibility of blood vessels, and the inertial as well as viscous properties of blood together result in pulsatile flow changes that are not always in precise phase with the pressure changes at any given location in the vascular tree. For that reason, the ratio of pressure to flow, which represents resistance at steady pressure and flow, does not adequately express the load against which the heart must pump.

Vascular impedance is a relationship between the time courses of flow and pressure that takes into consideration inertial, frictional, and elastic properties that are distributed along the vascular tree. Its largest component is, under most circumstances, the resistive component and, therefore, vascular resistance is a reasonable approximation to many pressure/flow relationships.

Regulation of Blood Flow

Table 6–2 summarizes important factors in the regulation of blood flow.

Myogenic autoregulation. Arterioles contract when they are distended by elevated luminal pressure and dilate when distending pressure is reduced. The net effect is to maintain a relatively constant organ blood flow over a wide range of arterial pressure (**autoregulation**). Autoregulation is strongly expressed in the brain, kidney, and heart. Its cellular mechanism is thought to reside in stretch-activated Na^+ and Ca^{++} channels of vascular smooth muscle. They cause membrane depolarization, which then activates L-type Ca^{++} channels and leads to muscle contraction.

Metabolic regulation. Vascular smooth muscle in most tissues will relax in the presence of either reduced pO_2 or increased accumulation of metabolites (CO_2 , adenosine compounds, lactate, H^+ , and others). Such tissues as the heart and the brain show an exquisitely sensitive positive correlation among work, metabolic activity, and blood flow. The mechanisms by which such correlation is achieved are mostly unknown.

Table 6–2

Summary of Factors That Constrict or Relax Vascular Smooth Muscle in the Regulation of Blood Flow

Mechanism	Detail
Myogenic	Stretch-activated cation channels cause vasoconstriction
Metabolic	Metabolic products cause vasodilatation
Shear dependent	Vasodilatation by NO secondary to altered electrochemical gradients
Neurogenic	<ul style="list-style-type: none"> • Sympathetic constrictor nerves in most tissues • Parasympathetic dilator nerves in some secretory and spongiform tissues • NANC fibers constrict or dilate in specific areas
Humoral	<ul style="list-style-type: none"> • Constriction by angiotensin II and III, epinephrine, vasopressin, and serotonin • Dilatation by ANP, histamine, or inflammatory mediators

ANP = atrial natriuretic peptide; NANC = nonadrenergic/noncholinergic; NO = nitric oxide.

Adenosine. Adenosine causes vasodilatation in most vascular beds, except the kidney and the pulmonary artery. The mechanism is activation of the adenosine A_{2A} membrane receptor in smooth muscle, leading to elevation in cAMP.

pO₂. Reduction in pO₂ increases production of vasodilator agents, such as PGI₂ and NO.

pCO₂. Elevated pCO₂, such as would be present with increased tissue metabolism, leads to elevated [H⁺] in the extracellular fluid. Extracellular acidosis causes membrane hyperpolarization and subsequent vasodilatation in all vascular smooth muscle, except the lung. This hyperpolarization is the result of increased K⁺ efflux and may be traced to K⁺_{ATP} channels because such channels are pH sensitive.

Shear-dependent regulation. Blood vessels of all sizes show shear-dependent increase in vasodilator synthesis (NO and PGI₂). Shear activates the inward-rectifier K⁺ current (K₁) and causes endothelial membrane hyperpolarization and a consequent increase in the electrochemical driving force for Ca⁺⁺. Enhanced Ca⁺⁺ entry enhances NO synthesis by the eNOS pathway.

Neurogenic regulation. Nervous control of the circulation (1) permits rapid, tissue-specific adjustments in accordance with centrally established criteria; (2) can override local needs in times of emergencies; and (3)

adjusts the ratio of precapillary to postcapillary resistance and, with that, adjusts capillary hydrostatic pressure and the rate of fluid translocation to the interstitial space.

Sympathetic nerves.

Constrictor nerves: Most blood vessels are innervated by the sympathetic nervous system. The fibers are nonmyelinated postganglionic fibers that synapse with vascular smooth muscle at varicosities that are spaced at 3- to 10- μm intervals along the terminal nerve. The common neurotransmitter is norepinephrine (noradrenaline), which is synthesized within the presynaptic terminal from the amino acid **tyrosine**. Tyrosine, in turn, is produced by the hydroxylation of the essential amino acid **phenylalanine**. Whole egg and dairy products are major sources of phenylalanine.

The dominant postsynaptic receptor in the vasculature is the α_1 -adrenoreceptor. Its activation elevates $[\text{Ca}^{++}]_i$ through the phospholipase C pathway.

Strong sympathetic nervous activity can co-release **neuropeptide Y**, **ATP**, **dopamine**, or **dopamine- β -hydroxylase** with norepinephrine, and they can each influence local vascular reactions by receptor-dependent or -independent mechanisms.

Sympathetic nerves generally carry a basal activity of one to two action potentials per second. The associated degree of vasoconstriction can be modulated by two mechanisms: (1) a change in action potential frequency and (2) modulation of the local effectiveness of a given action potential frequency.

Modulation of action potential effectiveness: Modulation can occur both in the amount of norepinephrine released by each action potential and in the degree of smooth muscle activation by each quantum of norepinephrine. Norepinephrine release can be inhibited by a presynaptic receptor-mediated mechanism using a variety of ligands including norepinephrine itself, acetylcholine released from nearby parasympathetic nerve terminals in some tissues, and NO. Equally, norepinephrine release can be augmented by angiotensin II and a variety of peptides co-released with norepinephrine. The effectiveness of a given quantum of norepinephrine can be augmented (1) by ligands acting through their respective postsynaptic receptors (such as neuropeptide Y, purinergic P_2 , or dopaminergic D_2) and (2) by locally acting agonists or antagonists (for example, amphetamines and cocaine block noradrenaline uptake from the synaptic cleft and thereby increase the degree of vasoconstriction that is associated with a given frequency of presynaptic action potentials).

Dilator nerves: Evidence for the existence in humans of active vasodilatation by sympathetic cholinergic nerves to large muscle groups is not universally accepted.

Parasympathetic nerves. Tissues whose normal function requires sudden increases in blood flow (for example, salivary glands and external genitalia) contain parasympathetic nerves. They release the neurotransmitter **acetylcholine**. The vasodilator action of acetylcholine is indirect and occurs by (1) inhibition of norepinephrine release from sympathetic nerve terminals, (2) release of NO from endothelial cells, or (3) promotion of bradykinin formation.

NANC (nonadrenergic, noncholinergic) fibers. At least three populations of NANC fibers have been identified. They include **purinergic fibers** (their neurotransmitter is ATP and they cause vasoconstriction), **nitro-idergic fibers** (their neurotransmitter is NO and they cause vasodilatation), and **peptidergic nerves** (their neurotransmitter is either **calcitonin gene-related peptide** (CGRP) or **vasoactive intestinal peptide** (VIP) and both cause vasodilatation).

Humoral regulation. The renin–angiotensin system, circulating epinephrine, vasopressin, and atrial natriuretic peptides form the major endocrine influences on peripheral vascular function.

Renin-angiotensin. The proteolytic enzyme **renin**, which cleaves **angiotensinogen**, is secreted mostly from juxtaglomerular cells in the renal afferent arteriole. The major stimuli for its secretion are diminished renal arteriolar blood pressure and local β_2 -adrenoreceptor activation. Nonrenal sources of prorenin and renin do exist. The major source of plasma angiotensinogen is the liver, but it is also formed for local use in the heart and the brain. Cleavage of angiotensinogen by renin or renin-like enzymes yields angiotensin I, which has no biologic activity. Further degradation of angiotensin I yields several biologically active compounds: (1) angiotensin II is produced from angiotensin I by endothelial angiotensin-converting enzyme (ACE) or by human heart chymase, (2) angiotensin III is produced from angiotensin II by aminopeptidase, (3) angiotensin 1-7 is produced from angiotensin I by prolyl-endopeptidase, and (4) angiotensin IV is produced from angiotensin 1-7 by aminopeptidase.

Of these compounds, angiotensin II makes the greatest contribution to peripheral vascular behavior. Its normal plasma concentration is 3 to 5 pmol/L, and this can increase 100-fold in conditions of severe dehydration or renal arterial stenosis. Angiotensin II is a potent constrictor of vascular smooth muscle, and this action is mediated by the AT_1 receptor, using the activation of phospholipase C as the intracellular effector pathway (Figure 6–21). Angiotensin III also interacts with the AT_1 receptor, but its concentration is normally much less than that of angiotensin II.

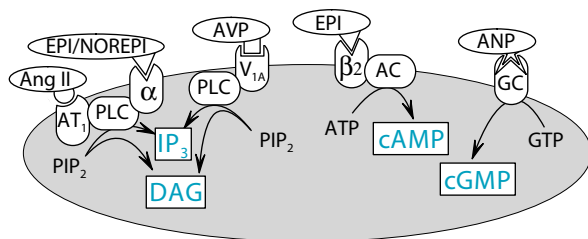


Figure 6–21 Vascular smooth muscle is richly supplied with a variety of receptors. The most important ones are those for angiotensin II (Ang II), epinephrine (EPI), norepinephrine (NOREPI), vasopressin (AVP), and atrial natriuretic peptide (ANP). Three second-messenger systems are involved. They are the phospholipase C (PLC) path, the adenylate cyclase (AC) path, and the guanylate cyclase (GC) path. α = alpha adrenoreceptor; AT_1 = angiotensin type-1 receptor; ATP = adenosine triphosphate; AVP = arginine vasopressin; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DAG = diacylglycerol; GTP = guanosine triphosphate; IP_3 = inositol trisphosphate; PIP_2 = phosphatidylinositol 4,5-bisphosphate; V_{1A} = vasopressin type 1A receptor.

Epinephrine (adrenaline). Epinephrine is produced in the chromaffin cells of the adrenal medulla and circulates at a normal plasma concentration of 40 to 100 pmol/L. It has relatively high affinity for both α - and β -adrenoreceptors so that it is sometimes difficult to predict whether its net effect will be one of constriction or dilatation. Blood vessels in the heart, splanchnic area, and skeletal muscle show mostly β_2 -mediated vasodilatation in response to epinephrine, whereas blood vessels in other organs show mostly α_1 -mediated vasoconstriction. Such differential responses help redirect cardiac output toward muscle during exercise, but they also contribute to the pooling of blood in the splanchnic area during a fainting spell caused by a strong emotion.

Vasopressin. Vasopressin is synthesized in the magnocellular portion of the supraoptic and paraventricular nuclei of the hypothalamus, transported by axonal mechanisms to the posterior pituitary and secreted from there into a portal circulation for distribution. Its vascular effects are exerted by the activation of V_{1A} receptors in the plasma membrane of smooth muscle. This causes vasoconstriction by a phospholipase C-mediated increase in cytosolic $[Ca^{++}]$.

Atrial natriuretic peptides. This family consists of the three members: ANP (28 amino acids), BNP (32 amino acids), and CNP (22 amino acids). The most significant contribution to vascular function is made by ANP, whose major source is cardiac atrial muscle cells and whose major stimulus for secretion is atrial stretch. Its main physiologic role is as a central

nervous system antagonist to sympathetic outflow in the maintenance of normal arterial blood pressure.

Serotonin. Serotonin is released from α -granules in platelets during clotting reactions. Vascular smooth muscle cells have a 5-HT₂ receptor whose activation by serotonin causes depolarization and subsequent activation of voltage-gated Ca⁺⁺ channels. Elevated [Ca⁺⁺]_i leads to vasoconstriction.

Histamine. The net effect of histamine in most vascular beds, except the lung, is vasodilatation, but it can be a vasodilator or a vasoconstrictor. This dual action results from its different effects on vascular smooth muscle, endothelium, or presynaptic sympathetic nerve terminals. Endothelial cells have H₁ receptors, and their activation causes vasodilatation by means of NO production. Presynaptic H₃ receptors can cause relative vasodilatation by inhibiting norepinephrine release from sympathetic terminals.

Vasoconstrictor actions arise from activation of VSM H₁ and H₃ membrane receptors. H₁ activation leads to VSM membrane depolarization and subsequent vasoconstriction. H₃ activation opens voltage-gated Ca⁺⁺ channels.

Inflammatory mediators. Inflammatory processes can cause local reddening and warming by locally increased blood flow. The cause is usually stimulation of eNOS by release of factors, such as kinins, histamine, prostaglandins, leukotrienes, or platelet activating factors.

Microcirculation

The microcirculation functions to exchange gases, nutrients, and waste products between blood and tissues. In addition, it controls the ratio of nutrient- to non-nutrient blood flow, the hydrostatic pressure within the capillary, the permeability of the capillary endothelium to fluids and macromolecules, the hydrostatic pressure and composition of the interstitial environment, and the growth of new capillaries in response to tissue demands.

Transcapillary exchange. Exchange of substances between blood and interstitium, across the capillary endothelium, is driven by physical forces and opposed by the selective permeability of the capillary wall. The most important three transmural forces that influence exchange are (1) differences in concentration, (2) differences in hydrostatic pressure, and (3) differences in protein osmotic (= **oncotic**) pressure.

Forces for transcapillary exchange.

Concentration gradients: Oxygen, carbon dioxide, and many other substances cross the capillary wall in response to differences in concentration.

Hydrostatic pressure: Cardiac action results in a capillary hydrostatic pressure that is normally 15 to 30 mm Hg (5 to 8 mm Hg in pulmonary capillaries), depending on whether or not the precapillary sphincter is closed or open. Within most capillaries, this pressure falls gradually from the arteriolar to the venular end when there is flow in the capillary and hemodynamic resistance can manifest its effects. Interstitial fluid pressure is normally between 0 and -7 mm Hg.

Oncotic pressure: Restricted capillary permeability to proteins allows these molecules to exert an osmotic force across the epithelium. Plasma oncotic pressure (plasma protein osmotic pressure) is normally near 28 mm Hg and changes little along the length of most capillaries because the amount of fluid that is lost by ultrafiltration from any one capillary is exceedingly small. Renal glomerular capillaries are an exception because they have a high filtration rate. Interstitial oncotic pressure depends on the endothelial permeability to protein and ranges between 20 and 60% of plasma oncotic pressure.

Exchange of fluids and electrolytes. Water and small solutes (up to a molecular weight of 10 kD) cross the endothelial barrier predominantly by way of the intercellular junctions in response to the locally prevailing net difference between the transepithelial gradients in hydrostatic and oncotic pressures (Figure 6–22). These differences change continuously, and the examples of Figure 6–22 should be regarded as illustrations only.

Capillary hydrostatic pressure is the most variable of the factors that determine transcapillary exchange. It is influenced by arterial and venous

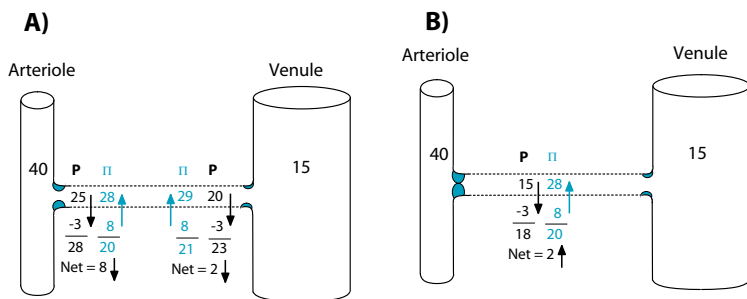


Figure 6–22 The Starling-Landis mechanism of fluid exchange across the capillary membrane. Net fluid movement occurs in response to a gradient in hydrostatic pressure or a gradient in oncotic pressure. *A*, When the precapillary sphincter is open, there is a hydrostatic pressure gradient (ΔP) of 28 mm Hg at the arteriolar end and 23 mm Hg at the venular end. The oncotic pressure gradients ($\Delta \pi$) are 20 and 21 mm Hg, respectively. The net filtration pressure is outward along the whole length of the capillary. *B*, When the precapillary sphincter is closed and capillary hydrostatic pressure is determined by local venous pressure, net filtration pressure is inward along the whole length of the capillary. P = hydrostatic pressure; π = oncotic pressure.

pressures, gravity, distance along the capillary, and any agents that change the arteriolar tone.

Figure 6–22 also illustrates the importance of capillary hydrostatic pressure to the overall capillary filtration/absorption balance. The old view that fluid leaves each capillary at its arteriolar end but re-enters at the venular end is not in agreement with current knowledge of prevailing pressures and interstitial fluid transport restrictions.

The most probable steady-state of microvascular fluid balance is one in which filtration and reabsorption are each intermittent phenomena, related to the phases of **vasomotion**.

Exchange of macromolecules. Transport by vesicles is likely to be a major factor for macromolecules greater than 3 nm in diameter.

Capillary angiogenesis. Capillaries have the potential to form collateral vessels for the purpose of perfusing hypertrophied tissue or bypassing obstructions. The following growth factors are involved to varying degrees: (1) **platelet-derived growth factors (PDGF)**, (2) **fibroblast growth factors (FGF)**, (3) **transforming growth factor beta (TGF β)**, and (4) **vascular endothelial growth factors (VEGF)**. The VEGF family, consisting of four different peptides and produced in many cells, is of particular importance in angiogenesis because it is able to trigger all components of the angiogenesis cascade. Endothelial cells are rich in VEGF receptors and are the only tissue to have such receptors.

Lymph Formation

The placement of initial lymphatics in the adventitia of arteries and arterioles allows them to be compressed and expanded in synchrony with the pulsatile changes in blood vessel diameter. In addition, the compression–relaxation cycles of parenchymal structures, such as muscle, intestine, or lung, in which the lymphatics are embedded are transmitted to the lymphatics. These external forces, acting on the overlapping leaflet structure of the initial lymphatics, act to collect and pump lymph. Further upstream, where it is propelled by peristaltic contraction of lymphangions, its rate of transport is modulated by transepithelial pressure (lymphangion preload), sympathetic nervous activity, α -adrenoreceptor agonists, and a variety of blood-borne agents.

Venous Return

Venous return is the average flow returning to the right atrium from the venae cavae. Because the heart and lungs have limited abilities to sequester

or supply blood, venous return can differ from cardiac output for only a few heart beats. Nevertheless, venous return is profoundly changed by factors that by themselves have little direct influence on the arterial side. Such factors include external pressures (arising, for example, from the **respiratory pump** or the **muscle pump**) and body orientation with respect to gravity (resulting in postural hypotension).

Respiratory pump. Inspiration is initiated by decreasing intrathoracic pressure. This is transmitted to the thoracic venae cavae and results in the augmentation of the pressure gradient from the extrathoracic veins to the intrathoracic veins. The net effect is increased venous return during inspiration.

Muscle pump. Muscle activity compresses veins from the outside and “massages” blood toward the heart in veins that are equipped with valves.

Orthostasis. The distance from, for example, the head and the absolute center of gravitational attraction (center of the earth) is significantly greater in the upright position than it is while supine. As a result, there are significant postural changes in gravitational hydrostatic pressure at the bottom of the column of blood that stands between the reference point for cardiovascular measurements (which is taken as the tricuspid valve) and a given measuring point, such as the superior sagittal venous sinus in the head or the great saphenous vein in the foot. Measured from the reference point and in an upright person, gravitational hydrostatic pressure increases toward the feet and decreases toward the head (Figure 6–23).

The total pressure measured at any point in the circulation is the sum of the remaining pressure created by the pumping action of the heart and the gravitational hydrostatic pressure arising from the weight of the column of blood that stands between the measuring point and the reference point at the tricuspid valve.

The space surrounding the outside of blood vessels is not a continuous column of fluid and, therefore, does not undergo the same pressure changes as the inside of blood vessels. As a result, the pressure difference across blood vessel walls (the transmural pressure) can change during postural changes. Arteries are strong vessels, little affected by postural changes. Veins are readily distended (or compressed) by changes in transmural pressure. For that reason, venous return is momentarily decreased as blood is pooled in the venous system on standing up suddenly, and it is increased momentarily as pooled blood is released from the venous system on lying down. The associated transient changes in cardiac output will cause commensurate changes in arterial blood pressure and can cause fainting on standing up suddenly.

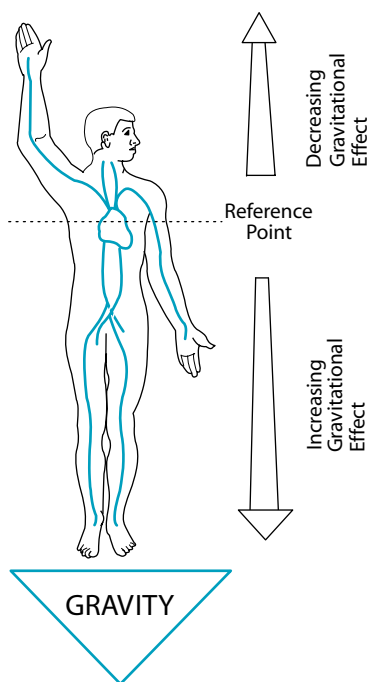


Figure 6–23 In an upright person and as a result of gravitational attraction, the total hydrostatic pressure within blood vessels increases from the heart toward the feet and decreases from the heart toward the head. The level of the tricuspid valve is universally taken as the reference point for gravitational effects.

Determinants of Arterial Blood Pressure

Arterial blood pressure changes with distance downstream from the heart and within each cardiac cycle, the arterial pressure fluctuates between **diastolic** and **systolic** pressures. **Pulse pressure** is the difference between systolic and diastolic pressures. The average pressure during a cycle is the **mean arterial blood pressure**.[§]

Diastolic arterial pressure. The diastolic blood pressure is the lowest pressure reached during a cardiac cycle. Given a systolic level from which the pressure begins to decline at the end of systole, diastolic arterial blood

[§]Because of the mathematical definition of the average value of a waveform, the formula for calculating mean ABP depends on the shape of the pressure pulse. In the region of the upper arm, mean ABP = diastolic ABP + one-third pulse pressure. In the region of the lower leg, mean ABP = diastolic ABP + half pulse pressure.

pressure is determined by (1) total peripheral vascular resistance, which is the major determinant of the rate of decline of ABP during ventricular diastole; the higher the peripheral resistance, the more gradual is the pressure decline in diastole (Figure 6–24); and (2) heart rate, which determines the duration of the diastolic interval and by that the point at which the steady decline of pressure in diastole is halted. The higher the heart rate, the higher is the diastolic arterial pressure (see Figure 6–24).

Systolic arterial pressure. Systolic blood pressure is the highest pressure reached during a cardiac cycle. Given a diastolic arterial blood pressure on which the effect of a subsequent cardiac contraction is superimposed, systolic arterial blood pressure is influenced by cardiac performance, aortic compliance, and total peripheral vascular resistance (TPR).

Total peripheral vascular resistance contributes because it determines the rate of outflow from the arterial system to the capillary network and, thereby, the net volume added to the arterial reservoir during systole (Figure 6–25). The contribution of TPR effects to systolic pressure is about 20% of that attributable to cardiac performance. As a result, cardiac performance and aortic compliance are the major factors that determine how high systolic pressure will rise above diastolic pressure in a cardiac cycle.

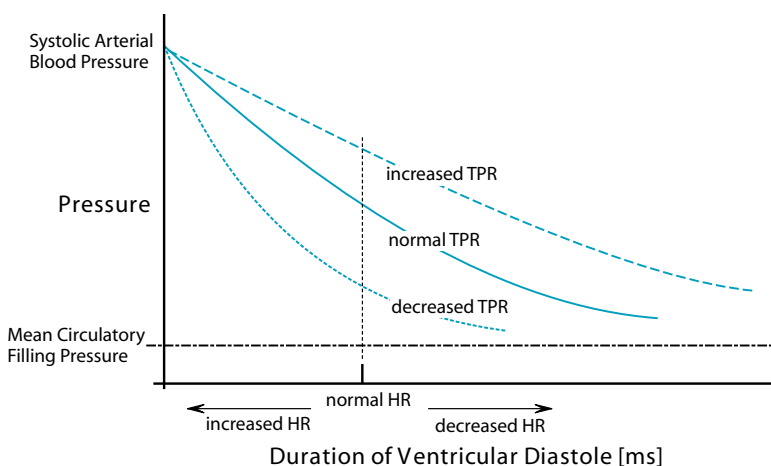


Figure 6–24 During diastole, the arterial pressure declines as blood leaves the arterial system through the arterioles. The rate of decrease is inversely related to total peripheral resistance (TPR). The pressure decline stops when the heart beats again. As a result, diastolic arterial pressure increases with increased TPR or increased HR. When the heart stops, the arterial pressure approaches mean circulatory filling pressure. HR = heart rate.

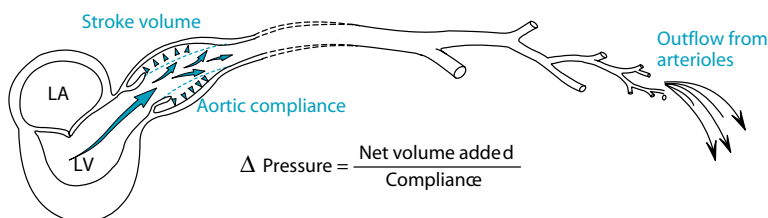


Figure 6–25 During systole, the stroke volume is rapidly ejected into the root of the aorta. At the same time, some blood leaves the arterial system through the arterioles. The net volume added during systole is the difference between left ventricular stroke volume and the normally very small peripheral outflow during the brief timespan of ventricular ejection.

Arterial pulse pressure. The pulse pressure, being the difference between systolic and diastolic pressures, is under most circumstances determined by cardiac performance and aortic compliance. Progressive increase in aortic stiffness (decrease in compliance) is the major reason for increased aortic pulse pressure in the elderly.

REGIONAL VASCULAR BEDS AND SPECIAL CIRCULATIONS

Circulation to the Skin

The metabolic needs of skin are low and consume a miniscule fraction of its total blood flow. The major fraction subserves the regulation of body temperature. These dual needs are met, in part, by the specialized anatomy of the cutaneous vasculature.

Anatomic Features

There is a large number of **arteriovenous anastomoses** (see Figure 6–15). They permit flows that are far in excess of metabolic needs.

The needs of skin tissue nourishment are met by a capillary plexus, and the needs of body temperature regulation are met by a venous plexus, controlled by A-V anastomoses.

Control of Skin Blood Flow

Skin blood flow is influenced by both body core temperature and local skin temperature. As core body temperature increases, so does skin blood flow. This results initially from hypothalamically directed withdrawal of sympathetic tone to the smooth muscle sphincters controlling A-V anastomoses.

At higher temperatures, release of bradykinin secondarily to cholinergic activation of sweat glands plays a major role in local vasodilatation.

Increasing local skin temperature also increases skin blood flow. The mechanism is thought to be a temperature-related reduction in the sensitivity of local vascular smooth muscle to norepinephrine. At extremely high local temperatures ($> 45^{\circ}\text{C}$), blood flow changes as part of a local injury response, and at low temperatures ($<10^{\circ}\text{C}$), there is cold vasodilatation because vascular smooth muscle is unable to contract.

Role of Skin Circulation in Heat Transfer

Blood carries heat to the body surface, where it can be transferred to cooler surroundings by conduction, convection, radiation, or water (sweat) evaporation.

Blushing and Flushing

Blushing and flushing are examples of centrally directed, regional dilations of the cutaneous circulation. These responses generally involve the face, ears and neck, sometimes the upper chest, and occasionally the epigastric area. They are observed in emotional settings characterized by high autonomic nervous activity. Although most blushing is not accompanied by noticeable eccrine sweating (dry flush), its frequent association with sweat gland stimulation (wet flush) suggests that bradykinin might be involved. On the other hand, the effectiveness of β -adrenergic antagonists in mild forms of hyperhidrosis and excessive facial blushing suggests that circulating adrenaline might be involved. In severe cases, thoracic sympathectomy between T2 and T4 is said to be effective. Ganglia in that region supply the heart and lung as well as upper body blood vessels, sweat glands, and arrectores pilorum muscles.

Cutaneous Response to Injury

Insect bites, allergic reactions, burns, and mechanical injury elicit a cutaneous vascular response consisting of three elements. The response is, therefore, called the **triple response**:

- Local dilatation at the site of injury (the red reaction) results from local release of vasodilators, such as histamine, bradykinin, prostaglandins, and NO.
- The appearance of local edema (the wheal) is caused, in part, by increased local capillary permeability to proteins (mediated by histamine and others) and, in part, by the elevated capillary hydrostatic pressure arising from arteriolar dilatation.

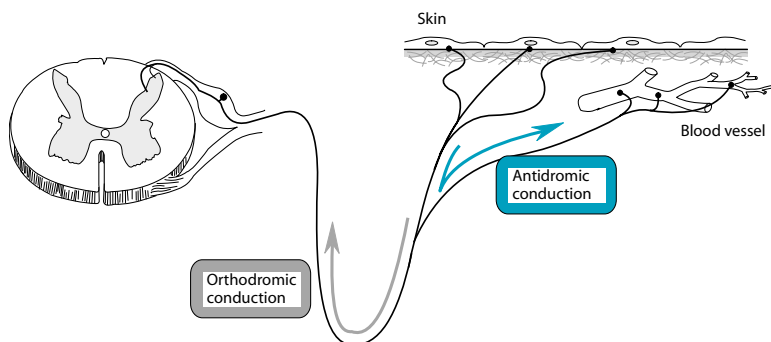


Figure 6–26 The axon reflex is thought to be responsible for the flare that accompanies cutaneous injury. Nociceptors that are located in the skin send their action potentials toward the central nervous system. However, they also are directed antidromically among nociceptive fibers that terminate near cutaneous blood vessels.

- The flare of adjacent vasodilatation is caused by an **axon reflex** that is initiated by local sensory fibers whose afferent action potentials are partly short-circuited to branching nociceptive fibers, where antidromic conduction causes release of calcitonin gene–related peptide (CGRP), the main neurotransmitter responsible for the vasodilatation of the axon reflex (Figure 6–26).

Circulation in Skeletal Muscle

When skeletal muscle is resting, its blood flow is low (3 to 4 mL/min•100 g), and its vessels are strongly influenced by centrally directed, α -adrenergic stimuli. As a result, resting skeletal muscle is a major locus of peripheral resistance adjustments.

During exercise, muscle blood flow can increase to as much as 80 mL/min•100 g, and this increase is brought about mostly by locally produced metabolic factors, such as CO_2 and H^+ , the latter arising mostly from production of lactic acid.

Coronary Circulation

Coronary O_2 demand and consumption are determined mostly by the wall tension that needs to be developed for the ejection of stroke volume.

The coronary circulation is unique in that systolic mechanical compression makes myocardial perfusion highly dependent on diastolic arterial pressure.

Anatomy of the Coronary Circulation

The main distributing coronary arteries run on the epicardial surface, penetrate perpendicularly into the myocardium, and then arborize in the endocardial layer of muscle (Figure 6–27). This physical arrangement makes them vulnerable to compression by cardiac tissue forces in the spirally arranged muscle fibers (see Figure 6–2).

Regulation of Coronary Blood Flow

Cardiac muscle has nearly maximal O_2 extraction. Therefore, increased needs for O_2 must be met by increased flow. This must be accomplished in spite of compression of the vascular supply while the heart is in systole.

Tissue pressure (vascular waterfall). Tissue pressure provides a strong mechanical impediment to flow during systole, particularly in the sub-endocardial vessels. This has been named the **vascular waterfall** because flow is not determined by the difference between coronary arterial and coronary venous pressures but by the difference between coronary arterial

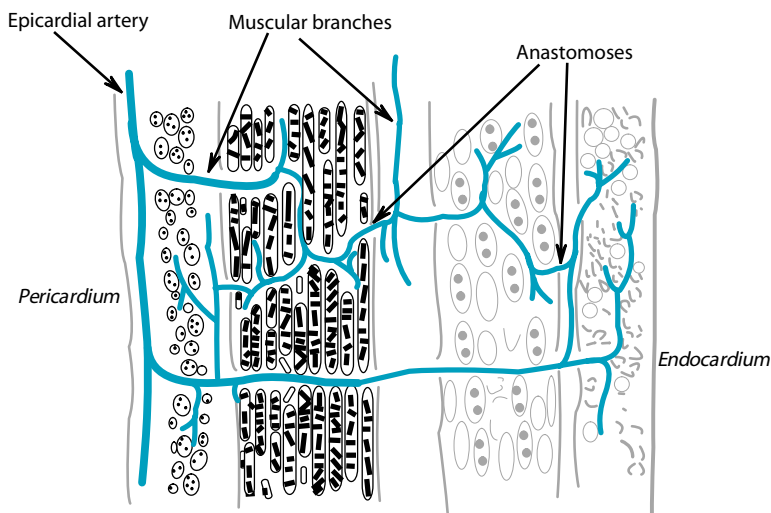


Figure 6–27 Coronary blood vessels penetrate perpendicularly from the epicardium to the endocardium and there run parallel to the endocardial surface. Those running parallel to the surface are readily compressed by pressure against the endocardium (left ventricular pressure), whereas those running perpendicularly are compressed by shear between adjacent layers as the contracting muscle bundles slide over one another.

and tissue pressures. Therefore, coronary blood flow is maximal during ventricular diastole.

Metabolic factors. There is a strong dependence of coronary flow on the rate of myocardial O_2 consumption (MVO_2), and this suggests that the heart regulates its own blood supply by elaborating coronary vasodilators in proportion to its rate of energy expenditure. The linkage is provided by **adenosine**. Adenosine derives from ATP, whose hydrolysis during the muscle power stroke produces ADP (Figure 6–28). The enzyme myokinase produces AMP from ADP, and dephosphorylation of AMP yields either IMP (imidazole monophosphate) if the enzyme **AMP deaminase** predominates or adenosine if the enzyme **5' nucleotidase** predominates. Adenosine diffuses out of the myocyte and causes vasodilatation by activating A_2 receptors and elevating cAMP.

Neurogenic factors. Coronary vessel sympathetic innervation is of the adrenergic type, and the dominant coronary vascular adrenoceptor is of the alpha type. Accordingly, cardiac sympathetic nerve stimulation causes net vasoconstriction in the coronary vascular bed viewed as a whole. However, in a functioning organism, the vasoconstrictor effect of sympathetic stimulation is quickly masked by the metabolic effects of β_1 -mediated increases in heart rate and cardiac performance.

Cerebral Circulation

Total cerebral blood flow is kept nearly constant in the range of 60 to 160 mm Hg arterial blood pressure by the myogenic mechanisms of autoregulation.

Blood–Brain Barrier

Bloodborne hydrophilic nonelectrolytes and ions do not generally have access to the brain because of the tight epithelium of most cerebral capil-

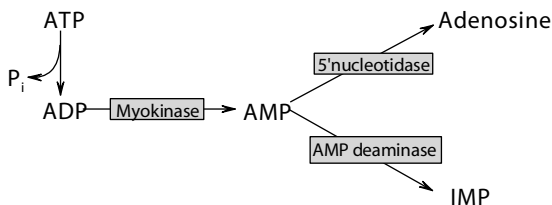


Figure 6–28 Adenosine or imidazole monophosphate (IMP) are produced from adenosine monophosphate (AMP) depending on the relative activity of 5' nucleotidase or AMP deaminase. ADP = adenosine diphosphate; ATP = adenosine triphosphate; P_i = inorganic phosphate.

laries. As a result, neurons and other cells of the central nervous system are bathed in a specifically regulated extracellular fluid, the cerebrospinal fluid.

Structure of the blood–brain barrier. Except in a few areas, most notably the circumventricular organs surrounding the third and fourth ventricles,^{||} most cerebral capillaries are of the nonfenestrated type, and their endothelial cells form tight intercellular junctions that prevent diffusion of many substances from the blood to the brain cells while permitting unrestricted diffusion to O_2 , CO_2 , and other lipid-soluble substances.

Transport functions of the blood–brain barrier. Substances such as amino acids, ketone bodies, organic acids, choline, and, most surprisingly, glucose are transported by specific membrane protein-dependent mechanisms. Although glucose is the major energy substrate in the brain, its rate of passive transport across capillary endothelium is slow. It moves across by way of the GLUT-1 transporter (not dependent on insulin), the GLUT-1 55K form being of particularly high concentration. Their aggregate rate of transport is double to triple the rate needed for normal metabolism. GLUT-3 is located in neuronal membranes and facilitates glucose uptake there.

Regulation of Cerebral Blood Flow

The blood–brain barrier prevents humoral regulators of vascular resistance, including plasma H^+ , from gaining access to cerebral vascular smooth muscle, and although the vasculature is innervated, nerves play a minor role in the control of vascular resistance. Metabolic chemical factors are the dominant regulator of cerebral blood flow.

Cerebral blood vessels are very sensitive to plasma pCO_2 because CO_2 readily diffuses into vascular smooth muscle cells. There it forms H_2CO_3 initially and then H^+ ions. Intracellular H^+ causes vasodilatation. Alterations in arterial pO_2 are less effective than pCO_2 but do exert noticeable influence on cerebral blood flow. Hypoxia increases cerebral blood flow, whereas hyperoxia decreases it.

Splanchnic Circulation (Gastrointestinal Tract, Liver, Spleen, and Pancreas)

This is a large, highly permeable vascular bed, containing mostly fenestrated capillaries. Its primary role is as a transport system for support of GI digestive functions. It can also serve as a reservoir for blood volume. This is

^{||}Area postrema, choroid plexus, subfornical organ, organum vasculosum of the lamina terminalis (OVLT).

thought to contribute to the cardiovascular events accompanying fainting caused by extreme emotional states.

Control of Vascular Resistance

Humoral mechanisms. Digestive enzymes like **gastrin** and **cholecystokinin** are prominent local vasodilators that increase local blood flow during periods of increased digestive activity. Additional vasodilator influence arises from the β -adrenergic receptor agonist action of circulating epinephrine.

Neurogenic mechanisms. Intestinal blood vessels are innervated both extrinsically by noradrenergic sympathetic fibers and intrinsically by fibers of the enteric nervous system. Extrinsic sympathetic activation causes vasoconstriction. However, the splanchnic circulation quickly escapes from sustained sympathetic constrictor activity. Enteric nervous fibers release a variety of peptidergic and nonpeptidergic neurotransmitters including **vasoactive intestinal peptide** (VIP) and NO. Both cause vasodilatation.

Pulmonary Circulation

Because of low pulmonary vascular resistance, the pressures in this region are low. As a result, blood flow distribution within the lung is greatly affected by posture (upright versus supine) and by fluctuations in alveolar pressure during respiration.

Transcapillary Exchange of Fluid and Proteins

The principles of microcirculatory function apply, but there are quantitative differences: (1) pulmonary capillary hydrostatic pressure is highly dependent on posture (upright versus supine), on location within the lung, and on whether or not there is a state of rest or exercise; the range that spans these conditions and locations is 6 to 15 mm Hg; and (2) the lungs have an extensive lymphatic network, and this creates both a substantially negative pulmonary interstitial hydrostatic pressure (~ -8 mm Hg) and an effective mechanism for clearing plasma ultrafiltrate.

Control of Pulmonary Vascular Resistance

Pulmonary arterioles and venules have little smooth muscle. As a result, neuronal and humoral effects are present, but they are weak.

Mechanical influences, such as the effect of gravity on intravascular distending pressure and the compressive effect of air-filled alveoli on blood vessel, exert major influences on pulmonary vascular resistance (Figure 6–29). Contrary to their effects in most vascular beds, hypoxia and hypercapnia

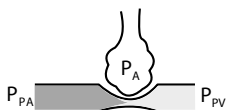


Figure 6–29 Blood flow in the lung is determined by pulmonary arteriolar pressure (P_{PA}), alveolar pressure (P_A), and pulmonary venular pressure (P_{PV}).

cause vasoconstriction in the lung. This unusual response of pulmonary vascular smooth muscle has the effect of shifting blood flow away from poorly ventilated alveoli.

CARDIOVASCULAR REGULATION

Maintenance of the extracellular milieu within the life-sustaining limits of each vital parameter requires two levels of cardiovascular regulation:

Individual tissues must be able to respond to their own metabolic needs and to adjust their own vascular resistance so as to receive sufficient blood flow for their needs.

The cardiovascular system as a whole must (1) maintain an adequate perfusion pressure for all tissues (= mean arterial blood pressure) because maintenance of arterial blood pressure at a constant level allows each organ to control its own perfusion by adjusting its vascular resistance and (2) preferentially direct cardiac output to the critical organs (brain and heart) when, under crisis conditions, blood pressure can no longer be maintained at an adequate level.

Maintenance of Arterial Blood Pressure

The normal ranges for blood pressure in the aorta of the human adult (aged < 60 years) are 70 to 89 mm Hg (9.3 to 11.4 kPa) diastolic and 110 to 130 mm Hg (14.6 to 17.3 kPa) systolic. Values beyond these are described as **hypertensive**. At any age, women generally show lower pressures than men, the major difference being in the systolic arterial blood pressure. In Western societies, there is a gradual increase in blood pressure with age, and beyond age 60 years, systolic arterial blood pressure increases relatively steeply up to 150 mm Hg (19.9 kPa) by age 80 years.

Both short-term and long-term control mechanisms help maintain arterial blood pressure within its normal limits.

Short-Term Mechanisms of Blood Pressure Regulation

These mechanisms account for regulatory responses that are seen within seconds after a sudden change and can be maintained for up to 2 weeks.

Dominant among them are the responses to peripheral neural sensors and to central nervous system ischemia (the **Cushing reflex**).

Neural control of cardiovascular function.

Peripheral sensors, afferent paths, and reflex effects. Afferent fibers arise from two classes of peripheral sensors, responsive to changes in their microenvironment: **mechanosensors** monitor stretch, and **chemosensors** monitor the chemical environment. Both classes exhibit a **stimulus threshold** and **sensor resetting**.

The stimulus threshold is that level of stimulus intensity below which the sensor gives no response. Most neural sensors respond with an almost linearly increasing number of action potentials for suprathreshold stimuli. Sen-

Table 6–3

Peripheral Sensors in Cardiovascular Control

Modality	Location	Afferent Path	Reflex Response to Receptor Excitation
Mechanosensors	Carotid sinus	Carotid sinus n. to glossopharyngeal n.	↓ HR; ↓ cardiac contractility; ↓ TPR
	Type I		
	Type II		
	Aortic arch	Aortic depressor n. to vagus	Same as carotid sinus, but at higher threshold
	Type I		
	Type II		
	Atrial wall	Vagus	↓ Vasopressin; ↑ HR; ↓ renal vascular resistance
	Ventricular wall	Vagus	↓ HR; ↓ cardiac contractility; ↓ TPR
		Sympathetic afferents	↑ HR; ↑ TPR
Chemosensors	Aortic body	Aortic depressor n. to vagus	↑ Ventilation; cardiovascular effects are secondary (respiratory pumping)
	Carotid body	Carotid sinus n. to glossopharyngeal n.	
	Ventricular wall	Vagus	↓↓ HR; ↓ renal vascular resistance
		Sympathetic afferents	↑ HR; ↑ TPR

HR = heart rate; TPR = total peripheral resistance.

sor resetting is a phenomenon by which the number of action potentials generated by a given stimulus intensity decreases if the stimulus is maintained at that intensity. Such resetting occurs within a few minutes in some sensors.

The sensors involved in cardiovascular regulation are concentrated in the carotid sinus and the cardiopulmonary area. Cardiovascular responses to input from mechanosensors normally dominate in importance over those from chemosensors.

Mechanosensors are found in the carotid sinus (carotid sinus baroreceptors), the aortic arch (aortic baroreceptors), the atrial myocardium, and the ventricular myocardium.

1. Carotid sinus stretch-sensitive afferents are collected into the carotid sinus nerve, a branch of the glossopharyngeal nerve. Two types can be distinguished, partly on the basis of fiber type and partly on the basis of resetting characteristics. Type I baroreceptors have primarily large, myelinated A-fiber afferents, contribute more to dynamic pressure changes, and, therefore, are the primary buffers against changes in arterial pressure. Type II baroreceptors have mostly smaller A-fiber and unmyelinated C-fiber afferents. Their firing patterns tend to be continuous, and their wide operating ranges suggest that they regulate primarily baseline, resting levels of arterial blood pressure. Excitation of either type leads to inhibitory responses characterized by bradycardia, decreased cardiac contractility, and decreased total peripheral vascular resistance.
2. Aortic arch stretch-sensitive afferents are collected into the aortic depressor nerve, a branch of the vagus nerve, and, like carotid sinus sensory endings, they also show type I and type II sensors. Their excitation, like that of carotid sinus mechanosensors, leads to inhibitory responses in the heart and peripheral vasculature. Compared with carotid sinus sensors, aortic arch sensors have a higher threshold and are, therefore, less effective at low arterial blood pressure.
3. Atrial stretch sensors have mostly myelinated vagal afferents. Their excitation leads to a pattern of reflex responses that appear to have the purpose of protecting the circulation from excess volume: vasopressin secretion is suppressed, heart rate is generally increased (Bainbridge reflex), and renal vascular resistance is decreased.
4. Ventricular stretch sensors can be connected to the central nervous system either by nonmyelinated vagal afferents or by sympathetic afferents. Activation of vagal ventricular stretch sensors leads to bradycardia, decreased cardiac contractility, and decreased total peripheral vascular resistance. Activation of sympathetic ventricular stretch sensors leads to excitatory responses (tachycardia and peripheral vasoconstriction). The physiologic purpose of such positive feedback is not clear.

Chemosensors are found in the carotid and aortic bodies as well as in the ventricular myocardium.

1. Carotid and aortic chemosensors are most sensitive to $p\text{CO}_2$, and input from them has its greatest effect on ventilation. This will secondarily affect cardiovascular function by means of the respiratory pump mechanism.
2. Ventricular chemosensors with vagal afferents are very responsive to serotonin but also respond to bradykinin, prostaglandins, and adenosine. Their excitation causes a profound bradycardia and renal arterial vasodilatation (= the Bezold-Jarisch reflex). Accordingly, their physiologic role may be protective in settings of deranged myocardial chemistry.
3. Activation of ventricular chemosensors with sympathetic afferents also leads to excitatory responses.

Central nervous system pathways. The cardiovascular reflex centers are located in the **midbrain** (pons and medulla) (Figure 6–30). Neurons in the nucleus ambiguus and the rostral ventrolateral medulla have tonic activity that sets basal rates of autonomic preganglionic outflow to the heart, blood vessels, and adrenal medulla. These basal rates are increased or decreased in accordance with nucleus tractus solitarius activity and central chemical signals. Sympathetic preganglionic activity can be modulated either by effects on rostral ventrolateral medulla (RVL) or secondarily by factors that regulate the inhibitory activity exerted by caudal ventrolateral medulla on RVL (see Figure 6–30).

Integration of cardiovascular function with other physiologic systems is achieved through tracts from the hypothalamus to the midbrain. Emotional correlates derive from limbic and cortical tracts.

Hormonal control of cardiovascular function.

Vasopressin. Diminished activity in myelinated vagal afferents from atrial stretch sensors promotes vasopressin release. This hormone has two primary targets. It causes (1) constriction in vascular smooth muscle by activating V_1 receptors and (2) increased water reabsorption from the renal collecting duct by insertion of aquaporins (water channels) into the luminal membrane. This is a V_2 receptor–mediated response.

Renin–angiotensin–aldosterone system. The juxtaglomerular cells of the renal afferent arteriole increase their release of renin in response to local stimuli, such as decreased vessel wall stretch, β_1 -adrenoreceptor activation, or decreased macula densa sodium chloride (NaCl) transport. The cascade leading from renin to the vasoactive angiotensins is described in more detail in an earlier section of this chapter.

Regulation of the heart. The total volume of blood ejected each minute from each ventricle (= the cardiac output [CO]) is the product of stroke volume (SV) and heart rate (HR):

$$\text{HR} \times \text{SV} = \text{CO}$$

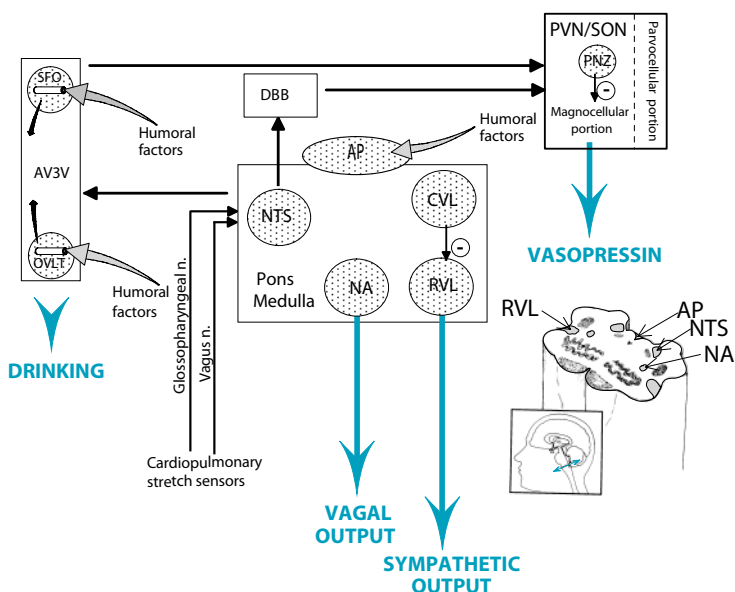


Figure 6-30 Central nervous system areas of cardiovascular control and integration with centers for fluid intake and vasopressin synthesis. The inset on the lower right shows the location of midbrain structures. Cardiopulmonary afferents enter the central nervous system and first synapse in the NTS. The NTS is extensively linked to the AV3V region, the DBB, the NA, the CVL, and the RVL. AV3V and DBB communicate with the PVN and SON. Chemical input reaches the AV3V region through the SFO and the OVLT and reaches the midbrain areas through the AP. AV3V integrates cardiorenal responses and drinking behavior. Pons and medulla in the midbrain govern autonomic nervous outflow through NA and RVL. PVN and SON are the sites of vasopressin synthesis. AP = area postrema; AV3V = anteroventral region of the third ventricle; DBB = diagonal band of Broca; CVL = caudal ventrolateral medulla; NA = nucleus ambiguus; NTS = nucleus tractus solitarius; OVLT = organum vasculosum of the lamina terminalis; PNZ = perinuclear zone of SON; PVN = paraventricular nucleus; RVL = rostral ventrolateral medulla; SFO = subfornical organ; SON = supraoptic nucleus.

In normal adults, HR ranges from 50 min^{-1} at rest to 180 min^{-1} during heavy exercise, SV ranges from 70 to 80 mL at rest to 110 mL in exercise, and CO ranges from 3.5 L/min to near 20 L/min, but values approaching 50 L/min have been reported in some athletes.

Regulation of the heart involves changes in both HR and SV. Myocardial contractility is the major short-term determinant of the completeness of systolic ventricular emptying and, therefore, of SV.

The heart is innervated by efferent vagal fibers as well as by postganglionic cardiac sympathetic fibers. Many of the sympathetic fibers originate in the **stellate ganglion**. Vagal fibers are distributed mostly to the atria and the region of the conduction system and, therefore, affect primarily heart

rate. Sympathetic fibers are distributed to all parts of the heart and, therefore, modulate both heart rate and cardiac performance.

Regulation of heart rate. Each heart beat begins with an action potential that is generated spontaneously in one pacemaker cell (the dominant pacemaker cell), normally located in the region of the SA node. Therefore, heart rate depends on the time required by the dominant pacemaker cell to reach the gating voltage for L-type Ca^{++} channels.

Minute-to-minute changes in heart rate are achieved mainly by changing the slope of the phase 4 membrane potential in the dominant pacemaker cell. As described in more detail under “Cardiac Excitation” and “Ion Currents,” sympathetic stimulation increases the slope and with that increases heart rate, and vagal stimulation decreases the slope and, therefore, decreases heart rate (Table 6–4).

Regulation of cardiac contractility. As described earlier under “Determinants of Cardiac Performance,” short-term changes in contractility arise predominantly from changes in Ca^{++} dynamics. They express themselves as an increase in the slope of the end-systolic pressure-volume relationship (see Figure 6–12).

In physiologic settings, contractility is influenced mostly by sympathetic discharge, circulating epinephrine, and coronary blood flow (see Table 6–4). The first two operate by activation of myocardial β_1 -adrenoreceptors. Such activation increases inotropic state primarily by increasing $[\text{Ca}^{++}]_i$ by mechanisms that depend on cAMP-mediated increase in L-type Ca^{++} current across the sarcolemma and increases lusotropic state by three mechanisms: (1) increased phosphorylation of phospholamban and consequently stimulated Ca^{++} uptake into the sarcoplasmic reticulum, (2) decreased Ca^{++} sensitivity of troponin-C, brought about by increased phosphorylation of troponin-I, and (3) increased rate of Ca^{++} removal

Table 6–4

Target Effects in Cardiovascular Regulation

Parameter	Increased by...Activity	Decreased by...Activity
HR	↑ Cardiac sympathetics ↓ Cardiac vagal	↑ Cardiac vagal
SV	↑ Cardiac sympathetics Positive inotropes	↓ Cardiac sympathetics Negative inotropes
TPR	↑ Peripheral sympathetics Vasoconstrictor chemicals	↓ Peripheral sympathetics Vasodilator chemicals

HR = heart rate; SV = stroke volume; TPR = total peripheral resistance.

from the cytosol by way of the sarcolemmal Ca^{++} -ATPase. Increased phosphorylation of C protein is also observed, but its role in diastolic relaxation is not yet clear.

The effects of an increase in cardiac contractility are to increase (1) left ventricular systolic pressure, (2) rate of rise of left ventricular pressure, (3) stroke volume by ejecting to a lower end-systolic volume, and (4) rate of early ventricular filling by greater ventricular elastic recoil and by increased rate of ventricular relaxation.

Regulation of peripheral resistance and cardiac output distribution.

The vascular architecture of most tissues consists of a large number of blood vessels that are connected in parallel. As a result, their resistance is determined both by the diameter of individual blood vessels and the total number of vessels being perfused.

Spontaneous activity, modulated by locally vasoactive factors, in pre-capillary sphincters determines whether a given capillary is open or closed and, thereby, determines the number of vessels being perfused. In a resting person, such random activity accounts for 80% of total peripheral resistance.

Short-term whole-body regulation of total peripheral resistance depends primarily on the activity in sympathetic adrenergic constrictor nerves and their activation of α -adrenoceptors in vascular smooth muscle. Additional contributions are made by the vasoconstrictor effects of vasopressin (V_1 receptors) and angiotensin II (AT_1 receptors).

The innervation of blood vessels is organized topographically so that there is a hierarchy to the sequence in which vascular beds are constricted or relaxed. For example, when the blood pressure falls and the system responds with vasoconstriction, the skin and splanchnic circulation are constricted first, while muscle perfusion is preserved until additional vasoconstriction is required.

The parallel arrangement of vascular beds (see Figure 6–1) means that the perfusion of any one bed and its share of cardiac output depend inversely on its vascular resistance.

Overall scheme of cardiovascular regulation. The average perfusion pressure of all vascular beds is mean arterial blood pressure (ABP). It is determined by flow (cardiac output [CO]) and resistance to flow (total peripheral resistance [TPR]):

$$\text{ABP} = \text{TPR} \times \text{CO}^\#$$

[#]This formulation assumes that the mean right atrial pressure is zero.

Mean arterial blood pressure is regulated to a **set point**, and it is this regulation that makes it possible for individual tissues to regulate their flow in accordance with their metabolic need.

Total peripheral resistance, as opposed to the vascular resistance of an individual tissue, is adjusted in concert with cardiac output for the purpose of regulating mean arterial blood pressure (Figure 6–31). Adjustment of *total* peripheral resistance often involves a conflict between local tissue demands and the central need for regulating mean arterial blood pressure.

In physiologic settings, a balance is struck between metabolically driven vasodilatation and neurohumoral vasoconstriction. Tissues with high metabolic activity have low vascular resistance because, in them, vasodilator actions of metabolites counteract centrally directed sympathetic vasoconstrictor influences. On the other hand, blood vessels in tissues that are less active are constricted by sympathetic nerves. In emergency settings, such as during blood loss, the extreme vasoconstriction that is necessary to preserve flow to the vital tissues, the heart, and the brain can cause local acidosis, tissue damage, and eventually a state of circulatory shock.

Long-Term Mechanisms of Blood Pressure Regulation

The three most important long-term mechanisms for the regulation of arterial blood pressure are cardiac hypertrophy, the renin–angiotensin–aldos-

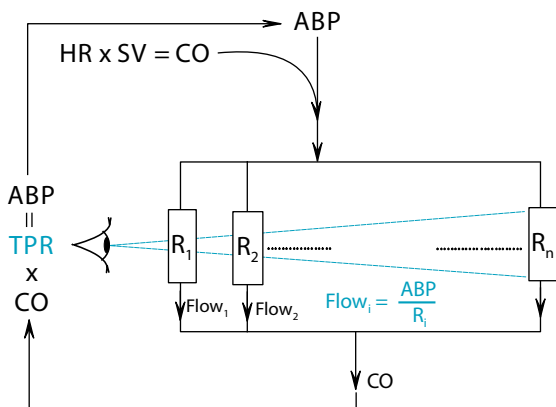


Figure 6–31 The scheme of overall cardiovascular regulation. The central system regulates mean arterial blood pressure (ABP). This allows each tissue to regulate its own flow by adjusting its vascular resistance (R_i). All resistances together form the total peripheral resistance (TPR), and this also is regulated by imposing an increase in resistance on those tissues that are not producing sufficient vasodilator metabolites to counteract the centrally imposed vasoconstrictor drive. CO = cardiac output; HR = heart rate; SV = stroke volume.

terone system, and a possible relationship between arterial blood pressure and renal sodium excretion (= **pressure natriuresis**).

Cardiac hypertrophy. Cardiac growth is a mechanism by which the normal heart adapts its performance to the requirements of the body. Hypertrophy allows the heart to perform increased work with normal systolic fiber shortening.

A chronic pressure overload leads predominantly to cell thickening by parallel deposition of new sarcomeres. The changes in wall geometry are symmetric and lead to **concentric hypertrophy**. There is no change in chamber radius or volume. A chronic volume overload leads predominantly to cell lengthening by serial deposition of new sarcomeres. The ratio between wall thickness and cavity size remains constant because the ventricle dilates and there is **eccentric hypertrophy**.

The changes in ventricular geometry and muscle mass are accompanied by a variety of changes in cellular composition and function, particularly as they relate to Ca^{++} dynamics. Hypertrophy is initially an adaptive response to increased work load. It can progress to diastolic dysfunction, impaired systolic function, and heart failure. These progressions to adverse remodeling and dysfunction appear to be driven, in still unknown ways, by locally elevated angiotensin II production.

Pressure natriuresis. Sodium excretion by the kidneys is correlated steeply and directly with slight changes in renal arterial blood pressure. This relationship is termed **pressure natriuresis**, and it is stated by many to be the most significant mechanism for long-term regulation of arterial blood pressure. Furthermore, the observation that the relationship is shifted toward a higher arterial blood pressure in hypertension has been interpreted as evidence that the disease is of renal origin and arises because the kidneys of hypertensive patients “require” an elevated pressure to maintain whole-body Na^+ balance. There are also those who argue that the “relationship” between Na^+ excretion and arterial blood pressure demonstrates nothing more than the observation that the kidneys will maintain body Na^+ balance, irrespective of the prevailing arterial blood pressure.

INTEGRATED CARDIOVASCULAR RESPONSES

Figure 6–32 shows a summary of the system that regulates arterial blood pressure in the short and intermediate term (seconds to weeks). Its aim is to maintain ABP at the set point that is determined by prevailing conditions as well as by emotions, pain, and the degree of wakefulness. The system has a centrally directed neurohormonal component (autonomic nervous system, epinephrine, and vasopressin) as well as a hormonal component that is based mostly in the kidneys and involves the renin–angiotensin–aldosterone sys-

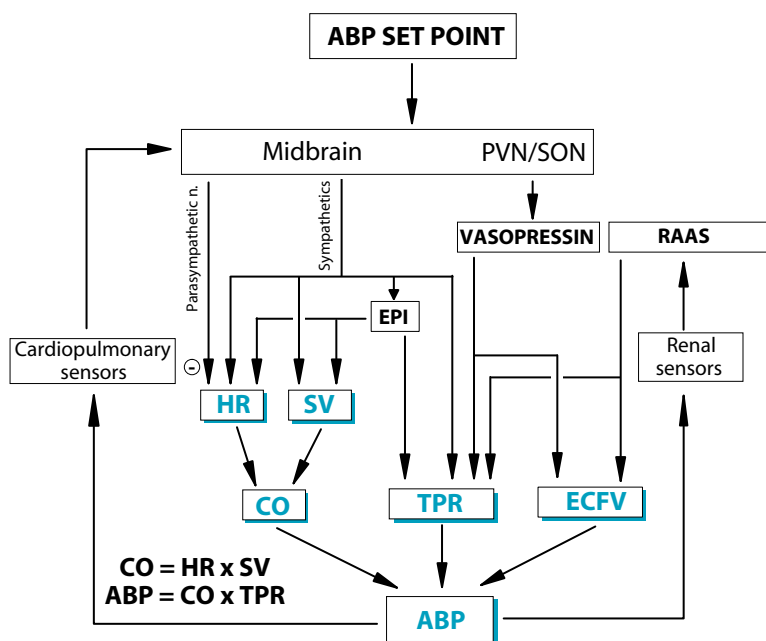


Figure 6–32 The components of blood pressure regulation in the short and intermediate terms. ABP is sensed predominantly by cardiopulmonary neural sensors but also by a stretch of juxtaglomerular cells in the renal afferent arterioles. Effector mechanisms include (1) central autonomic nervous system components (parasympathetic and sympathetic outflow) and vasopressin; (2) endocrine components such as vasopressin, EPI, angiotensin II, and aldosterone. Short-term mechanisms operate through effects on HR, ventricular SV, and TPR. CO is the product of HR and SV. ABP is the product of CO and TPR. Intermediate-term mechanisms also operate through renal mechanisms that alter ECFV. Only parasympathetic nervous activity is inversely related with its outcome, as indicated by the minus sign at the head of the arrow. All other effectors cause an increase in the variable at the head of the relevant arrow. ABP = mean arterial blood pressure; CO = cardiac output; ECFV = extracellular fluid volume; EPI = epinephrine; HR = heart rate; RAAS = renin–angiotensin–aldosterone system; SV = ventricular stroke volume; TPR = total peripheral vascular resistance.

tem. This latter component has actions on the peripheral vasculature through angiotensin II and III and on extracellular fluid volume through angiotensin II and aldosterone.

In most tissues, blood flow is increased as local tissue metabolism increases because locally produced metabolic factors relax vascular smooth muscle and decrease local vascular resistance. If a local change in flow or volume is large enough to affect systemic arterial blood pressure, there will be a change in the activity of stretch sensors. The cardiovascular regulatory system responds to patterns of afferent sensor activity with appropriate adjustments in heart rate, stroke volume, total peripheral resistance, and renal reabsorption of Na^+ and water.

Body Fluids and Electrolytes

BODY WATER AND ITS SUBDIVISIONS

Between 60 and 80% of the total body mass of an adult human is water. The wide range arises from individual variation in the amount of body fat, a tissue of low water content (Figure 7–1). Those with a higher proportion of body fat (women versus men; newborns versus elderly) have proportionately less body water.

Body water exists within anatomically defined compartments as **intracellular fluid** and **extracellular fluid**. Exchanges between intracellular and extracellular fluid are governed by the transport properties of the cell plasma membrane.

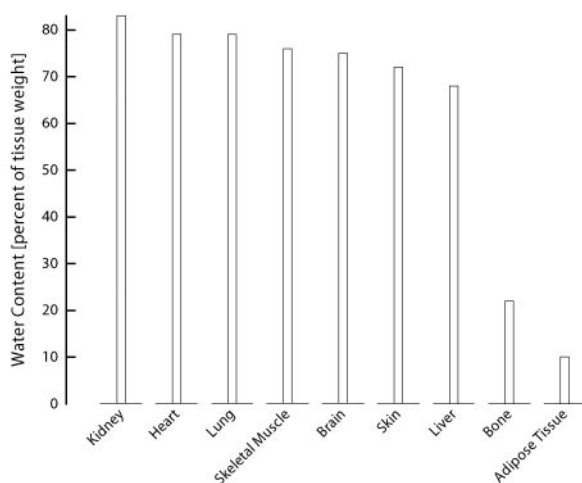


Figure 7–1 Water content of tissues in adult humans.

Extracellular fluid is further subdivided into **intravascular fluid** (**plasma**), **interstitial fluid**, and **transcellular fluid** (joints, pericardial space, and so on).

Exchanges between plasma and interstitial fluid are governed by the Starling-Landis mechanisms of transcapillary fluid exchange. Transcellular fluid is separated from interstitial fluid by a variety of epithelia.

Electrolyte Composition of Body Fluids

Intracellular and extracellular fluid differ greatly in their compositions because they are separated from each other by the plasma membrane, a structure of highly selective permeability and highly specific transport mechanisms. As shown in Table 7-1, Na^+ , Cl^- , and HCO_3^- are the major extracellular ions. Ca^{++} and Mg^{++} are present in smaller concentrations but are equally vital for normal function. K^+ , phosphates, Mg^{++} , and proteins carrying net charge are the major intracellular ions.

Intracellular Fluid

Net negative charge of the intracellular fluid, compared with the extracellular fluid, arises from an excess of negative charges over positive charges in a narrow band near the plasma membrane. However, the difference is too small to be measurable on an mmol concentration scale.

Extracellular Fluid

The membrane separating interstitial fluid from plasma is less selective than the plasma membrane of cells. However, it does restrict proteins from moving freely, and that alone is sufficient to create compositional differences between interstitial fluid and plasma. Plasma has a higher Proteinⁿ concentration than does interstitial fluid. This has three consequences:

1. The presence of net negative charge on protein molecules and the requirement for charge equality within a region dictate that cation concentrations are slightly higher in plasma, whereas anion concentrations are slightly higher in interstitial fluid. This is known as the **Gibbs-Donnan phenomenon**.
2. Plasma osmolarity exceeds interstitial osmolarity by about 1 mOsm/kg. The resulting water-attracting effect (**oncotic pressure**) is equivalent to a hydrostatic pressure of 25 mm Hg.
3. Plasma proteins bind a variety of substances. As a result, the total plasma concentration of bound substances can be much higher than the concentration of their free ionized form. Ca^{++} is a prominent example of such a bound substance.

Table 7–1

Electrolyte Composition of Major Body Fluid Compartments

Constituent	Intracellular Fluid		Extracellular Fluid	
	(Muscle)	Interstitial Fluid	Plasma	
	[mmol/L H ₂ O]*	[mmol/L H ₂ O]*	[mmol/L H ₂ O]*	[mmol/L]
Na ⁺	10	145	153	142
K ⁺	160	4.1	4.3	4
Ca ^{++†}	0.0001	1.1	1.3	1.2
Mg ^{++†}	20	1	1	1
Cl [−]	5	117	112	104
HCO ₃ [−]	7	27	26	24
Phosphate and organic anions	140	1	1	1
Proteins ^{n−}	60	<1	15	14
Other	13	9	7	6.5

*Composition measurements are generally reported in one of three ways. The most common are per liter of plasma or serum (mmol/L; last column). Precise measurements are given per liter of water. This is more accurate because it does not treat undissolved moieties like proteins or lipids as if they were part of the water phase.

†Free ionized portion only. The total (ionized + un-ionized) is higher.

Intake and Output of Fluid and Electrolytes

The daily intake in a western society is 50 to 350 mmol of Na⁺ (generally in the form of NaCl), 30 to 100 mmol of K⁺ (as the phosphate salt in most foods), and 1 to 2 L of water (in a temperate climate).

Water intake by drinking and metabolic production from hydrogen and oxygen are matched by water elimination in feces, urine, sweat, and exhaled air. Ingestion of nonmetabolized substances, such as Na⁺, K⁺, Cl[−], and Ca⁺⁺, is balanced by excretion in feces, urine, and sweat.

Most of the daily intake enters the body water space by way of blood vessels that line the intestinal wall and is distributed from there to other regions by physicochemical forces.

PHYSICAL CHEMISTRY OF BODY FLUIDS

Osmolality and Osmolarity

The **osmolality** of a solution is defined as the number of osmotically active particles *per kg of water*. It is independent of the volume occupied by the solutes in the solution.

Although it is not formally defined, **osmolarity** is usually taken as the number of osmotically active particles *per liter of solution*. Osmolarity, rather than osmolality, is the term that is in normal usage. It is measured in osmoles per liter (Osm/L) and is calculated from the concentration of a solute by the formula:

$$\text{Osmolarity (Osm/L)} = \text{Concentration (mol/L)} \times \sigma N$$

σ = activity. The degree to which a solute will dissociate in aqueous solution.

N = the maximum number of discrete particles into which the solute can dissociate in an aqueous solution.

Differences in osmolarity between body fluid compartments act as a force for the movement of water toward regions of higher osmolarity. The osmolarity of intracellular and extracellular fluids is approximately 290 mOsm/L, and any difference between the two is quickly abolished by the movement of water across the plasma membrane.

Osmotic Pressure and Oncotic Pressure

At body temperature, the osmotic pressure and osmolarity are approximately related by the formula:

$$\text{Osmotic Pressure (mm Hg)} = 19.3 \times \text{Osmolarity (mOsm/L)}$$

The osmotic pressure on one side of a selectively permeable membrane, such as the plasma membrane, is equal in magnitude to the hydrostatic pressure that would have to be exerted on the fluid to prevent net water movement across the membrane.

The term oncotic pressure refers to the osmotic pressure arising from plasma proteins. As a result of differences in protein concentration, plasma osmolarity is approximately 1 mOsm/L above interstitial osmolarity. The oncotic pressure arising from this is 25 mm Hg, a very considerable force in the regulation of fluid flux across the capillary endothelium.

Tonicity

An **isotonic** solution is one that will cause no change in the volume of individual cells that have been placed into it. On the other hand, **hypertonic** solutions will shrink cells by drawing water from them, and **hypotonic** solutions will lead to cell swelling. Solutions that are iso-osmotic relative to intracellular fluid are isotonic only if their osmotically active ingredients do not readily cross the plasma membrane.

Specific Gravity

The specific gravity of a solution is its weight in relation to the weight of an equal volume of distilled water. It can be used to estimate solute concentration and is often used for that purpose because it can be measured so much more easily than osmolarity.

EXCHANGES BETWEEN BODY FLUID COMPARTMENTS

Exchange of Fluids

Exchange across the Plasma Membrane

Routes of water transport. Most, but not all, plasma membranes are highly permeable to water because they contain **aquaporins**, a family of membrane proteins that behave like water channels. Net fluid movement occurs instantaneously in response to osmotic gradients and would cause long-term change in cell volume and intracellular concentrations unless there were regulatory mechanisms.

Challenges to cell volume. Human cells have developed both short-term and long-term volume-regulatory mechanisms for responding to changes in intracellular or extracellular osmolarity. Short-term cell volume regulation is achieved mostly by altering the number of osmotically active particles (**osmolytes**) within the intracellular fluid. Long-term regulation involves adaptations in intracellular metabolism.

Short-term volume regulation. Cells respond to an acute osmotic challenge with an immediate (30 seconds to 2 minutes) change in volume. Within the next 5 to 15 minutes, they show a **regulatory volume decrease** (RVD) or **regulatory volume increase** (RVI) by which their volume returns to a value very near the baseline.

Regulatory volume decrease. The RVD response is characterized by return of cells toward baseline volume after acute swelling. It involves (1) K^+ and Cl^- efflux through independent conductive channels and (2) joint KCl efflux through a special co-transporter protein (Figure 7-2).

Some cells also show net loss of nonelectrolytes, mostly taurine, glycine, alanine, and other free nonessential amino acids (see Figure 7-2).

Regulatory volume increase. Regulatory volume increase mechanisms are characterized by swelling of cells back to their baseline volume after shrinkage in a hyperosmotic medium. This requires the uptake of osmolytes.

The dominant pathway for osmolyte uptake in this response is activation of the $Na^+ - H^+$ exchanger (Figure 7-3). $Na^+ - H^+$ exchange requires a

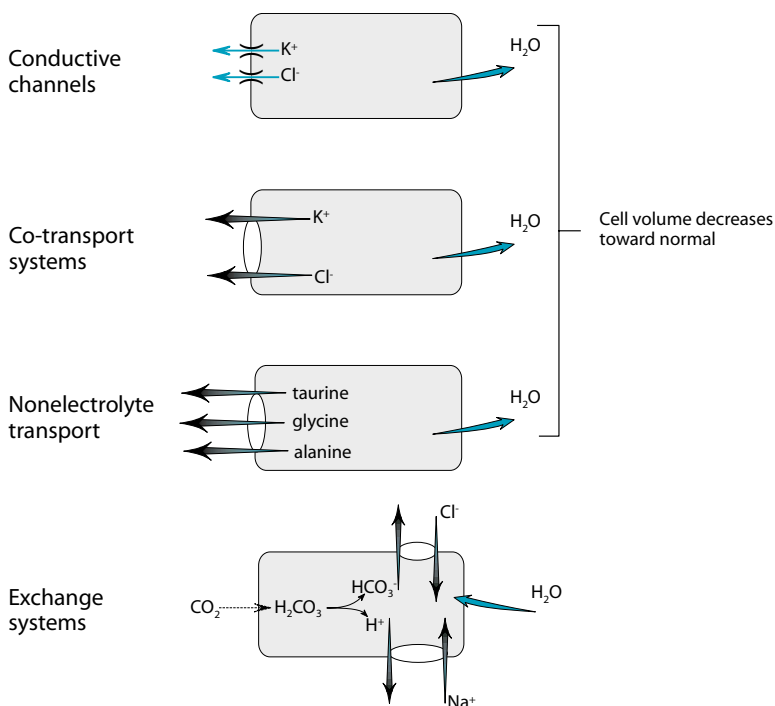


Figure 7-2 Cellular mechanisms of regulatory volume decreases (RVD). RVD responses operate to return cell volume toward normal after a primary volume increase. Note that the Na^+ - H^+ exchanger diminishes the effectiveness of the RVD responses because the global effect of Na^+ - H^+ exchange is to add osmotically active Na^+ and Cl^- to the cell interior.

supply of intracellular H^+ , and these are derived from H_2CO_3 formed in the cell by $CO_2 + H_2O$. The simultaneously produced HCO_3^- are exported by exchange for Cl^- . The global effect of Na^+ - H^+ exchange is, therefore, to take the osmotically inactive extracellular gas CO_2 and “convert” it to osmotically active Na^+ and Cl^- in the cell interior.

Many cells also show involvement of a furosemide-sensitive, inwardly directed $Na^+ - K^+ - 2Cl^-$ transporter.

Long-term volume regulation. Long-term volume regulatory responses involve three aspects: (1) increased transcription of osmolyte transporters; (2) up-regulation of exporters for betaine, taurine, and inositol; and (3) alterations in the transcription of proteins responsible for intracellular degradation or formation of macromolecules. Particular examples of (3) are (a) long-term increase in osmolyte by upregulation of **aldose reductase**, an enzyme that causes formation of **sorbitol** from glucose; sorbitol remains in the cell and will not denature proteins; and (b) increased rate of formation of **heat-shock protein-70** and **αB -crystallin**.

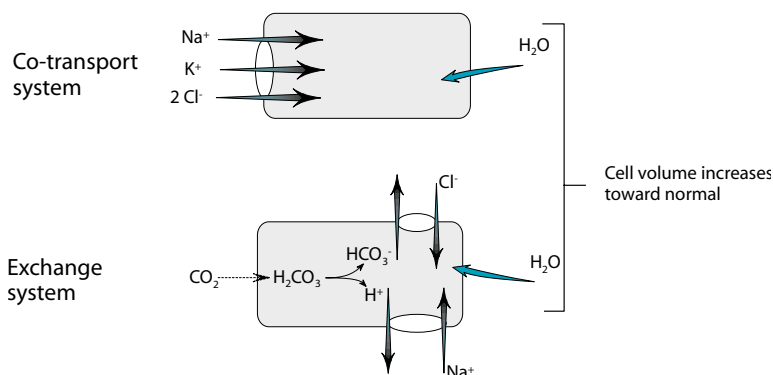


Figure 7–3 Cellular mechanisms of regulatory volume increases (RVI). RVI responses return cell volume toward normal after an imposed decrease.

Volume-sensing mechanisms. Both chemical and mechanical changes can act as volume-sensing signals. Chemical signals arise from changing concentrations of cellular contents. Mechanical signals could arise from membrane stretch as well as from cytoskeletal disruptions.

Exchange across the Capillary Endothelium

Net fluid movement is determined by capillary permeability and any imbalance between transcapillary gradients in hydrostatic or oncotic pressure. As explained elsewhere, the dominant influence is intracapillary hydrostatic pressure and its cyclic variations during **vasomotion**.

Exchange of Solutes

Exchange across the Plasma Membrane

Solutes are transported across the plasma membrane by active and passive mechanisms. They include (1) the $\text{Na}^+ - \text{K}^+$ pump, (2) secondarily active Na^+ -dependent transport of substances, such as glucose or H^+ , and (3) Na^+ -independent anion counter transport of Cl^- and HCO_3^- by **band 3 protein**.

Exchange across the Capillary Endothelium

The rate of transepithelial solute transport depends directly on the membrane permeability coefficient, total surface area available for exchange, and the concentration gradient between capillary plasma and interstitial fluid.

Within any one capillary, permeability and blood flow rate will affect epithelial transport. At the extremes,

- Transepithelial transport for highly permeant solutes depends mostly on the rate of capillary blood flow, and their transport is said to be **flow limited**. Such substances reach their venular (steady-state) concentration within a short intracapillary distance.
- Transepithelial transport for solutes with low permeability relative to the flow rate depends mostly on permeability, provided that there is some minimal flow. Such transport is said to be **diffusion limited**, and a steady-state venular concentration cannot be obtained before the venular end, except when capillary flow has been reduced to zero.

Lipophilic substances like O_2 , CO_2 , and the anesthetic gases traverse the capillary wall with great ease because they dissolve in the lipid cell membrane.

Small hydrophilic solutes (ions, glucose, urea, and amino acids) will readily permeate most capillaries in the body. It is likely that they use the same transport routes as does water, namely, the clefts between neighboring capillary endothelial cells. Hence, their passage is impeded by two physical obstacles: (1) the longitudinal strands that form tight junctions within the cleft and (2) the glycocalyx that forms a dense covering on the outside of the plasma membrane and also lines the clefts (Figure 7–4).

Role of the endothelium: The capillary endothelium behaves as if small hydrophilic molecules were transported through “pores” whose effective radius is 4 to 5.5 nm, occupying 0.1% or less of the capillary surface. Continuous capillaries in different tissues differ in the apparent number of such “pores.”

Large, macromolecular hydrophilic solutes like albumin do cross the endothelium, but at a slow rate. Their transport pathway appears to involve

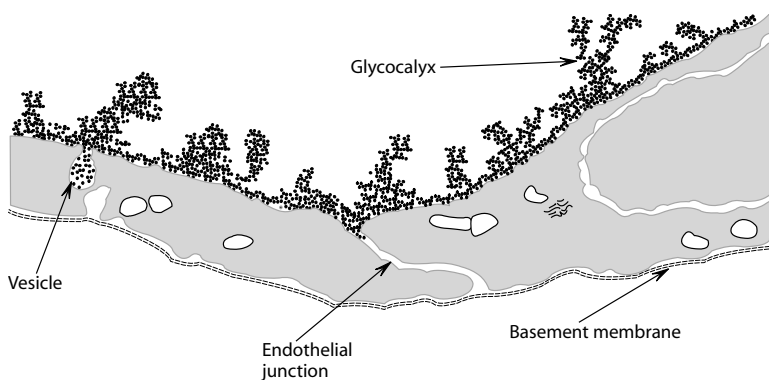


Figure 7–4 The junction between adjacent capillary endothelial cells provides openings for the transport of water soluble substances. Positively charged particles have been used to outline the glycocalyx, which is dominated by negative charges and provides an additional narrowing of the endothelial junction.

vesicles and occasional large (20 to 25 nm) **intercellular clefts** as they are found in discontinuous capillaries.

Role of the glycocalyx: The glycocalyx also bestows net negative charge on the luminal surface of capillaries. As a result, the effective dimension of the “pores” and their hindrance to the passage of small, water-soluble molecules are also affected by the abundance of charge-neutralizing positive moieties, such as the arginine groups that are found in plasma proteins, such as albumin or **orosomucoid**.

FUNCTIONAL ANATOMY OF THE KIDNEYS

Gross Anatomy

The kidneys communicate with the body by way of the renal artery and vein, nerves, lymphatics, and the ureter, all of which enter and exit through the region called the **hilus**. A longitudinal cut (Figure 7–5) shows that the kidney is arranged as a row of 4 to 14 **renal pyramids**.

The broad end of the pyramids is covered by a layer of tissue called the **renal cortex**, while their tips meet in the **renal papilla**. Collectively, the pyramids form the **renal medulla**.

The medulla is subdivided into the **outer** and **inner medulla** (Figure 7–6), the outer medulla being a deeper shade of red than the inner medulla because it is more densely vascularized. The outer medulla, in turn, is divided into the outer stripe and inner stripe (see Figure 7–6).

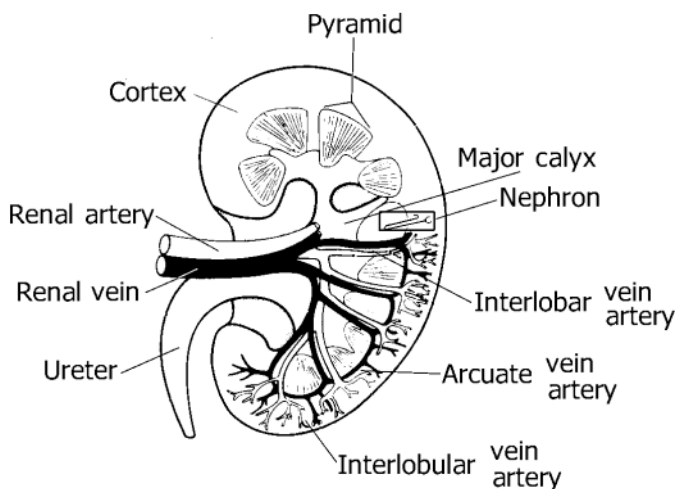


Figure 7–5 Gross anatomy of the pyramidal structure, renal vasculature, and urine collection system.

The tip of each pyramid projects into a **minor calyx**; several minor calyces join to form a **major calyx**, and the major calyces join in the **renal pelvis**. The calyces collect urine that has been formed by the **nephrons** (see Figure 7–6), and they convey urine through the left and right **ureters** and to the urinary **bladder**.

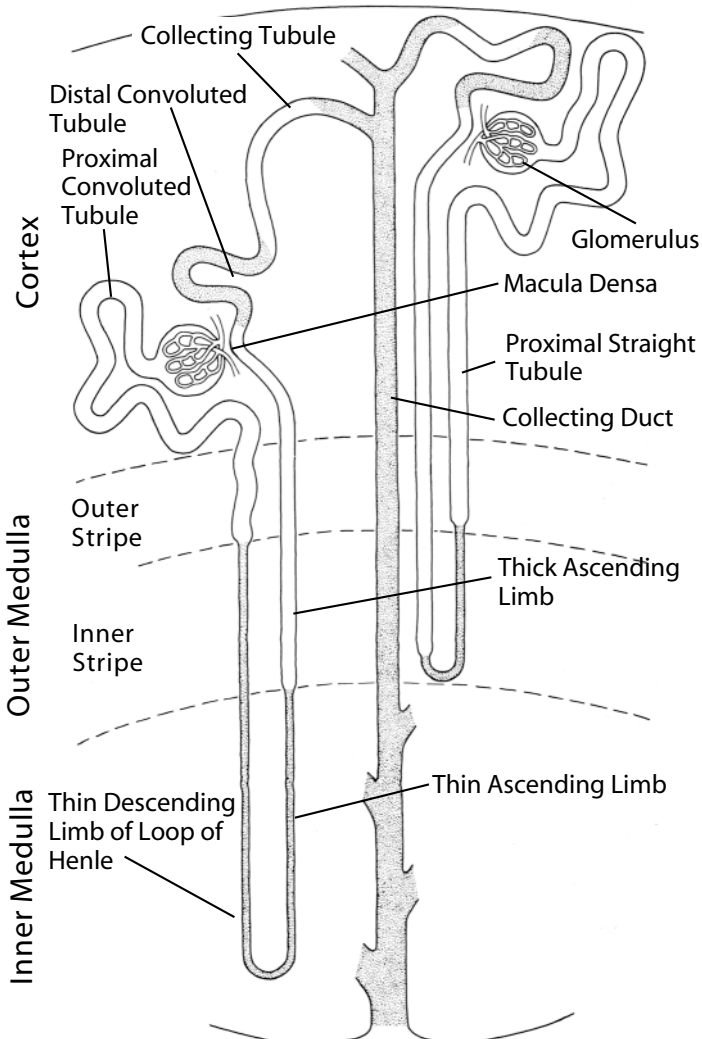


Figure 7–6 Cortical (*right*) and juxtamedullary (*left*) nephron.

Renal Vasculature

The kidneys receive nearly 25% of cardiac output at rest. This flow can be readily redirected to other vascular areas to meet cardiovascular emergencies.

Arterial Supply

The gross anatomy of the renal vasculature is shown in Figure 7–5. Blood flow enters the kidney at the hilus by way of the **renal artery**. This vessel branches and forms several **segmental arteries**. They, in turn, subdivide and form the **interlobar arteries**.

Interlobar arteries. Each interlobar artery ascends toward the cortex through rays of cortical tissue that separate neighboring pyramids. Before reaching the cortical surface, each interlobar artery divides into **arcuate arteries**.

Arcuate arteries. Arcuate arteries run along the cortex/medulla boundary and parallel to the kidney surface. They give rise to the interlobular arteries.

Interlobular arteries. These arteries penetrate the cortex perpendicularly toward the surface. Numerous arterioles, the **afferent arterioles**, arise from each interlobular artery.

Afferent arterioles. Each afferent arteriole divides to form the capillary network of a **glomerular capillary tuft**.

Renal Microvasculature

The microvasculature of the kidney is a serial arrangement of two capillary beds, the entrance to each being controlled by an arteriole.

Afferent arteriole and glomerular tuft. Each glomerulus is supplied by one **afferent arteriole**. It divides and forms the tuft of glomerular capillaries.

Efferent arteriole and peritubular capillaries. The glomerular capillaries join at their outflow ends to form the **efferent arteriole**. This vessel divides at its outflow end to form the **peritubular capillaries**. Peritubular capillaries are fenestrated, and the fenestrations occupy nearly half the available surface area.

Venous drainage. The renal venous system is named in parallel with the arterial system with only one exception: venous blood from the outer

cortex drains into **stellate veins** on the renal surface, and these are not accompanied by arteries. Stellate veins drain into interlobular veins.

The Nephron

Each nephron consists of a **glomerulus** and a **tubule** (see Figure 7–6). The majority of nephrons are **cortical nephrons**. Such nephrons are short and descend no further than the inner stripe of the outer medulla. **Juxtamedullary nephrons**, on the other hand, are long and descend far into the medulla, some as far as the tip of the papilla.

Glomerulus

Glomeruli are formed by a tuft of capillaries that are attached to a central stalk of mesangium and are surrounded by an extension of the associated proximal tubule. The space outside the tuft, but within the globe, is called **Bowman's space**.

Glomerular capillaries. Glomerular capillaries are extremely permeable to water and water-soluble molecules even though filtration is restricted to a ribbon of open area (filtration slits) between podocyte foot processes (Figure 7–7). Permeation of solutes depends on both molecular size and charge.

Molecules with a radius of 1.5 nm or less ($MW < 6$ kDa) are filtered freely, whereas molecules with a radius of 4 nm or more ($MW > 70$ kDa) are almost totally excluded. Negatively charged solutes are less readily filtered than neutral or positively charged solutes of the same radius. This selectivity is explained by a cloud of negative charges associated with each layer of the filtration barrier. Two factors contribute to this charge cloud: (1) the endothelial glycocalyx and the podocyte foot processes are rich in the negatively charged sialoprotein **podocalyxin**, and (2) the capillary basement membrane contains the negatively charged proteoglycan **heparan sulfate**.

Podocytes. These epithelial cells have long extensions that divide into the foot processes that enfold each capillary and attach to its basement membrane (see Figure 7–7). The open area between the foot processes forms the **filtration slits**.

Tubule

The renal tubule is formed by a single epithelial layer, and it separates two regions of extracellular fluid with distinct compositions. Solute can move between these regions either by the **transcellular path** (across the cells) or the **paracellular path** (through the lateral junctions between neighboring cells).

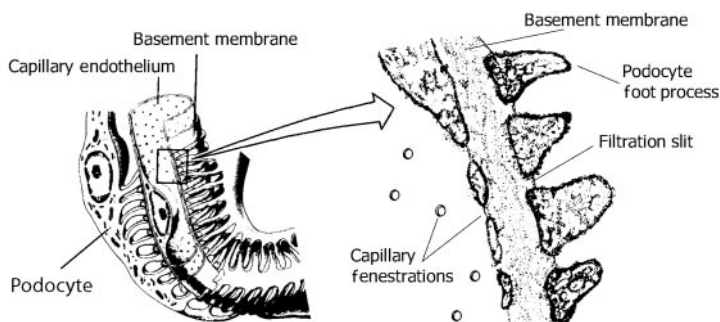


Figure 7-7 Microanatomy of the glomerular filtration barrier. Fluid is filtered through the capillary endothelium and the basement membrane but only at the filtration slits between adjacent podocyte foot processes.

Tubular transport processes.

Transcellular transport. Transcellular transport occurs by way of unidirectional channels and carrier proteins that are appropriately placed in either the luminal or basolateral portion of the epithelial plasma membrane. The transition from one membrane portion to the other occurs at the tight junction with the neighboring cell.

Cells showing high transport rates require a large number of transport proteins and have adapted to this need by increasing the surface area available for transport. Such cells show villi, membrane infoldings, and lateral finger-like processes. In some cells, villi are arranged so densely as to form a **brush border**.

Paracellular transport. Tubular epithelial cells are surrounded by a belt of junctions with adjoining cells. The junctional complex consists of the **zona occludens** (tight junction), the **zona adherens**, and, in the case of proximal tubular cells, **gap junctions**.

The tight junction is the barrier between the tubular lumen and the lateral intercellular space. The two most significant factors determining tight junction permeability are (1) the physical nature (lateral continuity, particle density, or parallelity of alignment) of the protein strands within the junction and (2) the distribution of charges within the junction.

Regional tubular anatomy.

Proximal nephron. The proximal nephron is divided into convoluted and straight tubules. The straight portion ends at the border between the outer and inner stripes of the outer medulla (see Figure 7-6). Proximal tubular cells (Figure 7-8) have (1) a vast surface (microvilli) and are rich in a variety of luminal cleavage enzymes that reduce filtered compounds to reab-

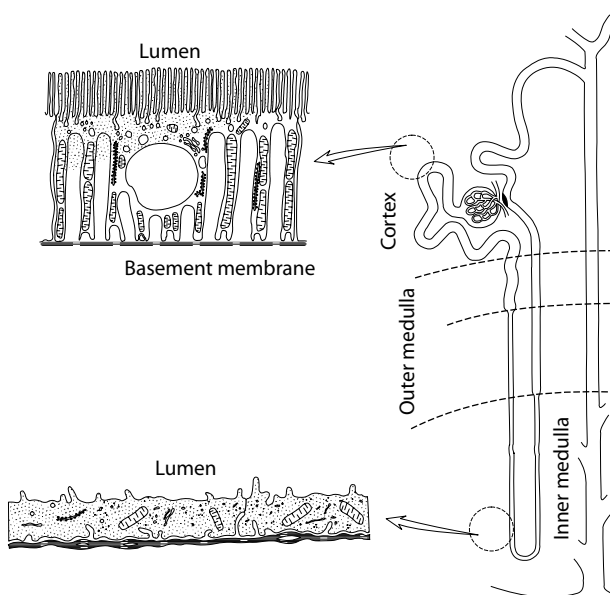


Figure 7-8 Sketch of the histology of cells in the proximal convoluted tubule and thin segment of the descending loop of Henle. Basal infoldings are shown empty where they would contain lateral processes from neighboring cells.

sorbable fragments and (2) a central raised core, in which the nucleus resides and from which lateral processes radiate.

The interdigitating lateral processes of neighboring cells frequently show gap junctions, and the proximal epithelial cells are the only renal epithelial cells that show such junctions. Their significance is not clear.

When there is a maintained increase in tubular load, proliferation of basolateral membrane is the major structural adaptation.

Loop of Henle.

Thin descending limb: The transition from proximal tubular cells to the flatter, more simply organized cells of the thin descending limb is abrupt (see Figure 7-8).

Thin ascending limb: The bend and the thin ascending limb have very flat, markedly interdigitating cells. Nothing in the appearance of this epithelium reveals its high permeability to ions and near impermeability to water.

Thick ascending limb: The transition from the thin ascending limb to the thick ascending limb defines the border between the inner medulla and

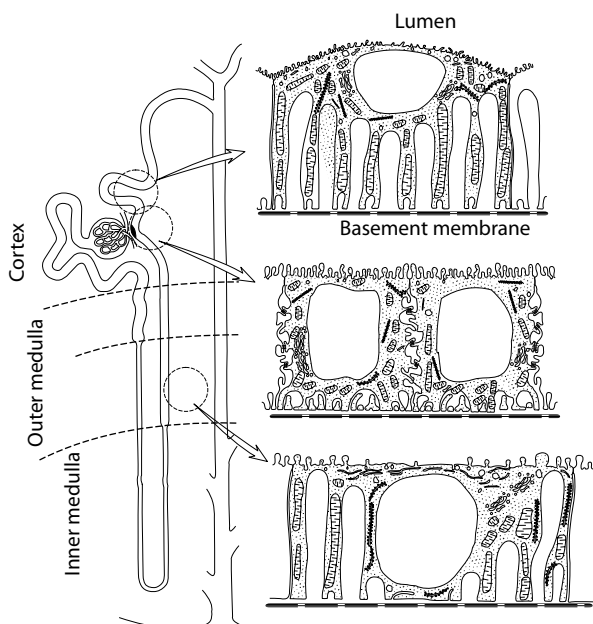


Figure 7-9 Sketch of the histology of cells in the thick ascending limb of the loop of Henle, macula densa, and distal convoluted tubule. Macula densa cells show greatly dilated lateral spaces between adjacent cells.

the inner stripe of the outer medulla (see Figure 7-6). The epithelium is composed of tall cells that are covered with short microvilli and have extensive lateral processes that interdigitate with those from adjacent cells (Figure 7-9).

Thick ascending limb epithelial cells contain accumulations of smooth vesicles filled with the **Tamm-Horsfall protein**. This glycoprotein is used as a specific cytochemical marker for the thick ascending limb cells.

The thick ascending limb ends in the area of the **macula densa**, which forms one component of the **juxtaglomerular apparatus**.

Juxtaglomerular apparatus. The juxtaglomerular apparatus consists of three components. They are (1) the macula densa region of the thick ascending limb, (2) extraglomerular mesangial cells that anchor the macula densa in place, and (3) granule-containing **juxtaglomerular cells** of the afferent arteriole. The granular cells are innervated by sympathetic nerves.

Macula densa: This is a region of two or three dozen cells that differ from their neighbors most prominently in that they have greatly dilated lateral spaces between them (see Figure 7-9) and are not linked by interdigitating lateral processes.

Extraglomerular mesangial cells: This group of mesangial cells forms the **polar cushion** and lies in the triangle formed by the macula densa and the afferent and efferent arterioles. They are (1) richly supplied with microfilaments and may be contractile, and (2) extensively interconnected by way of gap junctions and may, therefore, have a role in signal transmission between the distal and proximal regions of the nephron.

Juxtaglomerular cells: The terminal portion of the afferent arterioles includes a cluster of four to eight smooth muscle cells with a large number of membrane-lined vesicles that carry the enzyme **renin**, which is released by exocytosis to the interstitial space. The granular cells are extensively linked to neighboring cells by gap junctions. Several adjacent smooth muscle cells have the potential to be converted to granular cells and are converted in settings where high renin levels are required

Distal nephron. The distal nephron is the portion downstream from the thick ascending limb of the loop of Henle. It consists of the distal convoluted tubule, collecting tubule, cortical collecting duct, and inner medullary collecting duct (see Figure 7–6).

Each of these segments contains histologically distinct cells, and **intercalated cells** are interspersed as single cells among them.

Distal convoluted tubule: Distal convoluted tubule (see Figure 7–9) cells show the highest mitochondrial density and the highest $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity of any nephron segment. Prolonged increase in Na^+ delivery to the distal nephron increases cell volume, mitochondrial density, basolateral surface area, and $\text{Na}^+\text{-K}^+\text{-ATPase}$.

Collecting tubule: Cells of the collecting tubule epithelium are distinguished by the presence of the **basal labyrinth**, which is created by extensive infoldings of the basal membrane (Figure 7–10). Their structural and enzymatic responses to increased NaCl load resemble those of the distal convoluted tubule, but they have lower density of both $\text{Na}^+\text{-K}^+\text{-ATPase}$ and mitochondria. Collecting tubule cells are believed to be the locus for renal **kallikrein** synthesis.

Cortical collecting duct: Cortical collecting duct cells carry a distinctive single central cilium (see Figure 7–10). The cells often show tubular vesicles that are aligned perpendicularly or obliquely to the surface. The vesicles are thought to be loci for **aggrephore** (water channel) insertion into the membrane.

Mineralocorticoids or chronic intake of high K^+ or low Na^+ increase, over a time-course of 3 to 10 days, cell volume, basolateral surface area, and number of $\text{Na}^+\text{-K}^+\text{-ATPase}$ pumps as they increase Na^+ reabsorption and K^+ secretion. Similar effects follow prolonged increase in distal Na^+ delivery.

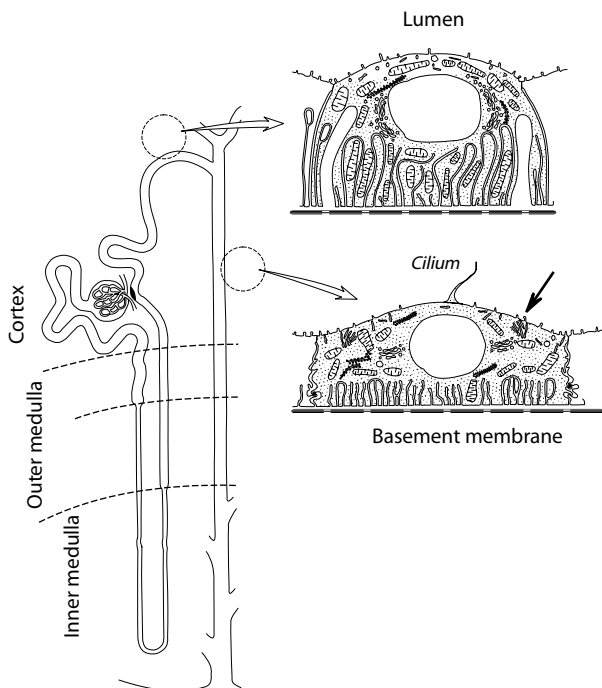


Figure 7-10 Sketch of the histology of cells in the cortical collecting tubule and cortical collecting duct. Collecting duct cells are characterized by the central cilium. The *solid arrow* points to an aggregate-containing vesicle.

Vasopressin increases water permeability of the luminal cell membrane by causing water channels to be translocated from cytoplasmic vesicles into the membrane by exocytosis.

Inner medullary collecting duct: The cells of the collecting duct epithelium change gradually until their cytoplasm shows prominent Golgi apparatuses, endoplasmic reticulum, and lysosomes.

Intercalated cells: In humans, these cells first appear in the late distal convoluted tubule, constitute up to 40% of cells in the collecting tubule and cortical collecting duct, and gradually disappear with distance along the medullary collecting duct. Intercalated cells differ structurally from their neighbors and frequently show accumulations of vesicles near the luminal membrane or continuous with it. These vesicles are covered by smaller vesicles, called **studs**. The studs are rich in H^+ -ATPase and might be involved in acid-base regulation.

There may be two subpopulations of intercalated cells. Both types contain carbonic anhydrase, but Type A cells actively transport H^+ into the lumen and have both a passive $HCO_3^- - Cl^-$ antiport (HCO_3^- out; Cl^- in) and a Cl^- outward leakage channel on the basal side. In type B cells, the location of the $H^+ - ATPase$ and the $HCO_3^- - Cl^-$ antiport are reversed, the active H^+ transport being into the peritubular interstitial space.

RENAL BLOOD FLOW, GLOMERULAR FILTRATION, AND TUBULAR TRANSPORT

From Renal Blood Flow to Glomerular Filtration

Renal blood flow and glomerular filtration rate are controlled by adjustment of vascular resistance. In most blood vessels of the body, this occurs in arterioles at the precapillary level. The kidney is capable of adjusting vascular resistance both upstream and downstream of the glomerular capillary tuft. Thus, while all renal blood flow passes through the glomerular capillary network, the fraction of renal plasma flow that is filtered out across the glomerular capillary membrane (= **filtration fraction**) can be changed by differential adjustment of preglomerular and postglomerular vascular resistance.

Glomerular capillary hydrostatic pressure is 50 to 60 mm Hg in all glomeruli, with a fall of only 1 to 2 mm Hg along the length of the capillary.

Preglomerular Resistance

In the kidney, the loci of preglomerular vascular control differ in different regions. In juxtamedullary glomeruli (15% of all glomeruli), the afferent arteriole is responsible for almost all of the preglomerular vascular resistance (Figure 7–11). In cortical glomeruli, which constitute 85% of all glomeruli, most of the preglomerular resistance is supplied by the interlobular artery, and interlobular dilatation is a more important mechanism for increasing cortical glomerular blood flow than is dilatation of the afferent arteriole.

Throughout the kidney, both the interlobular artery and the afferent arteriole are well supplied with vascular smooth muscle and react to sympathetic nervous activity and vasoactive chemicals.

Postglomerular Resistance

Efferent arterioles provide most of the postglomerular vascular resistance, and hydrostatic pressure along them is decreased from the glomerular capillary level of 50 to 60 mm Hg down to nearly 10 mm Hg (see Figure 7–11). Efferent arterioles also respond to sympathetic nervous and chemical stimuli.

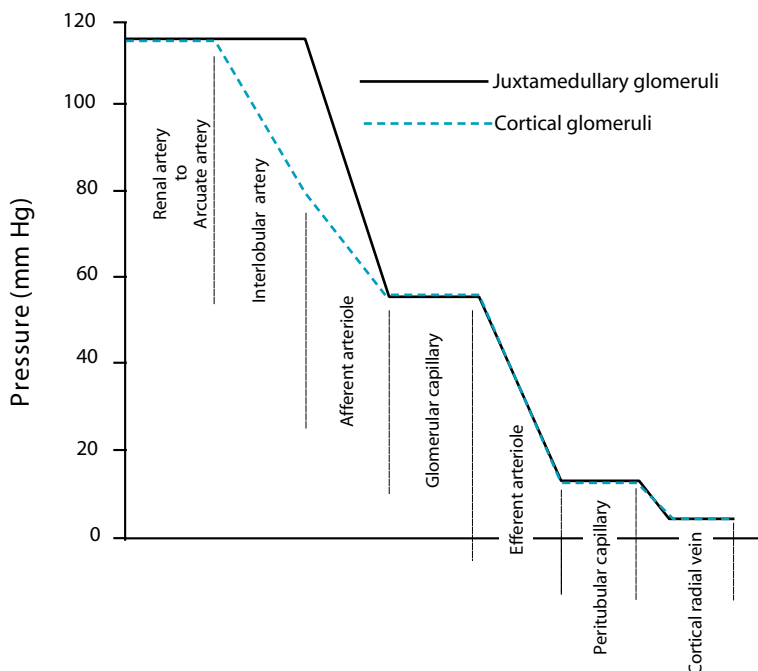


Figure 7-11 Progressive decrease in blood pressure across the renal vasculature. In juxtamedullary nephrons, the afferent arteriole offers almost all of the preglomerular resistance. In cortical nephrons, more than half of the preglomerular pressure decrease occurs along the interlobular artery.

Glomerular Filtration Barrier and Filtration Forces

Glomerular capillaries differ from other capillaries partly because their basement membrane is extensively covered by podocyte foot processes (see Figure 7-7), leaving only the filtration slits available for fluid transport. The slits are covered by the **slit membrane**.

At the slits, the **filtration barrier** is formed not only by the capillary endothelium and the basement membrane but also by the properties of the glycocalyx that is associated with endothelial cells and podocytes. Endothelium and basement membrane impose physical hindrance and size selectivity. Negative charges associated with glycocalyx proteins like **podocalyxin** or **heparan sulfate** bestow charge selectivity as well.

Glomerular filtration is driven by an imbalance between hydrostatic and protein-osmotic pressure gradients across the glomerular capillary wall. This imbalance is called the **net filtration pressure**. It is near 25 mm Hg at

the beginning of the glomerular capillary and decreases progressively along its length as capillary protein concentration rises with fluid loss to Bowman's capsule.

Two functional kinds of glomeruli are distinguished: (1) glomeruli in **filtration pressure equilibrium** reach zero net filtration pressure at or before the end of the capillary. In them, filtration rate is positively correlated with renal blood flow; and (2) most glomeruli are in **filtration disequilibrium** in that they have a positive net filtration pressure at the end of the glomerular capillary.

Because the majority of glomeruli are in filtration disequilibrium, glomerular hydrostatic pressure is normally a more important determinant of glomerular filtration rate than is glomerular capillary flow.

Regulation of Renal Blood Flow and Glomerular Filtration Rate

Autoregulation

Total renal blood flow and glomerular filtration are kept relatively constant over a range of renal arterial blood pressure between 80 and 120 mm Hg. Two intrarenal mechanisms are chiefly responsible: the **myogenic response** and **tubulo-glomerular feedback**.

Myogenic response. Vascular smooth muscle responds with constriction to an increase in stretch and with relaxation to a decrease in stretch. Its cellular mechanisms involve both stretch-activated cation channels and release of endothelial vasoactive factors.

Tubulo-glomerular feedback. This mechanism, which is more important than the myogenic response, couples distal tubular NaCl load inversely to preglomerular vascular resistance. Before more sensitive assays became available, it was hypothesized that changes in Na^+ load to the macula densa were directly related to renin secretion from the juxtaglomerular cells and that subsequently formed angiotensin II then constricted the afferent arteriole and decreased glomerular filtration rate.

More recent findings are that juxtaglomerular renin release is inversely related to macula densa load, that angiotensin II causes little change in glomerular filtration rate, and that tubulo-glomerular feedback is not abolished by blockade of angiotensin II formation. The current belief is that (1) the sensed signal is NaCl transport by macula densa cells and (2) negative feedback changes in afferent arteriolar resistance are the result of complex interactions among local effects of angiotensin II, prostaglandins, and adenosine.

Neural Factors

Sympathetic catecholaminergic fibers reach the afferent and efferent arterioles, proximal and distal tubules, thick ascending limb of the Loop of Henle, and juxtaglomerular apparatus. Increased sympathetic activity increases afferent and efferent arteriolar resistance and, consequently, decreases glomerular filtration rate and overall renal electrolyte excretion (Figure 7–12).

Under resting circumstances, the major influence of renal sympathetic nerve activity is not on hemodynamic factors, such as renal blood flow or glomerular filtration, but on tubular reabsorption. When the renal nerves are cut, there is an increase in basal urinary excretion of water, Na^+ , and other ions (by α_1 -mediated mechanisms). This demonstrates that renal sympathetic activity normally increases tubular reabsorption. However, the renal nerves are not normally required to maintain whole-body sodium balance

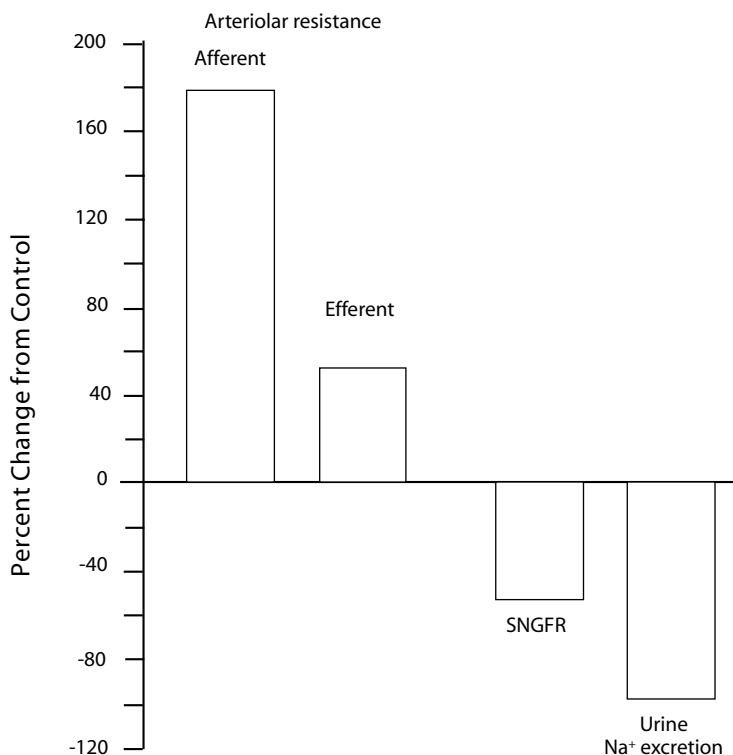


Figure 7–12 Increased activity in renal sympathetic nerves constricts afferent and efferent arterioles. The relatively greater constriction of afferent arterioles causes decreased filtration (SNGFR). SNGFR = single nephron filtration rate.

because of other compensatory mechanisms. Their presence is, however, required for maintenance of sodium balance in conditions of severe dietary sodium restriction, when maximal tubular reabsorptive capacity is necessary.

Hormonal Factors

The renin-angiotensin system, prostaglandins, kinins, and circulating catecholamines are the major hormonal influences on kidney hemodynamics and filtration.

Renin-angiotensin system. Secretion of the enzyme, renin from storage granules in juxtaglomerular cells of the afferent arteriole is increased by three mechanisms: (1) diminished stretch of the afferent arteriolar wall (the renal vascular baroreceptor mechanism), (2) increased distal tubular delivery of NaCl to the macula densa cells, and (3) β_1 adrenoreceptor activation by sympathetic nerves supplying the juxtaglomerular apparatus. Stimulation rates below 1 Hz will increase renin release, even though they have no effect on renal blood flow.

The principal action of renin is to produce the 10 amino acid peptide **angiotensin I** from the freely circulating substrate **angiotensinogen** (Figure 7–13). Subsequent steps involve **converting enzyme**, which is located mostly in endothelial cells.

Converting enzyme is a carboxypeptidase that splits off histidyl-leucine from angiotensin I. It also inactivates **bradykinin**. As a result, inhibitors of converting enzyme (ACE inhibitors) elevate plasma bradykinin levels.

Angiotensin I is biologically inactive. The effects of angiotensin II and III arise mostly from interaction with the AT_1 receptor and consequent intracellular activation of the phospholipase C pathway.

Angiotensin II is both a potent vasoconstrictor and a promoter of aldosterone synthesis. Most of its biologic actions result from activation of the angiotensin I receptor, which activates the phospholipase C pathway and leads to elevated intracellular Ca^{++} and diacylglycerol (DAG) (see Chapter 1, “General Physiologic Processes” for details).

The acute renal effects of angiotensin II are rapid vasoconstriction and acute reduction in renal blood flow with little or no change in glomerular filtration rate. As a result, the filtration fraction increases.

Mesangial cells also have AT_1 receptors and, therefore, respond to angiotensin II with constriction and consequent reduction in glomerular capillary filtration area and filtration coefficient.

In addition to and independent of its hemodynamic and filtration barrier effects, angiotensin II increases tubular Na^+ reabsorption in both proximal and late distal segments of all nephrons.

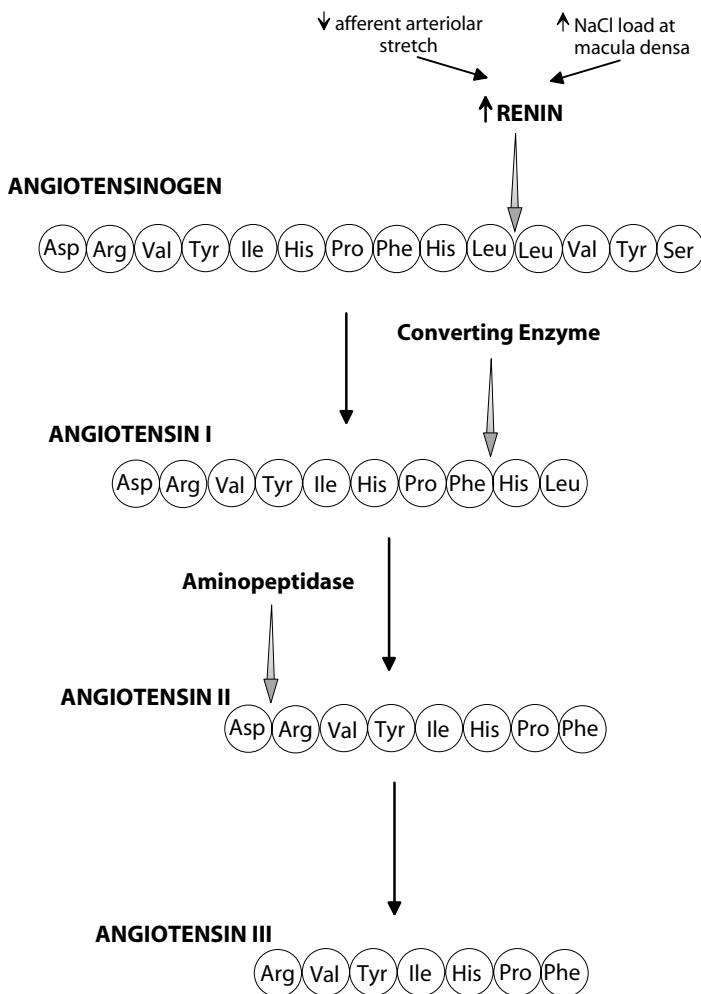


Figure 7-13 Formation of biologically active angiotensin II and angiotensin III from the substrate angiotensinogen. Renin cleaves angiotensinogen to yield angiotensin I, which is biologically inactive. The octapeptide angiotensin II is produced from angiotensin I by converting enzyme (ACE) that is both freely circulating and located in vascular endothelial cells. Subsequent removal of the terminal Asp by aminopeptidase A yields angiotensin III, an agent of greatly diminished biologic potency.

Prostaglandins. The prostaglandins are produced by action of cyclooxygenases (COX-1 and COX-2) on arachidonic acid (AA). The usual rate-limiting step is AA supply. Its metabolic paths are determined mostly by local enzyme availability.

AA production from plasma membrane phospholipids is primarily by action of phospholipase A₂. This enzyme, in turn, is linked through G proteins to plasma membrane receptors for several peptide and nonpeptide agonists. Accordingly, there is no single, simple scheme for the role of prostaglandins in nephron function. They act on target cells in an autocrine or paracrine fashion.

The dominant renal prostaglandin is PGE₂, a vasodilator and inhibitor of tubular Na⁺ reabsorption. It has little effect at rest but counteracts the vasoconstrictor actions of increased sympathetic nervous activity.

Kinins. The kinins are renal vasodilators, formed by the action of **kallikrein** on **kininogen substrate**, an α_2 -globulin that is synthesized chiefly in the liver. In humans, renal kallikrein is localized mostly in the distal convoluted tubule. Kinin synthesis is complexly linked to the renin-angiotensin system, the prostaglandin system, and others. The complexity is illustrated by the observation that kallikrein is stimulated by vasodilator prostaglandins as well as by vasoconstrictor angiotensin II.

Intrarenal Distribution of Blood Flow and Filtration

Because of the greater number of cortical nephrons, 85 to 90% of renal blood flow is distributed to the glomeruli and peritubular capillaries in the renal cortex, and the medulla receives most of the rest. Only 1 or 2% of renal blood flow reaches the papilla. Juxtamedullary nephrons are longer (see Figure 7–6) and, therefore, reabsorb a greater fraction of their Na⁺ and water load than do cortical nephrons. As a result, overall body fluid and electrolyte homeostasis might be affected by the relative distribution of blood flow between the renal cortex and medulla.

Tubular Reabsorption and Secretion

Approximately 20% of renal plasma flow is filtered through the glomeruli and enters the nephrons. There, it undergoes processes of reabsorption and secretion before the remainder is excreted as urine.

Tubular Reabsorption

In a temperate climate and on a western diet, the kidneys typically reabsorb 25 mol of Na⁺ per 24 hours along with 178 L of water. Water reabsorption is by passive transport mechanisms only. Solute reabsorption occurs by both active and passive mechanisms in the normal operation of the kidney.

Solute reabsorption provides the drive for most reabsorptive activity in the kidney because it establishes both electrochemical and osmotic gradi-

ents across the tubular wall. Such gradients are then used for reabsorption of other solutes or fluid.

Reabsorptive mechanisms are classified into those exhibiting a **transport maximum** (T_m -limited) and those exhibiting a **gradient-time maximum**.

T_m -limited transport. T_m -limited transport occurs by way of a limited number of specific carriers. The reabsorption maximum (T_m) is reached when all carriers are occupied.

If a filtered load less than T_m is presented to the tubules, all the filtered substance will be reabsorbed, and none will be excreted. On the other hand, if substance in excess of T_m is presented in the filtrate, all the excess will be excreted.

Glucose and HCO_3^- are transported by T_m -limited mechanisms.

Gradient time-limited transport. Epithelia can sustain only a finite transmural difference in concentration or electrical potential before paracellular back leakage becomes large enough to cancel transcellular transport in the forward direction. Whether or not the limiting gradient is reached depends on the time of contact between tubular fluid and tubular cell.

Na^+ is transported by a gradient time-limited mechanism.

Tubular Secretion

Secretion is analogous to tubular reabsorption, but it transfers solutes into the tubular lumen.

The most important examples of secreted substances in humans are creatinine, H^+ , and K^+ .

Clearance

The total amount of a substance that is excreted in urine in 1 minute can be considered to have come from a hypothetical volume of plasma that is now completely cleared of the substance (Figure 7-14). This hypothetical minute-volume is defined as the **renal clearance** of the substance. As a result of the definition, the calculation of clearance is based on the observation that

$$\text{Amount excreted} = \text{Clearance} \cdot \text{Plasma concentration}$$

That is, the clearance of any substance, X , is calculated as follows:

$$\text{Clearance}_X = \frac{\text{Urine concentration}_X}{\text{Plasma concentration}_X} \cdot \text{Urine flow rate}$$

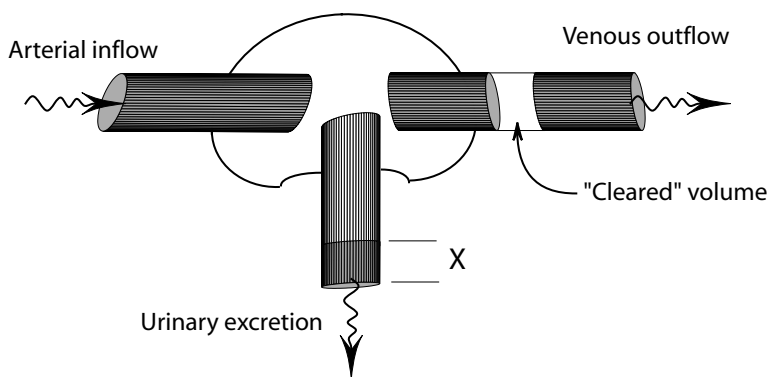


Figure 7-14 The amount of a substance “X” excreted in urine each minute ($U_X \cdot \dot{V}$) is equal to the plasma concentration of “X” multiplied by the hypothetical volume of plasma that is completely cleared of “X” as a result of glomerular filtration.

Clearance of Inulin as a Measure of Glomerular Filtration Rate

The concept of clearance is important because of the way in which the polysaccharide **inulin** (mol.wt. = 5.2 kDa) is handled by the nephron. It is freely filtered, but the nephron lacks inulin transporters for reabsorption or secretion. As a consequence, the amount of inulin appearing in the urine each minute at steady state is equal to the amount of inulin filtered each minute through all glomeruli, that is,

$$U_{IN} \cdot \dot{V} = P_{IN} \cdot \text{GFR}$$

From this, it follows that

$$\frac{U_{IN}}{P_{IN}} \cdot \dot{V} = \text{GFR}$$

Since

$$\frac{U_{IN}}{P_{IN}} \cdot \dot{V}$$

is defined as C_{IN} , the clearance of inulin, C_{IN} is identical to the rate of glomerular filtration (GFR) and C_{IN} is used as a measure of GFR.

Clearance of Para-aminohippuric Acid as a Measure of Renal Blood Flow

The amount of any nonmetabolized substance entering the kidney via the renal artery ($P_{A,X} \cdot \text{RPF}^*$) must be equal to the amount leaving in the

*RPF = renal plasma flow.

urine ($U_X \cdot \dot{V}$) plus the amount leaving in the renal vein [$P_{V,X} \cdot (RPF - \dot{V})$], that is,

$$P_{A,X} \cdot RPF = U_X \cdot \dot{V} + [P_{V,X} \cdot (RPF - \dot{V})]$$

para-aminohippuric acid (PAH) is freely filtered at the glomerulus and is also actively secreted into the nephron with such vigor that practically all of it is removed from renal plasma in one passage through the kidney, and there is virtually no PAH in renal venous blood. As a result, $P_{V,PAH} = 0$ and

$$P_{A,PAH} \cdot RPF = U_{PAH} \cdot \dot{V}$$

From this, it follows that

$$RPF = \frac{U_{PAH}}{P_{A,PAH}} \cdot \dot{V}$$

Therefore, clearance of PAH can be used to estimate renal plasma flow.

NEPHRON FUNCTION

The Proximal Tubule

The convoluted and straight portions are important because they iso-osmotically reabsorb two-thirds to three-quarters of the glomerular filtrate. Na^+ , Cl^- , HCO_3^- , and water form the bulk of the reabsorbate.

In humans, the rates of reabsorption are highest within the first 2 mm of the glomerulus and decline over the remaining 6 mm (Figure 7–15).

Water reabsorption occurs along the whole length of the tubule. Na^+ and water are reabsorbed iso-osmotically. The anion accompanying Na^+ is HCO_3^- in the early part of the tubule and Cl^- in more downstream parts.

Amino acids and glucose are reabsorbed early in the proximal convoluted tubule (see Figure 7–15) and by symports with Na^+ . Such Na^+ reabsorption has two effects: (1) it causes the lumen of the early proximal convoluted tubule to have a negative electrical potential relative to the peritubular space and (2) it allows a build-up of Cl^- in the early tubule segments. Electronegativity and the concentration gradient drive Cl^- out of the tubular lumen by the paracellular pathway and make the later portions of the proximal tubular lumen about 2 mV positive with respect to the peritubular interstitial space.

Mechanisms of Epithelial Transport

Proximal tubular transport depends on both Na^+/K^+ -ATPase and the Na^+ concentration gradient maintained by that enzyme. Both paracellular and transcellular routes are used.

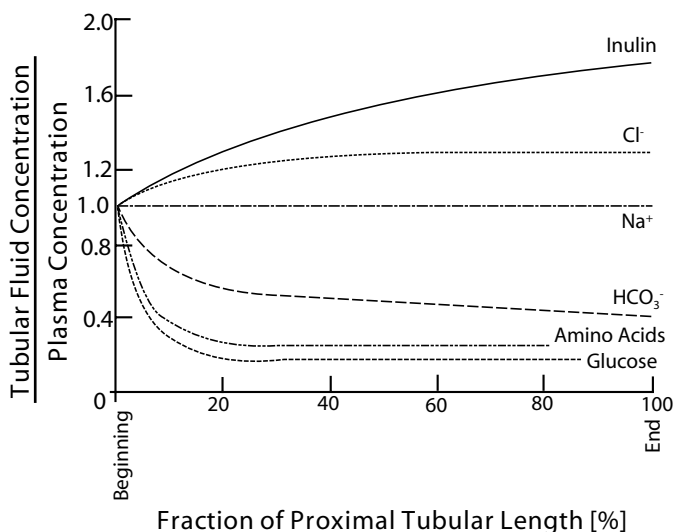


Figure 7-15 Progressive changes in the concentration ratios (proximal tubular fluid to plasma) of various substances along the length of the tubule. The inulin ratio increases progressively because water is reabsorbed from the tubule, but inulin is not. The ratio for Na^+ remains near unity because Na^+ is reabsorbed iso-osmotically. It is also evident that amino acids and glucose are reabsorbed from the filtrate in the early segments of the tubule.

Sodium reabsorption. The proximal tubule reabsorbs 40 to 45% of filtered sodium. The mechanisms involve passive Na^+ entry on the luminal side by pathways that include (1) a H^+ - Na^+ antiport and symports for Na^+ -glucose and Na^+ -amino acids, as well as (2) an amiloride-sensitive channel.

Net exit of Na^+ from epithelial cells occurs mostly in the lateral intercellular spaces because of the high concentration of membrane Na^+ - K^+ -ATPase in that region.

Glucose reabsorption. Glucose reabsorption involves two distinct carriers: (1) an Na^+ -dependent co-transporter at the luminal membrane (inhibited by **phlorhizin**) and (2) an Na^+ -independent GLUT-2 transporter on the basolateral side (inhibited by **phloretin**). Transport across the cell is by simple diffusion.

Reabsorption of amino acids and proteins. Most amino acids enter the luminal membrane by co-transport with Na^+ in an electrogenic process. Between five and seven specific carriers are involved, distinguished by

whether they transport amino acids that are acidic, dibasic, neutral, or members of either the imino family or the β and γ families.

Filtration of albumin (molecular radius = 3.6 nm) and larger proteins is low in the healthy human kidney. However, proteins smaller than albumin and up to a radius of 3.0 nm do appear in significant amounts in the glomerular filtrate if they circulate freely in plasma and are not bound to larger proteins.

Filtered proteins are quickly and almost completely reabsorbed by luminal T_m -limited processes. Some oligopeptides, such as the hormone angiotensin II, are then hydrolyzed, and others are catabolized within the absorbing cell. The resulting amino acids are returned to the peritubular interstitial space for reabsorption into the circulation.

Potassium reabsorption. Three mechanisms participate in K^+ reabsorption by the proximal tubule. They are (1) solvent drag through the paracellular pathway (20%), (2) passive diffusion through the paracellular pathway (60%) because basolateral Na^+-K^+ pumps set up a favorable concentration gradient for K^+ , and (3) active transport on the luminal side combined with basolateral exit by way of a K^+-Cl^- co-transporter that is also involved in proximal Cl^- reabsorption (20%).

Phosphate reabsorption. Normally, 80% of filtered phosphate (P_i) load is reabsorbed in the proximal convoluted tubule and contributes to the metabolic functions of the proximal epithelium. Inhibition of P_i entry on the luminal side abolishes, within a short time, all cellular active transport processes.

Phosphate (mostly in the divalent form) enters epithelial cells on the luminal side by way of co-transport with Na^+ . Once it is in the epithelial cell, P_i enters the metabolic pool where it contributes to cellular **phosphorylation potential** and acts as a substrate for ATP formation.

When P_i entry exceeds metabolic needs, P_i exits passively on the basolateral side. The mechanisms include a $Na^+-P_i^{2-}$ co-transporter and a band 3 $P_i^- - HCO_3^-$ exchanger.

Bicarbonate reabsorption. The H^+-Na^+ antiport is important for Na^+ reabsorption in the early proximal tubule. However, its more significant role is to prevent loss of filtered HCO_3^- from the body buffer stores.

Reabsorption of filtered HCO_3^- into tubular epithelial cells occurs secondarily to H^+ secretion by a mechanism that involves formation of H_2CO_3 from secreted H^+ and filtered HCO_3^- (Figure 7-16).

HCO_3^- leaves the epithelial cell on the basolateral side mostly by 3:1 co-transport with Na^+ .

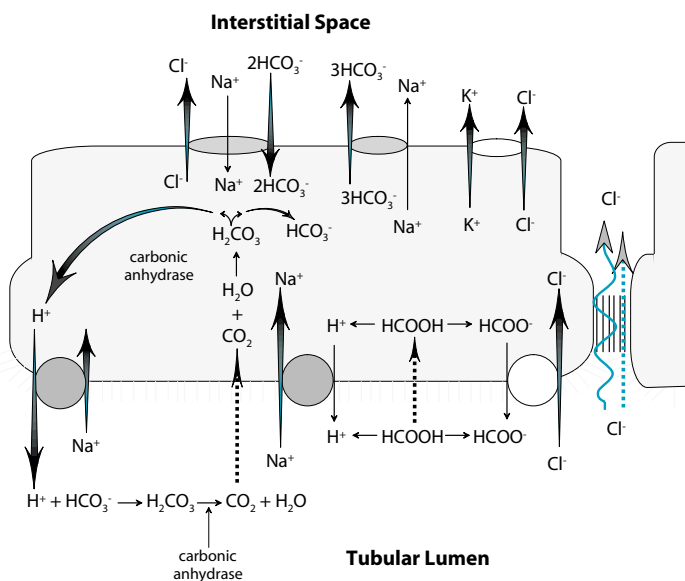


Figure 7-16 Mechanisms of HCO_3^- and Cl^- reabsorption in the proximal tubule of mammalian nephrons. Secreted H^+ combines with filtered HCO_3^- and forms H_2CO_3 in the lumen. The presence of carbonic anhydrase in tubular fluid ensures rapid dissociation of H_2CO_3 into CO_2 and H_2O . CO_2 thus formed diffuses into the epithelial cell and catalyzed there by cytosolic carbonic anhydrase, H_2CO_3 is formed. Subsequent dissociation of cellular H_2CO_3 provides H^+ for further HCO_3^- reabsorption.

Chloride reabsorption. Preferential transport of HCO_3^- in the early segments of the proximal convoluted tubule increases luminal $[\text{Cl}^-]$ and creates a concentration gradient for Cl^- .

Fifty percent of proximal Cl^- reabsorption is through the paracellular path by passive diffusion and solvent drag. The other 50% of proximal tubular Cl^- reabsorption occurs through a transcellular route that begins on the luminal side with a Na^+ -linked acid diffusion mechanism (HCOOH) (see Figure 7-16). Cl^- leaves the tubular cell on the basolateral side by a Na^+ -dependent Cl^- - 2HCO_3^- antiport and a K^+ - Cl^- symport (see Figure 7-16).

Water reabsorption. Both transcellular and paracellular pathways are used. Transcellular movement involves osmotic gradients acting across water channels that are permanently inserted in both the luminal and basolateral cell membranes. Within the epithelial cells, water is driven from the tubular to the basolateral side by both diffusion and regional differences in hydrostatic pressure. Paracellular water transport occurs because osmotic gradients are created by Na^+ - K^+ -ATPase activity in the lateral intercellular spaces.

As a consequence of water transport into the peritubular interstitial space, local hydrostatic pressure increases, and oncotic pressure decreases. These changes favor the uptake of interstitial fluid into the peritubular capillary network.

Regulation of Proximal Tubular Reabsorption

Net filtration pressure across peritubular capillary epithelium is believed to be the rate-limiting factor controlling proximal tubular reabsorption. This pressure is significantly influenced by the glomerular **filtration fraction** (FF).

Filtration fraction. In a single nephron, the tone in the afferent and efferent arterioles determines both vascular resistance and the magnitude of renal blood flow at a given renal arterial pressure. Moreover, the relative resistances in the afferent and efferent arterioles determine (1) net glomerular filtration pressure and (2) the FF (Figure 7–17).

Filtration fraction expresses the partitioning of flow between glomerular filtrate and peritubular capillary flow. The filtration fraction is normally 20% of renal plasma flow. It is increased by a relatively greater increase in efferent arteriolar resistance (see Figure 7–17).

The functional importance of the filtration fraction is as a direct determinant of peritubular oncotic pressure. Therefore, it sets the balance of Starling-Landis forces that determine reabsorption across the peritubular capillary epithelium.

Neurohumoral influences on proximal tubular reabsorption. α_1 -adrenergic agonists, such as efferent sympathetic nerve activity, stimulate proximal reabsorption and consequent antidiuresis and antinatriuresis. Angiotensin II at low doses has a similar effect. Both are thought to arise from phospholipase C activation and its attendant elevation of $[Ca^{++}]_i$. The links between $[Ca^{++}]_i$ and reabsorption have not been clearly delineated.

Loop of Henle

Thin Segment of the Loop of Henle

In juxtamedullary nephrons, the thin segment includes descending and ascending limbs, and the loop may descend all the way to the tip of the papilla (see Figure 7–6). In the more numerous, shorter, cortical nephrons, the thin segment consists of only a short descending limb, just long enough to traverse the inner stripe of the outer medulla.

Properties of thin descending limbs. The thin descending limb functions to increase tubular osmolarity. The mechanisms are passive transfer of

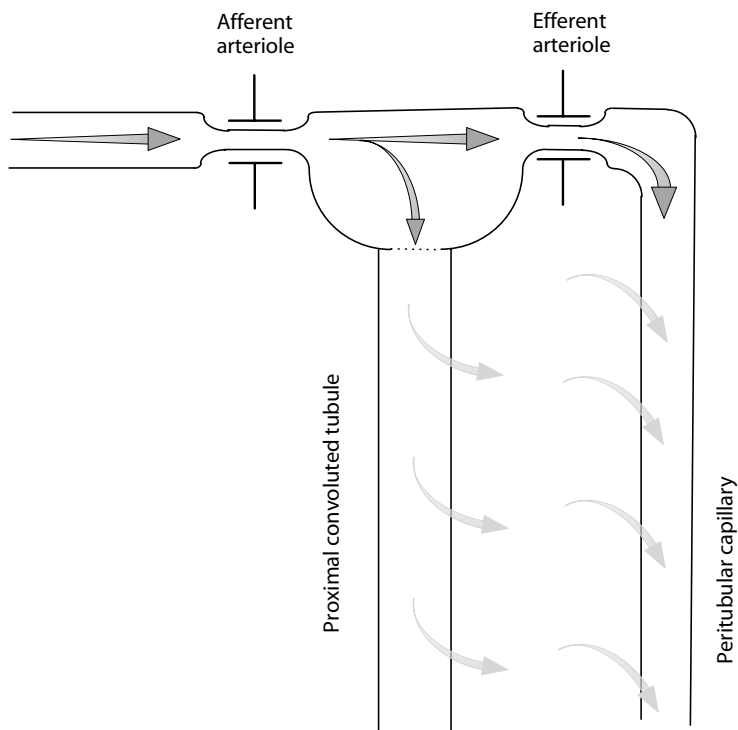


Figure 7-17 Influence of vascular resistance in the afferent and efferent arterioles on the physical factors controlling glomerular filtration rate and proximal tubular reabsorption. Changes in the filtration fraction have a direct effect on protein concentration in the peritubular capillary and, with that, on the rate of reabsorption from the interstitium. Filtration fraction is altered by relative changes in afferent and efferent arteriolar resistance: increased afferent resistance decreases renal plasma flow and glomerular filtration rate equally. Increased efferent resistance causes a relative increase in glomerular filtration rate compared with renal plasma flow.

water, urea, Na^+ , and Cl^- , each in accordance with local epithelial permeability and prevailing concentration gradients.

Short nephrons. The major concentrating mechanisms are water extraction and urea addition.

Long nephrons. The outer medullary portion of thin descending long limbs is more permeable to Na^+ and Cl^- than it is to urea. As a result, concentration of tubular fluid in the early portion of long thin descending limbs results from water extraction and NaCl addition. This leads to progressively increasing interstitial urea concentration, but increasing tubular NaCl concentration toward the papilla.

Water permeability changes little along the length of the descending thin limb, but Na^+ and Cl^- permeabilities decrease, whereas urea permeability increases. These changes (1) prevent dissipation of the increasing concentration gradient for NaCl from lumen to interstitium and (2) facilitate urea entry into the lumen down the increasing urea concentration gradient from interstitium to lumen.

Properties of thin ascending limbs. Cells in the thin ascending limb contain very little $\text{Na}^+/\text{K}^+/\text{ATPase}$. Their outstanding properties are (1) low permeability to water, coupled with (2) high permeabilities to Na^+ , Cl^- , and urea.

As a result of these properties, tubular fluid becomes progressively dilute as Na^+ , Cl^- , and urea diffuse out into the interstitial space. This explains why fluid from the ascending limb is more dilute than fluid from the descending limb at the same level.

Thick Ascending Limb of the Loop of Henle

The thick ascending limb begins at the boundary between outer and inner medulla (see Figure 7-6) and ends a few μm beyond the macula densa. It has two significant features: (1) its epithelium has very low water permeability and can withstand a large osmotic gradient, and (2) the luminal membrane contains a furosemide-sensitive, electroneutral, lumen to cytosol $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ co-transporter (Figure 7-18).

In spite of the low water permeability, ions can pass readily from lumen to interstitial space through both paracellular and transcellular paths.

Handling of water, Na^+ , and Cl^- by the thick ascending limb. The electroneutral, lumen to cytosol $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ co-transporter is driven by the Na^+ concentration gradient and inhibited by **furosemide**.

Both the furosemide-sensitive co-transporter and the ubiquitous $\text{Na}^+/\text{K}^+/\text{ATPase}$ add K^+ to the cell interior (see Figure 7-18). When K^+ diffuses back into the lumen (through a barium-sensitive channel), it creates electropositivity in the lumen. The $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ co-transporter also adds Cl^- to the cell. This Cl^- leaves the cell on the basolateral side by two routes: (1) by electroneutral co-transport with K^+ (about 30% of Cl^- transport) and (2) through a Cl^- -selective channel.

The net result of K^+ diffusion into the lumen and Cl^- diffusion into the interstitial space is a lumen-positive transepithelial voltage of approximately +10 mV that drives transcellular reabsorption of Na^+ , Ca^{++} , or Mg^{++} into the renal interstitium (see Figure 7-18).

The net effects of solute reabsorption in the thick ascending segment *without accompanying water* are the creation of (1) high osmolarity in the

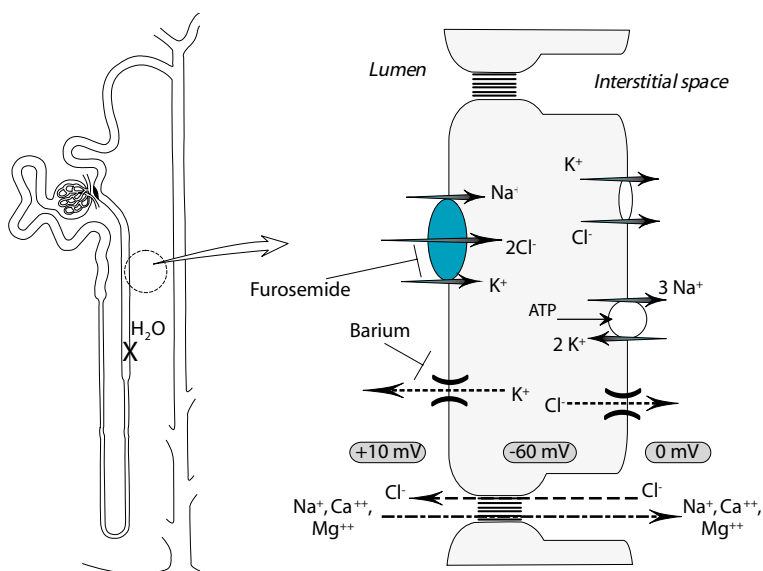


Figure 7-18 The luminal membrane in the thick ascending limb of the loop of Henle is characterized by the presence of a furosemide-sensitive $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ co-transporter and a K^+ channel. The basolateral membrane contains $\text{Na}^+ - \text{K}^+ - \text{ATPase}$, a $\text{K}^+ - \text{Cl}^-$ co-transporter and a Cl^- channel. The net effects of reabsorptive activity in this part of the nephron are (1) K^+ is continuously recycled across the luminal membrane; (2) Na^+ and Cl^- are reabsorbed by a transcellular path; (3) a lumen-positive, $+10 \text{ mV}$ transepithelial voltage is established; and (4) tubular fluid is made hypo-osmotic and interstitial fluid is made hyperosmotic with respect to normal extracellular fluid.

interstitium of the cortico-medullary region and (2) hypotonic tubular fluid at the beginning of the distal convoluted tubule.

Regulation of thick ascending limb function. Absorption in the thick ascending limb is modulated by (1) physical factors, such as flow velocity, and (2) hormones that activate adenylate cyclase (parathyroid hormone [PTH], calcitonin, vasopressin, glucagon, and β_2 agonists).

The major effect of hormonal stimulation is enhanced reabsorption of Ca^{++} , Mg^{++} , and K^+ . NaCl reabsorption in the thick ascending limb is only slightly altered by hormones in humans.

Distal Nephron

The distal nephron consists of the **distal convoluted tubule**, the **collecting tubule**, and the **cortical** and **medullary collecting ducts**. The distal nephron is the site where there is fine transport adjustment for the purpose of body electrolyte and volume homeostasis.

Distal Convoluted Tubule

The distal convoluted tubule is less than 1 mm long. It consists mainly of (1) **distal convoluted tubule cells**, containing both $\text{Na}^+\text{-K}^+\text{-ATPase}$ and $\text{Ca}^{2+}\text{-Mg}^{2+}\text{-ATPase}$ at high concentrations, and (2) some **intercalated cells**, which are relatively rich in carbonic anhydrase but contain no $\text{Na}^+\text{-K}^+\text{-ATPase}$ or $\text{Ca}^{2+}\text{-Mg}^{2+}\text{-ATPase}$.

Transport of Na^+ and Cl^- .

Paracellular transport. At the beginning of the distal convoluted tubule, there is an interstitium to lumen concentration gradient for both Na^+ and Cl^- , and they are secreted electroneutrally into the lumen. However, transcellular reabsorptive mechanisms favor Na^+ uptake, and this causes increasing lumen negativity with distance along the tubule. Such a change in potential difference will increasingly promote both (1) outward Cl^- diffusion through the tight junctions and (2) Na^+ backdiffusion into the tubule.

Transcellular reabsorption. (1) Transport across the luminal membrane: Na^+ enters passively from the lumen, partly through an amiloride-sensitive channel and partly through thiazide-sensitive co-transport with Cl^- (Figure 7–19). (2) Transport across the basolateral membrane: Having diffused through the cytosol, Na^+ is transported actively into the interstitium by $\text{Na}^+\text{-K}^+\text{-ATPase}$, and Cl^- leaves passively, at least in part, through a Cl^- -selective channel.

Regulation of Na^+ and Cl^- reabsorption in the distal convoluted tubule.

Reabsorption varies directly with delivered tubular load. The changes that are evident after an increase in tubular load are both morphologic and functional. Morphologic changes include increases in cell size, basolateral membrane area, and mitochondrial size. The functional changes include increased $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity and increased number of thiazide-sensitive $\text{Na}^+\text{-Cl}^-$ co-transporters.

Secretion of K^+ . The distal convoluted tubule receives low- $[\text{K}^+]$ fluid from the thick ascending limb and secretes K^+ into it.

Paracellular secretion is promoted by lumen negativity. Transcellular secretion involves active K^+ transport into the cell by way of the $\text{Na}^+\text{-K}^+$ pump and passive exit on the luminal side. Both $\text{K}^+\text{-Cl}^-$ co-transport and a barium-inhibited K^+ channel are involved (see Figure 7–19).

Reabsorption of Ca^{++} in the distal convoluted tubule.

Transport across the luminal membrane. Ca^{++} enters epithelial cells passively down a large electrochemical gradient. The major pathway is a

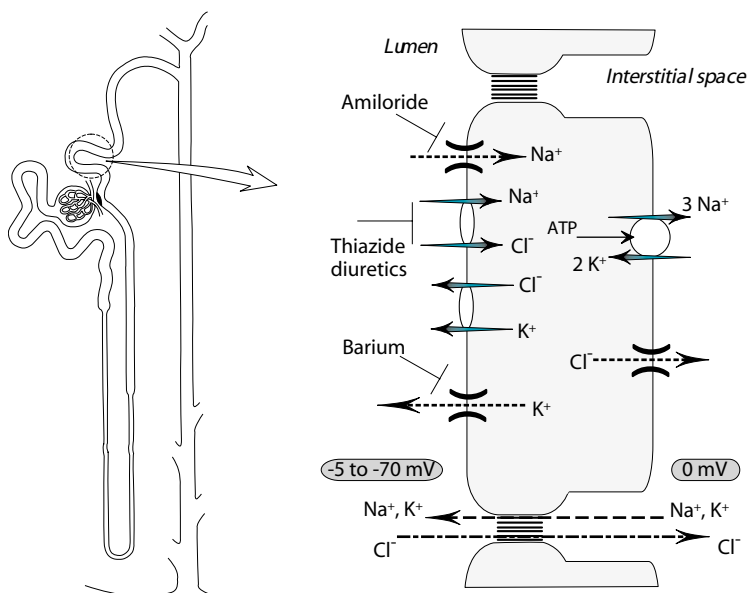


Figure 7-19 Mechanism for the transport of Na^+ , Cl^- , and K^+ in the distal convoluted tubule. Na^+ and Cl^- enter the luminal side by passive mechanisms and are extruded on the basolateral side by both active and passive mechanisms. K^+ enters actively by way of Na^+ - K^+ -ATPase on the basolateral side and leaves passively on the luminal side through both a K^+ - Cl^- co-transporter and a barium-sensitive channel. The transepithelial voltage gradient is lower at the beginning of the distal convoluted tubule than it is in the later portion, the luminal voltage ranging from -5 to -70 mV.

PTH-modulated, dihydropyridine-sensitive channel, but voltage-gated channels are present as well.

Transport across the basolateral membrane. Extrusion of Ca^{++} on the basolateral side is by active extrusion (Mg^{++} -sensitive Ca^{++} -ATPase) and Na^+ -driven Ca^{++} - 3Na^+ exchange.

Collecting Tubule

Reabsorption of Na^+ and Cl^- . Both Na^+ and Cl^- are reabsorbed by paracellular and transcellular mechanisms similar to those described for other segments. Transcellular reabsorption involves luminal entry by three mechanisms: (1) an amiloride-sensitive Na^+ channel, (2) an Na^+ - H^+ antiport, and (3) an Na^+ and Cl^- transporter that consists of an Na^+ - H^+ antiport linked to a Cl^- -base $^-$ antiport by a diffusional path for reconstituted HBase. An example is shown in Figure 7-16.

Na^+ exits on the basolateral side by the Na^+/K^+ pump, whereas Cl^- leaves primarily through a Cl^- -selective channel.

Secretion of potassium. K^+ is secreted by mechanisms that are identical to those in the distal convoluted tubule, and the secretion rate is load dependent.

Cortical Collecting Duct

The cortical collecting duct is composed of **principal cells** and **intercalated cells**. Principal cells reabsorb Na^+ and Cl^- and secrete K^+ . Intercalated cells reabsorb K^+ and secrete either H^+ (A-type cells) or HCO_3^- (B-type cells).

Reabsorption of Na^+ and Cl^- in the cortical collecting duct. The elements of the transport mechanisms are identical to those described for other segments (Figure 7–20). They include, in the luminal membrane, Na^+ entry by (1) an amiloride-sensitive Na^+ channel, (2) a barium-sensitive K^+ channel, (3) a band 3 $\text{Cl}^-/\text{HCO}_3^-$ exchanger in some species, and (4) a thiazide-sensitive Na^+/Cl^- co-transporter in other species. Na^+ leaves on the basolateral side, where the dominant transport mechanism is active Na^+/K^+ pumping, but K^+ -selective and Cl^- -selective channels are found as well.

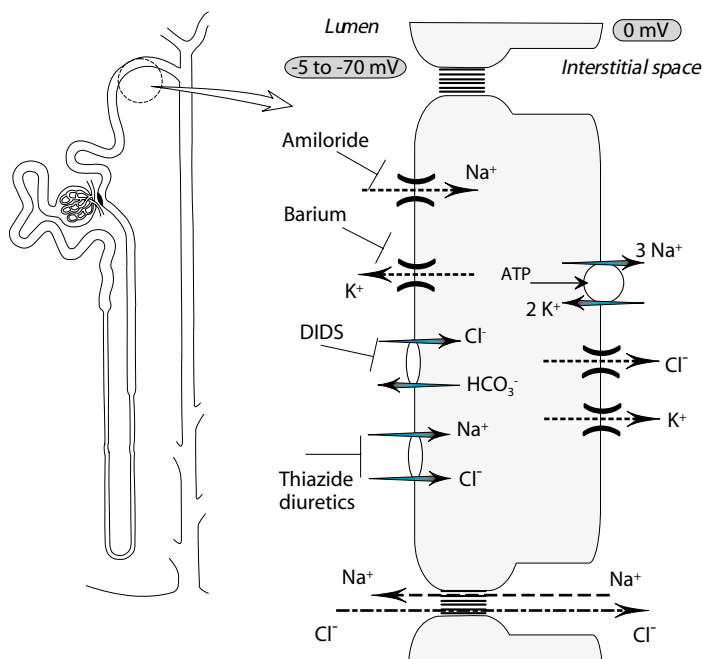


Figure 7–20 Major transcellular ion transport mechanisms in principal cells of the inner cortical collecting duct. DIDS = 4,4'-di-iso thiocyanostilbene-2,2'-disulfonate.

Transport of K^+ in the cortical collecting duct. The cortical collecting duct is the major site for regulated K^+ secretion.

K^+ transport across the luminal membrane. There is a high concentration of K^+ channels. They form two major classes: (1) K^+ channels mainly responsible for regulating cell volume are voltage sensitive, activated by elevated intracellular $[Ca^{++}]$, and inhibited by Ba^{++} ; (2) K^+ channels mainly responsible for K^+ secretion are activated by decreased intracellular $[H^+]$ or elevated protein kinase A.

K^+ transport across the basolateral membrane. K^+ channels in the basolateral membrane are activated by hyperpolarization, cell wall stretch, or elevated intracellular $[ATP]$.

K^+ transport through these channels maintains negative intracellular potential and contributes to cell volume regulation.

Regulation of Na^+ , Cl^- , and K^+ transport in the cortical collecting duct. Ion transport in this nephron segment is regulated primarily by the actions of **aldosterone** and **vasopressin** (Figure 7–21). Prostaglandins, bradykinin,

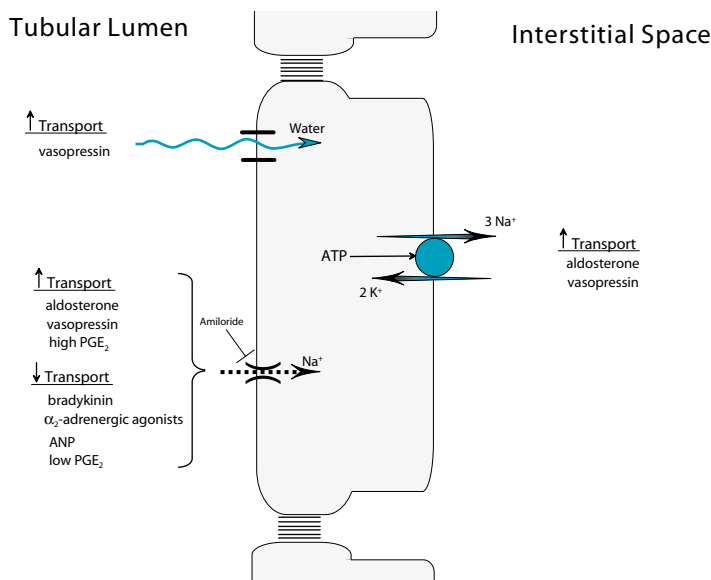


Figure 7–21 Hormonal control of water and electrolyte reabsorption in the cortical collecting duct. Most effects are due to primary changes in the conduction of the amiloride-sensitive Na^+ channel. The effect of PGE_2 varies with concentration. Beta-adrenergic agonists affect intercalated cells only. PGE_2 = prostaglandin E_2 ; ANP = atrial natriuretic peptide.

adrenergic agonists, and atrial natriuretic peptides are involved as well and may provide synergistic and antagonistic effects.

Aldosterone. Aldosterone is a steroid. Therefore, its major effects are on protein synthesis and occur on a timescale of several hours (Figure 7–22). However, there are early effects: (1) aldosterone acts initially (during the first 30 minutes) by increasing the number of amiloride-sensitive Na^+ channels in the luminal membrane and by increasing the rate of active $\text{Na}^+ - \text{K}^+$ pumping; (2) the later phase of aldosterone action (>1 hour) is mediated by both a nuclear receptor and elevated cytosolic $[\text{Na}^+]$ and results in increased synthesis and basolateral insertion of $\text{Na}^+ - \text{K}^+ - \text{ATPase}$; and (3) aldosterone may also stimulate insertion of barium-sensitive K^+ channels into the luminal membrane.

The direct effect of increased aldosterone is increased Na^+ reabsorption and, consequently, increased electronegativity of the lumen. This increases the driving force for passive reabsorption of Cl^- by the paracellular path.

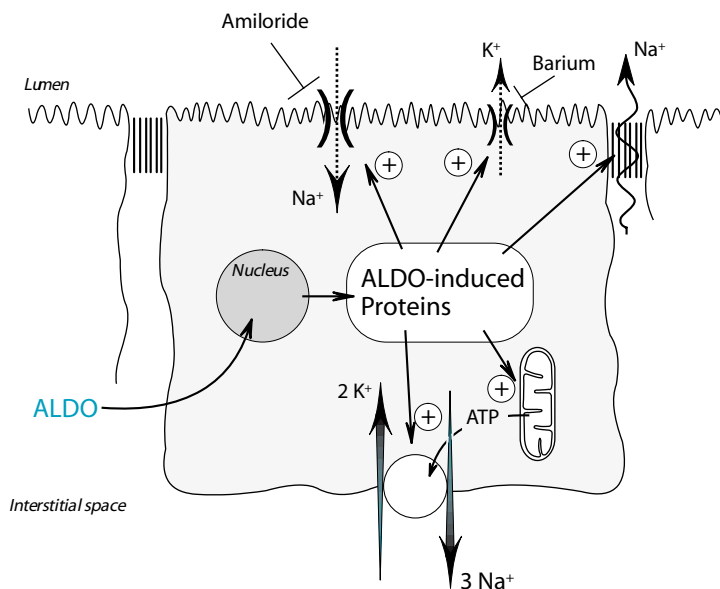


Figure 7–22 Summary of aldosterone effects in the cortical collecting duct. Aldosterone binds to its nuclear receptor to form an aldosterone-receptor complex that induces synthesis of several aldosterone-induced proteins. These proteins stimulate a number of passive and active ion transport mechanisms. Increased Na^+ reabsorption increases the electrical driving force for paracellular Na^+ backflux.

Vasopressin. Vasopressin modulates both electrolyte transport and water conductivity in the cortical collecting duct.

Vasopressin effects on electrolyte transport express themselves as a rapid and sustained increase in reabsorption of Na^+ and Cl^- . They are achieved by V_2 receptor activation and consequent protein kinase A–driven increases in (1) luminal, amiloride-sensitive Na^+ conductance and (2) turnover of basolateral Na^+/K^+ -ATPase (Figure 7–23).

Increased Na^+ reabsorption increases lumen negativity and, thereby, increases electrically driven Cl^- reabsorption by the paracellular path.

The lowest water conductivity of any plasma membrane is found in the unstimulated luminal membrane of principal cells in the cortical collecting duct. Vasopressin acts at this membrane by activating V_2 receptors. The consequent activation of protein kinase A results in translocation of aggregophores to the luminal membrane and subsequent increase in the water conductance of that membrane (see Figure 7–23).

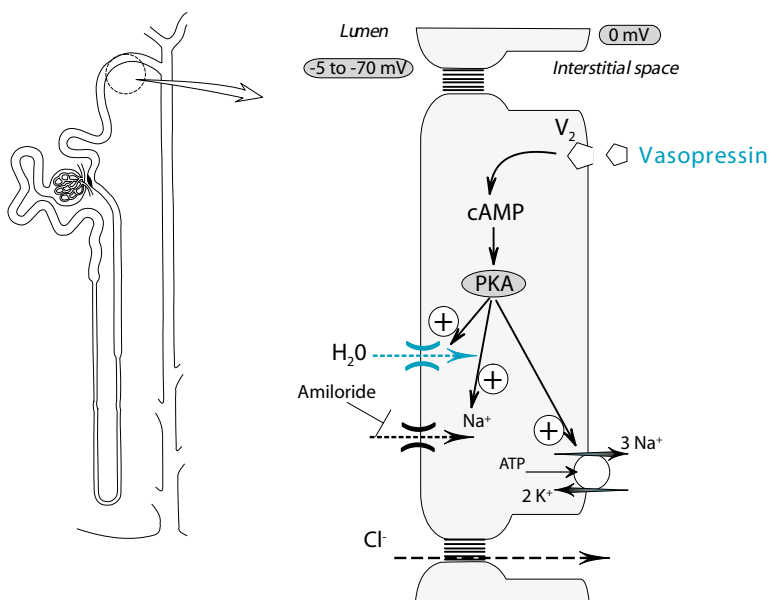


Figure 7–23 Summary of vasopressin effects on reabsorption of water and electrolytes in the cortical collecting duct. Vasopressin activates the V_2 receptor and thereby enhances the formation of cAMP. Subsequent effects are due to protein kinase A (PKA). In the luminal portion of the epithelial cell membrane, vasopressin increases synthesis and insertion of amiloride-sensitive Na^+ channels. On the basolateral side, it increases turnover of Na^+/K^+ -ATPase. Increased Na^+ reabsorption increases the electrical driving force for paracellular Cl^- reabsorption. Most importantly, vasopressin causes migration of aggregophores to the luminal membrane and a consequent increase in water transport across that barrier.

Prostaglandins. PGE₂ is the major prostaglandin in this area. It acts locally on two classes of PGE receptors, both involving G proteins and the modulation of cytosolic [cAMP]. The high-affinity EP₃ receptor causes inhibition of Na⁺ reabsorption, whereas the lower-affinity EP₂ receptor stimulates Na⁺ reabsorption.

As a result of receptor differences in ligand affinity, the effect of PGE₂ on collecting duct Na⁺ reabsorption varies with concentration: low PGE₂ concentrations inhibit Na⁺ reabsorption (EP₃ action), whereas high PGE₂ concentrations stimulate Na⁺ reabsorption (EP₂ action).

The primary mechanism of these effects is cAMP-dependent conduction changes in the luminal, amiloride-sensitive Na⁺ channel.

Bradykinin. Bradykinin activates phospholipase C, which causes elevation of both [Ca⁺⁺]_i and diacylglycerol (DAG). Diacylglycerol is further split to produce arachidonic acid and thereby enhances PGE₂ synthesis. Such synthesis is, however, of relatively low magnitude and activates mostly EP₃ receptors.

Elevated [Ca⁺⁺]_i and EP₃ activation both inhibit the amiloride-sensitive Na⁺ channel. As a result, bradykinin inhibits Na⁺ reabsorption in the cortical collecting duct.

Adrenergic agonists. The cortical collecting duct contains α₂- as well as β₁- and β₂-adrenoreceptors. α₂ Activation reduces passive Na⁺ entry on the luminal side. This results from decreased intracellular [cAMP].

Beta-adrenergic agonists have no effect on Na⁺ transport in this nephron segment. However, they stimulate (1) luminal active H⁺ secretion in A-type intercalated cells and (2) the luminal Cl⁻(in), HCO₃⁻(out) antiport in B-type intercalated cells.

Atrial natriuretic peptides. Activation of ANP-R (guanylate cyclase-A) receptors elevates intracellular [cGMP] and, thereby, inhibits Na⁺ reabsorption by inhibiting the luminal, amiloride-sensitive Na⁺ channel.

Medullary Collecting Duct

The medullary collecting duct can be subdivided into an outer and inner medullary portion.

Outer medullary portion. The outer medullary portion resembles the cortical collecting duct in structure, function, and mechanisms of ion transport. It contains both principal cells and intercalated cells. Principal cells transport Na⁺, Cl⁻, and K⁺. Intercalated cells are responsible for urine acidification.

Inner medullary portion. The inner medullary portion is more highly branched than the outer portion and contains no intercalated cells. Its function is more complex than that of other nephron segments because it can move NaCl either into the duct lumen or out of it. Such bi-directional transport involves three elements: (1) Na^+ enters passively from the lumen through an amiloride-sensitive Na^+ channel and is actively transported from the cell by basolateral $\text{Na}^+\text{-K}^+\text{-ATPase}$; (2) an $\text{Na}^+\text{-H}^+$ exchanger, located in the basolateral membrane, functions to extrude intracellular H^+ ; and (3) a furosemide-sensitive $\text{K}^+\text{-2Cl}^-\text{-Na}^+$ inward co-transporter is present in the basolateral membrane and might be one of the mechanisms required for secretion of NaCl into the tubular lumen.

Regulation of ion transport in the medullary collecting duct. The major regulator of electrolyte transport in the inner medullary collecting duct is **atrial natriuretic peptide** (ANP). Its effect is mediated by inhibition of the luminal, amiloride-sensitive Na^+ channel. Thus, elevated ANP reduces Na^+ reabsorption and leads to natriuresis.

URINARY CONCENTRATION AND DILUTION

Osmolarity as the Driving Force

Whereas the osmolarity of plasma and of glomerular filtrate is remarkably constant at about 290 mOsm/kg, urine osmolarity ranges from 50 mOsm/L in conditions of excess water intake to 1,200 mOsm/L in severe dehydration. Three factors are vital to the production of urine with such a range of osmolarity: (1) presence of a very high osmolarity in the renal medullary interstitium, (2) anatomic routing of the water-permeable collecting duct through the region of high medullary interstitial osmolarity, and (3) modulation of water permeability in the collecting duct by the hormone **vasopressin**.

Medullary Interstitial Osmolarity

Renal interstitial osmolarity increases progressively from renal cortex to renal medulla and reaches its highest levels in the region of the papilla. It is created in approximately equal proportions by NaCl and urea. Two aspects contribute to the creation of highly concentrated tubular fluid in this region: (1) the local anatomy forces tubular flow in one portion of the nephron to be parallel and oppositely directed to flow in a downstream portion of the nephron. Such an arrangement defines a **countercurrent multiplier**; and (2) the permeabilities to solute and water in the two portions with oppositely directed flow are differentially selective.

Accumulation of NaCl in the Renal Medullary Interstitium

The thin descending limb and the thick ascending limb are arranged in parallel (see Figure 7–6) and in close proximity to each other. The relevant epithelial properties are (1) the thick ascending limb transports Na^+ and Cl^- from tubular lumen to interstitium and is *impermeable to water*, and (2) the thin descending limb is permeable to Na^+ , Cl^- , and water.

As tubular fluid enters the descending limb of the loop of Henle, Na^+ and Cl^- , which are pumped out of the adjacent thick ascending limb, diffuse down their concentration gradients from interstitium to thin descending lumen (Figure 7–24), while water is extracted from the thin descending limb down the osmotic gradient. The net result is an increase in the osmolarity of thin descending tubular fluid as it flows toward the papilla.

At each level on the way toward the papilla, more NaCl is transferred from the thick ascending limb to the surrounding interstitium and the adjacent thin descending limb. The maximal NaCl concentration is reached at the hairpin turn of the loop; the longer the nephron, the higher is the

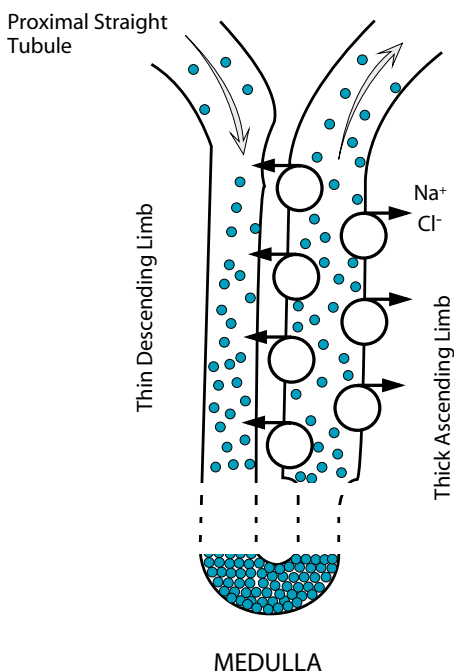


Figure 7–24 The renal countercurrent mechanism. Progressive increase in tubular and interstitial osmolarity is created by the addition of Na^+ and Cl^- to the descending thin limb fluid.

osmolarity at the hairpin turn. At steady state, each depth of the renal interstitium is characterized by a fixed concentration difference between ascending fluid and its surroundings.

Accumulation of Urea in the Renal Medullary Interstitium

Urea is formed in the liver during protein metabolism (see Chapter 8, “Gastrointestinal System” for details). Most of it is excreted in urine, where it contributes approximately half the total urine osmolarity.

Urea enters the nephron by glomerular filtration. Its concentration changes along the length of the nephron because urea permeability varies in the different sections.

Urea concentration in tubular fluid remains low until the fluid reaches the thin descending segment of the loop of Henle. The reason for this is that urea permeability of the proximal tubule is high, and urea quickly moves down any concentration gradient that arises from water reabsorption.

Along the thin descending limb, urea concentration increases slightly, partly because, in this region, water reabsorption occurs more readily than urea reabsorption and partly because urea is added to the tubular fluid from the interstitium in response to a concentration gradient. Urea becomes highly concentrated by water extraction in the distal convoluted tubule and early collecting tubule because both are impermeable to urea. The inner medullary collecting duct has both high urea concentration and high urea permeability. As a result, urea enters into the renal interstitium at this site and contributes to the tonicity of interstitial fluid around any nephron segment with low urea permeability.

REGULATION OF EXTRACELLULAR VOLUME AND OSMOLARITY

Water and electrolytes normally enter by mouth. Some of the intake travels through the gastrointestinal system and leaves the body with stool.* Most of the intake crosses the intestinal wall and enters the plasma in the adjacent blood vessels. Once in the plasma, water can follow four different paths: (1) some water leaves by way of the lungs; (2) some water and electrolytes leave the body as sweat; (3) some water and electrolytes leave the body by way of the kidneys; and (4) the remaining water and electrolytes exchange first with the interstitial space across the capillary endothelium and then with the intracellular fluid across the plasma membrane of cells.

Extracellular osmolarity and extracellular fluid volume give the appearance of being regulated in that they quickly recover from environmental dis-

*Most of the water in stool derives from secretions of the gastrointestinal tract.

turbances. Under normal conditions of diet, physical activity, and ambient temperature, plasma osmolarity is maintained at a level about halfway between its threshold for triggering vasopressin secretion and its (higher) threshold for thirst. A voluntary or involuntary increase in the intake of fluid or salt is soon followed by appropriate changes in urinary excretion of water and salt.

While the regulation of extracellular osmolarity is readily evident, it is not clear whether volume is in fact being regulated or which volume is being regulated. **Extracellular fluid volume**, **effective circulating blood volume**, and **'fullness' of the arterial circulation** have each been proposed as the regulated parameter.

When there is a simultaneous and conflicting need to regulate osmolarity or volume (such as during severe sweating in heat stress), regulation of osmolarity will win out.

Sensory Mechanisms of Extracellular Volume and Composition

Pressure Sensors

Specialized neurons that respond with changes in firing frequency to changes in ambient stretch (mechanosensors) are located diffusely throughout the cardiovascular system. They are concentrated in the aortic arch, carotid sinus, cardiac ventricular wall, and cardiac atrial wall. Their action potentials are conveyed to the central nervous system (CNS) by (1) sympathetic afferents or (2) branches of the vagus and glossopharyngeal nerves.

The juxtaglomerular cells of the renal afferent arteriole are an additional stretch-sensitive mechanism. They synthesize the proteolytic enzyme renin and release it when afferent arteriolar stretch is decreased. Renin cleaves angiotensinogen (a freely circulating plasma α_2 -globulin) and, with that, initiates a cascade whose final products are the biologically active peptides **angiotensin II** and **angiotensin III** (see Figure 7–13).

Volume Sensors

Both neural and humoral mechanisms of volume detection have been identified:

- The walls of the cardiac atria contain stretch-sensitive vagal neurons whose activation triggers a reflex, the effector response of which includes both diuresis (resulting from vasopressin inhibition) and natriuresis (resulting from inhibition of both vasopressin and efferent renal sympathetic nerve activity).
- Atrial muscle cells contain secretory granules filled with the immediate precursor to **atrial natriuretic peptides**, a family of small peptides

released mostly in response to atrial wall stress.* Its actions are receptor mediated, using cGMP as a second messenger. They include increased glomerular filtration rate and inhibition of collecting duct Na^+ reabsorption.

Flow Sensors

There is a direct relationship between macula densa Na^+ load (load = concentration \times flow) and afferent arteriolar resistance. The relationship is called **tubulo-glomerular feedback**, and its mechanisms are not yet clear. (See Regulation of Renal Blood Flow and Glomerular Filtration Rate, earlier in this chapter, for greater detail.)

Osmolarity Sensors

Selected cells within the portal venous circulation of the liver and especially cells within two cerebral circumventricular organs, the **organum vasculosum of the lamina terminalis** (OVLT) and the **subfornical organ** (SFO), respond to changes in extracellular osmolarity. They form the afferent arm of a reflex whose efferent arm is the modulation of vasopressin release.

At plasma osmolarities below a certain threshold, plasma vasopressin is suppressed to levels that are lower than detectability. Above the osmolarity sensor threshold, plasma vasopressin concentration rises steeply with even small increases in extracellular osmolarity.

Direct Effects of Compositional Variables

Volume changes brought on by such procedures as intravenous saline loading are not pure volume changes but involve decreases, for example, in plasma oncotic pressure and hematocrit. Such physical factors have profound influences on vascular resistance and on peritubular capillary Starling-Landis forces governing tubular reabsorption.

Reflex Centers for Extracellular Volume and Composition

Two central nervous areas are significantly involved in the regulation of body fluid balance and its integration with cardiovascular function. They are the hypothalamus and the brainstem (Figure 7–25).

*Wall stress = $\frac{\text{Pressure} \times \text{Chamber diameter}}{\text{Wall thickness}}$

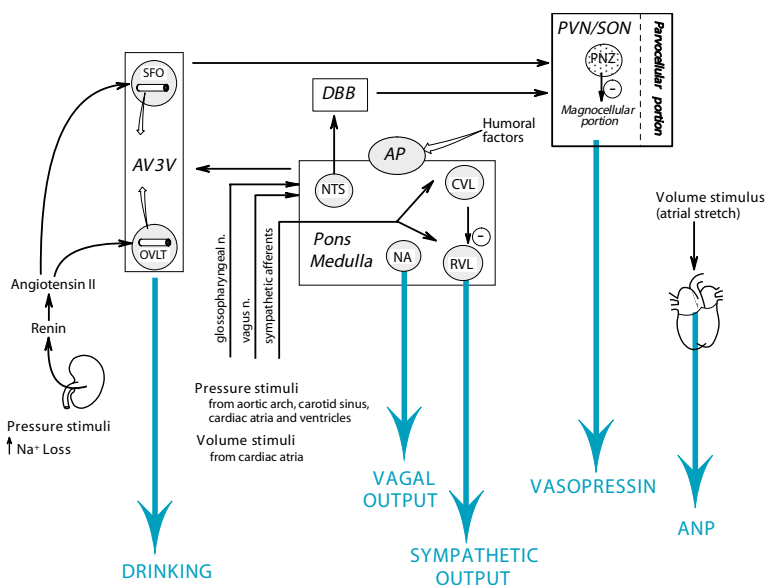


Figure 7–25 Summary of mechanisms regulating body fluid volumes and electrolytes. Afferent signals derive from both pressure and volume stimuli. Most enter the central nervous system through the vagus and glossopharyngeal nerves into the nucleus tractus solitarius (NTS). Some enter through sympathetic afferents. Appropriate changes are brought about through both nervous and chemical effector mechanisms. ANP = atrial natriuretic peptide; AP = area postrema; AV3V = anteroventral region of the 3rd ventricle; DBB = diagonal band of Broca; CVL = caudal ventrolateral medulla; NA = nucleus ambiguus; NTS = nucleus tractus solitarius; OVLT = organum vasculosum of the lamina terminalis; PNZ = perinuclear zone of SON; PVN = paraventricular nucleus; RVL = rostral ventrolateral medulla; SFO = subfornical organ; SON = supraoptic nucleus.

Hypothalamus

Three areas within the hypothalamus are important for the regulation of extracellular volume and composition.

Anteroventral region of the third cerebral ventricle (AV3V). The AV3V region in the hypothalamus controls drinking behavior and communicates with the other CNS areas involved in cardiovascular/renal integration.

Paraventricular and supraoptic nuclei. The magnocellular portion of the paraventricular and supraoptic nuclei synthesizes vasopressin and conveys it to the posterior pituitary for storage and demand-driven release.

Brainstem

The **pons/medulla** region of the brainstem contains three regions that contribute significantly to CNS mechanisms of extracellular fluid regulation (see Figure 7–25). (1) the **nucleus tractus solitarius** receives incoming information from peripheral sensors and conveys it to other central nervous loci; (2) the **area postrema** forms the gateway by which circulating chemicals can influence brainstem function because the area postrema lacks a blood-brain barrier; and (3) the **rostral ventrolateral medulla** forms the origin of efferent sympathetic activity.

Effector Mechanisms for Extracellular Volume and Composition

Thirst and **renal excretion** are the two major components of the systems that regulate body fluid volume and osmolarity.

Thirst

Water intake is regulated by the sensation of thirst. It emanates from neurons within the AV3V region, where the local level of angiotensin II has been identified as an important stimulus for water intake.

Renal Excretion of Water and Sodium

Renal excretion of water and Na^+ is important in the regulation of body fluid volume and composition. Their excretion is modulated by hormones and nerves.

Hormones regulating renal excretion. Both glomerular filtration rate and tubular reabsorption are influenced by hormones.

Hormones affecting glomerular filtration rate. In humans, the most significant hormonal regulators of glomerular filtration rate are (1) circulating factors, such as epinephrine, angiotensin II, and atrial natriuretic peptides; and (2) locally produced factors, such as angiotensin II, bradykinin, prostaglandins, and endothelium-derived factors.

Angiotensin II is produced locally, following increased renin release from juxtaglomerular cells when afferent arteriolar stretch is diminished. It has two relevant actions: (1) it preferentially constricts efferent arterioles and thereby increases filtration fraction; and (2) it sensitizes the tubuloglomerular feedback mechanism by which increased electrolyte transport in macula densa cells increases afferent arteriolar resistance.

Bradykinin is synthesized in the collecting tubule endothelium. It affects renal blood flow by its vasodilator actions.

Hormones affecting renal tubular reabsorption. Significant hormonal influences on tubular reabsorption arise from angiotensin II, vasopressin (ADH), aldosterone, bradykinin, and atrial natriuretic peptide.

Angiotensin II: Angiotensin II increases Na^+ reabsorption in proximal and late distal tubule.

Vasopressin: The plasma concentration of vasopressin is regulated by input from hypothalamic osmoreceptors and cardiac atrial mechanosensors. Vasopressin has major actions in the thick ascending limb of the loop of Henle and in the cortical collecting duct. These effects are mediated by activation of V_2 receptors. As detailed elsewhere, the V_2 receptor-mediated effects of vasopressin are to increase (1) electrolyte transport in the thick ascending limb of the loop of Henle and the cortical collecting duct and (2) water reabsorption in the cortical collecting duct.

Aldosterone: Aldosterone is synthesized in the **zona glomerulosa cells** of the adrenal cortex. The plasma concentration of aldosterone can be elevated by one of three factors: (1) an increase in adrenocorticotrophic hormone (ACTH), accounting for increased aldosterone synthesis in psychological or physical stress; (2) an increase in angiotensin II, accounting for increased aldosterone in cardiovascular stress; and (3) an increase in plasma $[\text{K}^+]$. The cellular transduction mechanisms are described in Chapter 9, “Endocrinology.”

Aldosterone acts mostly in the cortical collecting duct to increase Na^+ reabsorption and K^+ secretion directly and Cl^- reabsorption indirectly. The details are described earlier in this chapter under Regulation of Na^+ , Cl^- , and K^+ Transport in the Cortical Collecting Duct.

Bradykinin: Bradykinin inhibits Na^+ reabsorption in the cortical collecting duct by inhibiting amiloride-sensitive Na^+ channels.

Atrial natriuretic peptide: Atrial natriuretic peptide is released from atrial myocytes in response to increased wall stress. It increases glomerular filtration rate, but its dominant effect is to inhibit Na^+ reabsorption in the inner medullary collecting duct by inhibiting amiloride-sensitive Na^+ channels. This is a receptor-mediated mechanism, relying on elevation in cytosolic $[\text{cGMP}]$ and operating by inhibition of the amiloride-sensitive Na^+ channel in the luminal membrane.

Nerves regulating renal excretion. Activity in renal efferent sympathetic nerves has three effects on different aspects of renal function: (1) it modulates the tone of vascular smooth muscle in the afferent and efferent arterioles and, thereby, modulates the physical factors that determine renal plasma flow and glomerular filtration rate; (2) it stimulates renin release from juxtaglomerular cells; and (3) it stimulates Na^+ reabsorption in many parts of the nephron.

REGULATION OF K^+ Balance

Physiologic Importance of Potassium

K^+ resides mostly inside cells and is a major determinant of intracellular osmolarity and cell volume.

Most human cells are quite permeable to K^+ even when they are at electrical rest. As a result, the concentration gradient for K^+ across the plasma membrane is a major determinant of resting membrane potential. This, in turn, influences neuromuscular excitability, ion transport forces, and lymphocyte activation.

Extracellular $[\text{K}^+]$ is directly related to release of insulin, glucocorticoids, and mineralocorticoids.

Distribution of Potassium within the Body

In normal, healthy humans, K^+ enters the body by the gastrointestinal tract, and adult daily intake ranges from 30 to 100 mmol (Figure 7–26A). It is found in most foods, including fruits, vegetables, and meats. Fecal K^+ excretion ranges from 5 to 10 mmol/d, and loss via insensible perspiration is between 2 and 4 mmol/d. Therefore, under most circumstances, the bulk of daily K^+ intake is secreted into urine, and this maintains K^+ balance and normal intracellular and extracellular concentration.

Whole-body K^+ balance is regulated by factors governing temporary storage in (or release from) the intracellular depot, as well as by factors that modulate permanent elimination of the ion, chiefly by the kidney.

Internal Distribution of K^+

Ninety-eight percent of body K^+ resides in the intracellular compartment (about 3,500 mmol) at a concentration range of 140 to 150 mmol/L. The normal extracellular concentration range is 3.5 to 5.0 mmol/L, and the steep intracellular to extracellular gradient is maintained by Na^+-K^+ -ATPase.

Na⁺-K⁺-ATPase.

Biochemistry of Na⁺-K⁺-ATPase. Na⁺-K⁺-ATPase is a carrier protein that functions to pump 3 Na⁺ ions out of the cell and 2 K⁺ ions in. Each such cycle requires hydrolysis of one ATP molecule and causes net loss of one positive charge from the cell interior. The coupling ratio of 3:2 is constant over a wide range of conditions, but the rate of pumping is influenced by several factors, including small increases in extracellular [K⁺], insulin, and sympathetic nervous activity.

Physiologic regulation of Na⁺-K⁺-ATPase. Minute-to-minute regulation of internal K⁺ distribution is influenced significantly by only **insulin** and **catecholamines**. **Aldosterone** is crucial for the renal aspects of K⁺ homeostasis, but it also contributes to the regulation of internal distribution, though not at the same level of importance as the other two.

Insulin Effects on Na⁺-K⁺-ATPase: Insulin is the major controller of extracellular K⁺ concentration. Increased extracellular [K⁺] depolarizes pancreatic B cells and increases insulin secretion by a Ca⁺⁺-mediated mechanism that is described in greater detail in Chapter 9, "Endocrinology." Once released, insulin binds to the insulin receptor that is found most abundantly in the liver, fat cells, and skeletal muscle.

Activation of the insulin receptor hyperpolarizes the cell within seconds to minutes (in part by stimulation of the 3Na⁺-2K⁺ pump), and then K⁺ redistributes itself in accordance with the membrane potential that now requires a greater K⁺ gradient for steady state. This is achieved by decreased extracellular [K⁺].

Catecholamine effects on Na⁺-K⁺-ATPase: Basal catecholamine activity is necessary for the maintenance of normal potassium homeostasis and β -adrenergic effects dominate.

β_2 -Agonists enhance cellular K⁺ uptake by cAMP-mediated stimulation of Na⁺-K⁺ pumping.

α -Agonists depress Na⁺-K⁺ pumping and promote K⁺ loss from cells.

Aldosterone effects on Na⁺-K⁺-ATPase: Aldosterone increases the rate of Na⁺-K⁺-ATPase cycling (by a fast-acting, nongenomic mechanism) and, by a genomic mechanism, induces synthesis of new Na⁺-K⁺-ATPase and its insertion into the plasma membrane.

Renal Excretion of K⁺

Renal excretion is the major route of K⁺ elimination from the body. It is regulated to suit homeostatic needs.

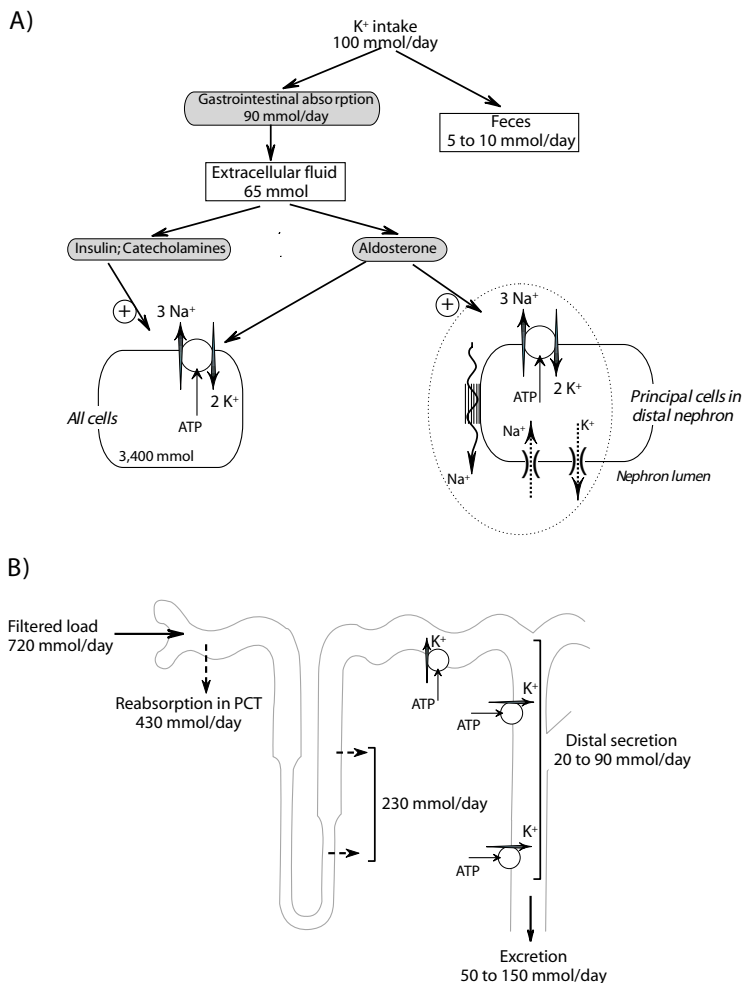


Figure 7-26 A, Distribution of dietary K^+ in the body. B, Sites of K^+ reabsorption and secretion in the nephron.

K^+ transport in different nephron segments.

Glomerulus and proximal tubule. Fifty percent of filtered K^+ is reabsorbed in the proximal convoluted tubule in response to concentration gradients that are created by reabsorption of Na^+ and water (Figure 7-26B).

Thin descending limb of the loop of Henle. K^+ diffuses into the nephron, driven by high interstitial K^+ concentration that is created by reabsorption in the thick ascending limb.

Thick ascending limb of the loop of Henle. K^+ is reabsorbed in this segment by luminal entry through a furosemide-sensitive, passive $Na^+-K^+-2Cl^-$ co-transporter and leaves on the basolateral side through passive co-transport with Cl^- (see Figure 7–18). Most K^+ that is presented at this nephron segment is reabsorbed. Only 5 to 15% of filtered K^+ remains as the tubular fluid enters the distal convoluted tubule.

Distal tubule and collecting duct. The distal convoluted tubule receives low- $[K^+]$ fluid from the thick ascending limb and secretes K^+ into it by both a paracellular and a transcellular path.

Paracellular secretion is driven by lumen negativity that results from greater net reabsorption of Na^+ than Cl^- . Transcellular secretion is a two-step process, in which K^+ enters the cytosol by means of basolateral $Na^+-K^+-ATPase$ and is transferred to luminal fluid down an electrochemical gradient through barium-sensitive K^+ channels.

Regulation of renal K^+ secretion. The dominant site of regulation is the cortical collecting duct and aldosterone is the major vehicle for regulation. Aldosterone enhances active Na^+-K^+ co-transport and increases the number of barium-sensitive K^+ channels in the luminal membrane.

Aldosterone effects on $Na^+-K^+-ATPase$. Aldosterone-mediated up-regulation of active Na^+-K^+ pumping places more K^+ into the cytosol of collecting duct cells and the aldosterone-dependent number of luminal membrane K^+ channels determines K^+ conductance of that membrane. However, transfer of K^+ from the cytosol to tubular fluid also depends critically on conditions in the tubular lumen:

- Na^+ reabsorption in preference to anions can alter the voltage of the tubular lumen, relative to blood, over the range -5 to -70 mV and, thereby, alter the electrical gradient for K^+ secretion.
- Tubular concentration of K^+ will influence the transepithelial concentration gradient for that ion.
- Tubular concentration of Na^+ drives passive entry of Na^+ into the collecting duct cells and determines cytosolic availability of that ion for Na^+-K^+ pumping, which is a requisite step in K^+ secretion.
- Ion composition of tubular fluid determines which ions will be available to move in response to the electrical gradient that is established by Na^+ reabsorption. For example, high tubular $[Cl^-]$ will depress K^+ secretion. The reason is that an ample supply of readily reabsorbed ions like Cl^- requires relatively less K^+ reabsorption for elimination of the electrical gradient.

- The flow rate of tubular fluid determines the extent to which local secretion-promoting gradients can be maintained. High rates of tubular flow prevent a local build-up of secreted K^+ and, therefore, promote K^+ secretion.

RENAL HANDLING OF CALCIUM, PHOSPHATE, AND MAGNESIUM

Calcium

Only 1% of total body calcium is found outside bone, and most of that is in the extracellular fluid (Figure 7–27A). However, this small fraction is of crucial importance in the function of nerves, muscle, blood coagulation, and intracellular communication in many tissues.

Of the normal plasma calcium concentration (near 2.5 mmol/L), about 45% is bound to plasma protein, about 50% is ionized, and the remainder is complexed with strong anions such as HPO_4^{--} , SO_4^{--} , and citrate. It is ionized calcium (Ca^{++}) that governs physiologic processes, such as muscle contraction or neurotransmitter release.

Phosphate

Eighty-five percent of the total body phosphorus store is in bone (Figure 7–27B), and most of the remainder is in the intracellular space.

Intracellular phosphorus is mostly of the **organic form**, namely, phospholipid, nucleic acids, nucleotides, phosphoproteins, and metabolic intermediates. **Inorganic phosphate** exists mostly as the charged moieties HPO_4^{--} and $H_2PO_4^-$.

Only 1% of total phosphorus stores is in blood. Of that, 70% is in the organic form in red cells, leaving only a small proportion as **plasma phosphate**.

Plasma Phosphate

The normal range of plasma phosphate concentration is 1 to 1.6 mmol/L. About 20% of plasma phosphate is bound to plasma proteins or exists in the form of phospholipids. The remaining 80% is called **acid-soluble phosphate** because it remains in plasma from which proteins and phospholipids have been precipitated by treatment with trichloroacetic acid. Acid-soluble phosphate exists in four forms: PO_4^{---} (<0.01%), $H_2PO_4^-$ (10%), HPO_4^{--} (50%), and the remaining 40% is complexed with ions, such as Ca^{++} , Mg^{++} , Na^+ , and H^+ . One of the major functions of plasma phosphate is buffering of hydrogen ions.

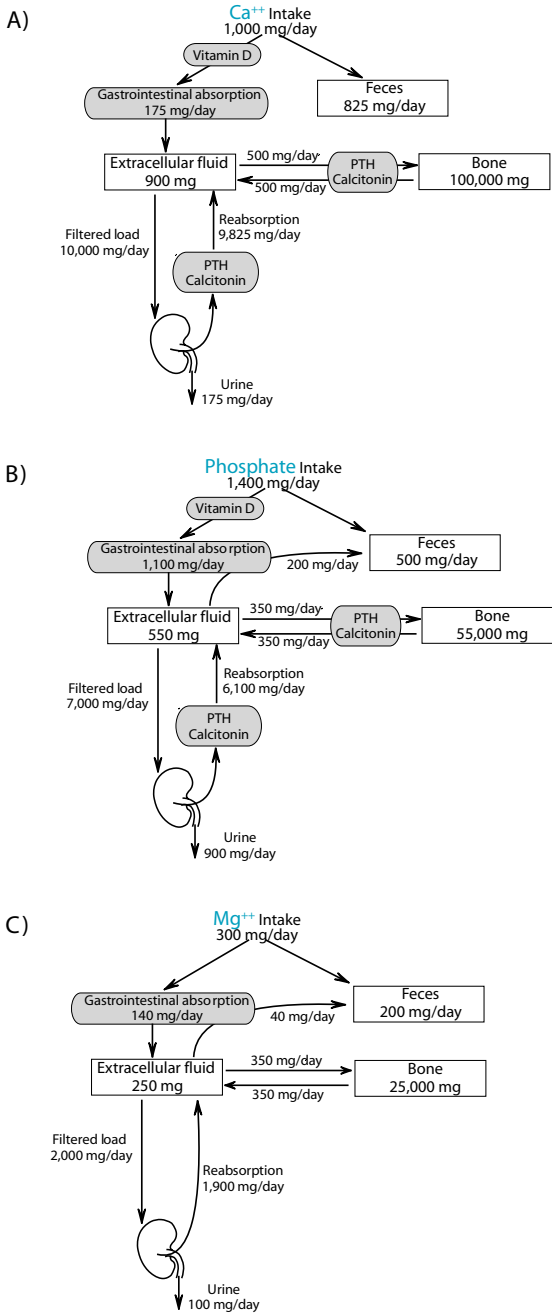


Figure 7-27 Distribution of A, Ca⁺⁺, B, phosphates, and C, Mg⁺⁺ in the body. PTH = parathyroid hormone.

Magnesium

Fifty to 60% of total body magnesium is in bone, and the remainder is located mostly in intracellular fluid, where it serves as an essential co-factor in many reactions. Its normal total extracellular concentration is between 0.8 and 1.3 mmol/L, of which about 30% is bound to plasma proteins, about 50% is in the ionized form, and the remainder is complexed with the same anions that bind Ca^{++} , namely, HPO_4^{--} , SO_4^{--} , and citrate.

Reabsorption and Secretion of Calcium, Phosphate, and Magnesium in the Nephron

Daily intake of calcium, phosphorus, and magnesium is much less than the amount that is filtered at the glomerulus. Therefore, negative balances are prevented by avid tubular reabsorption of each of them.

Segmental Transport of Calcium, Phosphate, and Magnesium in the Nephron

Transport in the proximal convoluted tubule. The proximal tubule reabsorbs about 60% of the filtered Ca^{++} load, 80% of the filtered phosphate load, which is mostly in the form of HPO_4^{--} , and 40% of filtered Mg^{++} (Figure 7–28).

Proximal Ca^{++} reabsorption. The major route for Ca^{++} reabsorption is the paracellular pathway. The mechanisms are passive, driven by the gradi-

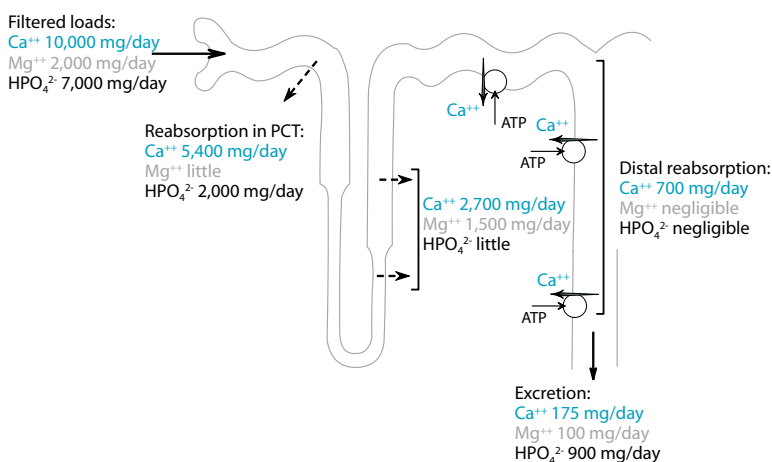


Figure 7–28 Sites along the nephron where Ca^{++} , Mg^{++} , and phosphate are reabsorbed.

ents in charge and concentration that results from active reabsorption of Na^+ and from the electrical gradient that is established by Cl^- reabsorption. Plasma levels of PTH have a negligible influence on proximal Ca^{++} reabsorption.

Proximal reabsorption of HPO_4^{--} . HPO_4^{--} enters proximal tubular epithelial cells in co-transport with Na^+ and becomes part of the cell metabolic pool. When phosphate entry exceeds the metabolic needs of the cell, it leaves on the basolateral side by two mechanisms: an Na^+ - HPO_4^{--} co-transporter and an HPO_4^{--} - HCO_3^- anion exchanger.

Proximal Mg^{++} reabsorption. Mg^{++} is poorly reabsorbed in the proximal tubule. Its transport mechanisms are coupled to Na^+ reabsorption.

Transport in the thick ascending limb of the loop of Henle. This portion of the nephron is the major site for reabsorption of Ca^{++} and Mg^{++} . Both use the paracellular route and are driven by electropositivity in the lumen. That positivity is created by the Na^+ - K^+ - 2Cl^- co-transporter and the associated diffusion of K^+ back into the lumen.

There is little HPO_4^{--} reabsorption in the thick ascending limb.

Transport in the distal convoluted tubule and cortical collecting duct. These sites reabsorb negligible Mg^{++} or HPO_4^{--} and only a small fraction of filtered Ca^{++} (see Figure 7–28). Their importance lies in their ability to modulate the amount of Ca^{++} that is finally excreted. This modulation resides mostly in PTH sensitivity of luminal, dihydropyridine-sensitive Ca^{++} channels. Increased PTH increases conductance of these luminal Ca^{++} channels and increases Ca^{++} reabsorption.

Ca^{++} exit on the basolateral side is by a Mg^{++} -sensitive Ca^{++} -ATPase as well as by an Na^+ -driven Ca^{++} - 3Na^+ antiport.

Regulation of Reabsorption and Secretion of Calcium, Phosphate, and Magnesium

Parathyroid hormone and vitamin D are the two most important regulators for renal excretion of Ca^{++} and HPO_4^{--} . Renal Mg^{++} excretion is not under hormonal control.

Parathyroid hormone and renal handling of Ca^{++} , HPO_4^{--} , and Mg^{++} . Parathyroid hormone secretion from the **chief cells** of the parathyroid glands is stimulated by a decrease in the plasma concentration of free, ionized calcium. Parathyroid hormone stimulates renal HPO_4^{--} excretion, suppresses renal Ca^{++} excretion, and stimulates vitamin D production.

Vitamin D and renal handling of Ca^{++} , HPO_4^{--} , and Mg^{++} . The active form of vitamin D is $1,25(\text{OH})_2\text{D}_3$. Mitochondria in proximal tubular cells are the major locus of the enzyme **1 α -hydroxylase**, which converts a mildly bioactive precursor into the biologically potent form.

$1,25(\text{OH})_2\text{D}_3$ production is stimulated by a decrease in plasma $[\text{HPO}_4^{--}]$ as well as increased plasma levels of PTH. $1,25(\text{OH})_2\text{D}_3$ stimulates renal reabsorption of Ca^{++} and HPO_4^{--} .

THE ROLE OF THE KIDNEY IN ACID-BASE BALANCE

The kidney plays three parts in maintaining the H^+ concentration of extracellular fluid within its normal, narrow limits: it (1) reclaims any HCO_3^- that was filtered through the glomerular membrane and has entered the nephron; (2) generates new HCO_3^- to replenish body buffer stores; and (3) excretes fixed acids.

Reclaiming of Filtered HCO_3^-

Bicarbonate ions are the major extracellular buffer for free H^+ ions. Filtered HCO_3^- would be lost in the urine if it were not reabsorbed. Reabsorption of HCO_3^- occurs mostly in the proximal convoluted tubule because the presence of **carbonic anhydrase** in proximal tubular fluid (but not in the more distal luminal fluids) and in proximal tubular cells allows the required chemical reactions to proceed rapidly. The reabsorptive mechanisms are summarized in Figure 7–29 and consist of three major steps: (1) filtered HCO_3^- combines with H^+ to yield CO_2 in the proximal tubular lumen; (2) CO_2 diffuses into the cells and forms intracellular HCO_3^- and H^+ ; and (3) the H^+ thus formed is transferred to the lumen in exchange with Na^+ , and the HCO_3^- is transferred to the interstitium in co-transport with Na^+ .

Although a great deal of H^+ is secreted in the process of HCO_3^- reabsorption, this mechanism does not eliminate H^+ from the body.

Generation of New HCO_3^-

New HCO_3^- is generated in the proximal and distal tubules as well as in the collecting duct by a mechanism that depends on intracellular hydrolysis of body CO_2 . This reaction forms H^+ and HCO_3^- . The HCO_3^- moiety is reabsorbed across the basolateral membrane and enters the renal interstitium as new HCO_3^- . The H^+ moiety is transferred into the tubular lumen (in exchange for Na^+), where it forms either **titratable acid** (H_2PO_4^-) or **ammonium** (NH_4^+) and is excreted in those buffered forms.

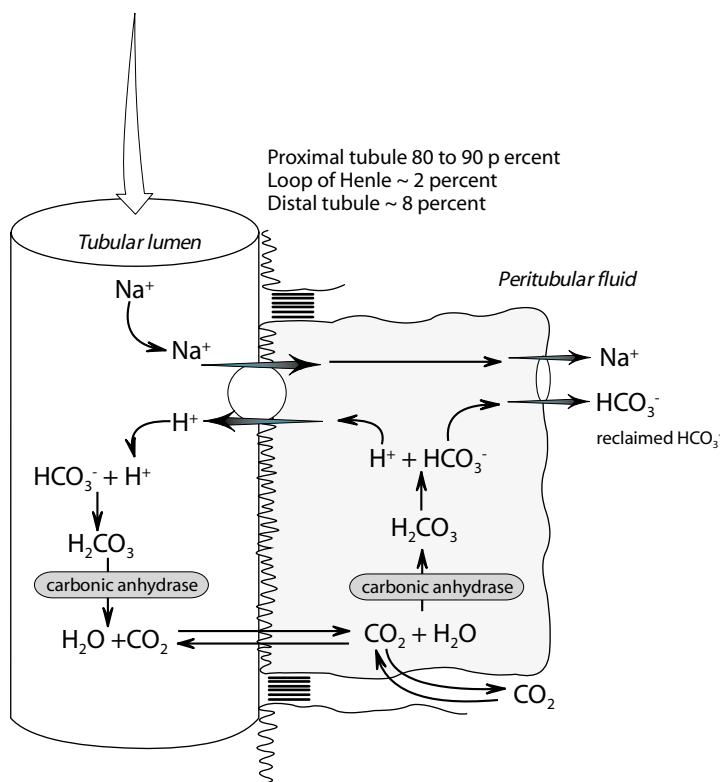


Figure 7–29 Mechanism by which filtered HCO₃⁻ is reclaimed in the kidney so that this vital buffer is not lost in the urine.

Excretion of Titratable Acid

Buffered H⁺ that is excreted as titratable acid appears mostly as H₂PO₄⁻ because HPO₄⁻ is the most readily available buffer anion (Figure 7–30). H₂PO₄⁻ is termed titratable acid because it will liberate its H⁺ if the urine were titrated back to plasma pH. It should be noted that NH₄⁺ would give up little of its H⁺ during titration to plasma pH because of the high pK of the ammonia–ammonium system.

Excretion of NH₄⁺

Breakdown of dietary or endogenous protein yields the amino acid glutamine. The epithelium of proximal tubular cells is the major site of conversion of glutamine to glutamate and NH₄⁺ because the mitochondria in those cells contain the enzyme **glutaminase**.

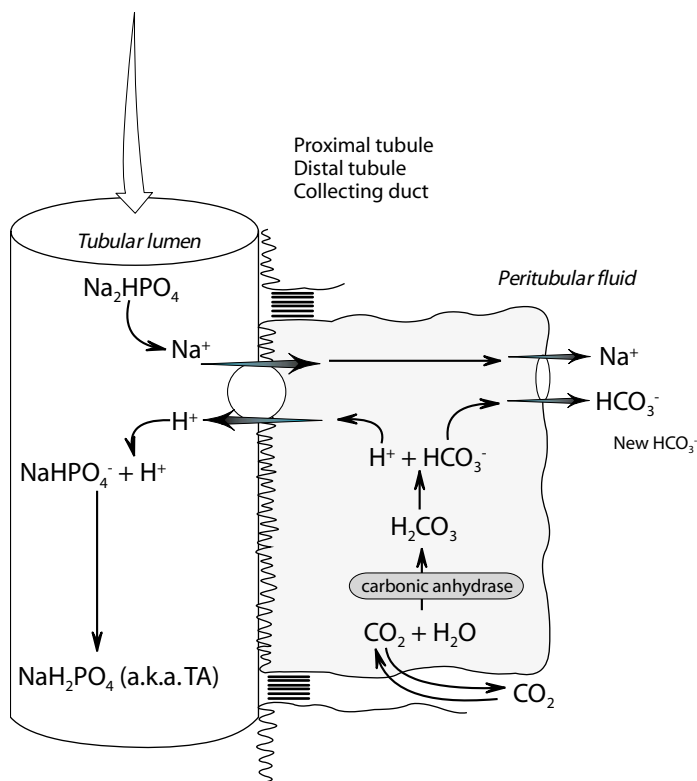


Figure 7-30 Mechanisms by which non-volatile acid like phosphoric acid is excreted as titratable acid (TA).

NH_4^+ is secreted into the luminal fluid (probably by substituting for H^+ in the Na^+ - H^+ antiport) and is reabsorbed in the thick ascending limb of the loop of Henle, where it can substitute for K^+ in the furosemide-sensitive Na^+ - K^+ -2 Cl^- co-transporter.

In the interstitium, NH_4^+ dissociates into H^+ and the gas NH_3 (ammonia), the ratio of the two being determined by the prevailing pH in accordance with the Henderson-Hasselbalch relationship. Finally, in the collecting duct, NH_3 diffuses into the collecting duct lumen, where secreted H^+ ions are used to form NH_4^+ (Figure 7-31).

Excretion of H^+

Although the kidney does excrete some acid in the form of free H^+ , the properties of the distal nephron are such that it cannot maintain, across the tubular cell, a gradient in H^+ concentration of sufficient magnitude to meet the

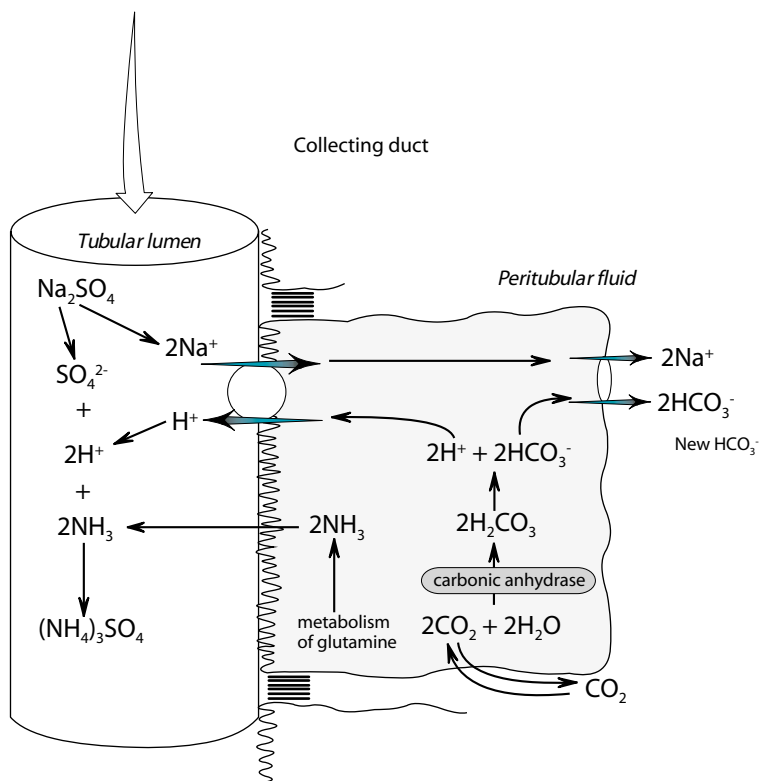


Figure 7-31 Collecting duct mechanisms by which non-volatile acid like sulfuric acid is excreted along with ammonium (NH_4^+).

body needs for H^+ excretion. As a result, transported H^+ diffuses back from the tubular lumen into the cells and most acid excretion takes place in buffered form, the H^+ appearing in urine either as titratable acid or as NH_4^+ .

MICTURITION

Gross Anatomy of the Bladder and Urinary Tract

The bladder is a smooth muscle chamber formed by the **detrusor muscle**. The ureters and the urethra connect to the bladder through the **trigone**, a triangular area of fine smooth muscle fibers located near the neck of the bladder. The urethra is surrounded near its origin by a ring of striated muscle forming the external sphincter.

Innervation of the Bladder and Urinary Tract

Sympathetic efferents supply the portion of the detrusor muscle surrounding the bladder neck (Figure 7–32). However, they have little influence on normal bladder function. Their major role may be closure of the internal sphincter during orgasm.

Parasympathetic nerves are the major innervation of the bladder wall and urethra. Afferent fibers, arising from endings that respond to stretch and pain, also travel with parasympathetic nerves. Somatic nerves control the striated muscle of the external sphincter (see Figure 7–32).

Functions of the Bladder

Bladder Filling

The bladder fills passively, the urine being propelled by peristaltic waves in the ureters. During filling, (1) reflux into the ureters is prevented by the nature of the ureter–trigone junction; the oblique angle of entry of the ureters creates a sphincter-like junction. It can be relaxed only by contraction of the detrusor muscle, and (2) escape into the urethra is prevented by

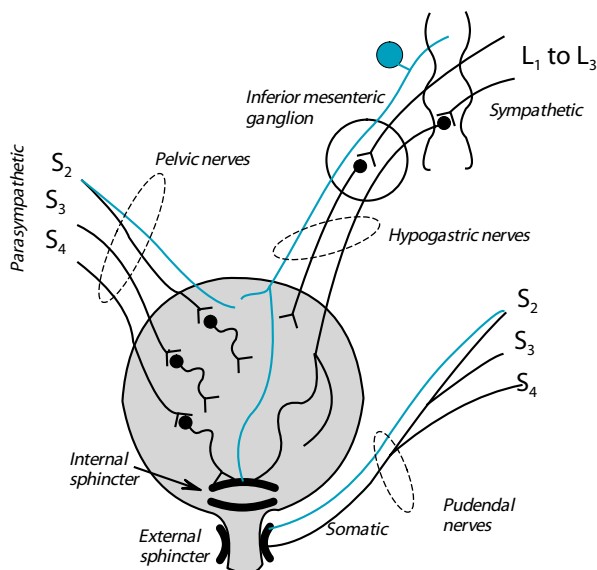


Figure 7–32 Nervous control of the bladder is exercised by parasympathetic, sympathetic, and somatic nerves. Afferent fibers are shown in color. L₁₋₃ = lumbar segments 1 to 3; S₂ to S₄ = sacral segments 2 to 4.

tonic constriction of the external sphincter by somatic input from the sacral spinal cord.

As wall stretch increases, the distension excites stretch-sensitive afferents projecting to the brainstem. When about 300 mL of urine have collected and the chamber pressure reaches about 20 mm Hg, afferent neuronal activity is sufficient to elicit a conscious desire to empty the bladder. At 400 to 500 mL, the desire becomes very strong.

The urge to void can be suppressed for a while by inhibitory activity from the cerebral cortical and hypothalamic centers to prevent emptying at unsuitable times. Such suppression is called **continence**. If the urge is not suppressed, then the **voiding reflex** is initiated.

Bladder Emptying (Voiding)

Voiding begins with contraction of the detrusor muscle in response to parasympathetic nerve activity and contraction of abdominal muscles (somatic control). Such muscle contractions increase bladder pressure and further excite stretch-sensitive afferents.

When the pressure in the bladder approaches 40 mm Hg, somatic input to the external sphincter is reduced and the sphincter relaxes. Once the bladder has begun to empty, the process accelerates dramatically until emptying is completed.

Central Nervous System Influence on Bladder Function

Higher nervous function contributes to bladder control but is not essential. Therefore, individuals with transection of the spinal cord above the sacral level can learn to control bladder evacuation on the basis of local, spinal reflex paths. Such control involves initiation of detrusor contractions at suitable intervals by momentary elevation of bladder pressure above a tension threshold and can be accomplished by slight tapping of the abdomen.

Gastrointestinal System

FUNCTIONAL ANATOMY OF THE GASTROINTESTINAL TRACT

The Muscle Coat of the Gastrointestinal Tract

In the early sections of the esophagus, there is skeletal muscle surrounding the tract. From the midesophagus onward, almost all the gastrointestinal (GI) muscle coat is smooth muscle, arranged in three layers from the lumen outward (Figure 8–1): (1) a submucosal layer, arranged longitudinally; (2) a middle, circular layer; and (3) an outer, longitudinal layer. The region between each pair of layers includes a network of neurons that collectively form the **enteric nervous system**.

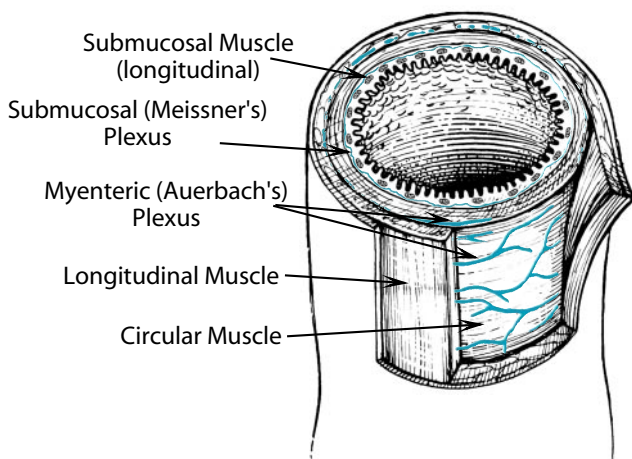


Figure 8–1 The important muscle layers and nerve plexuses of the GI tract.

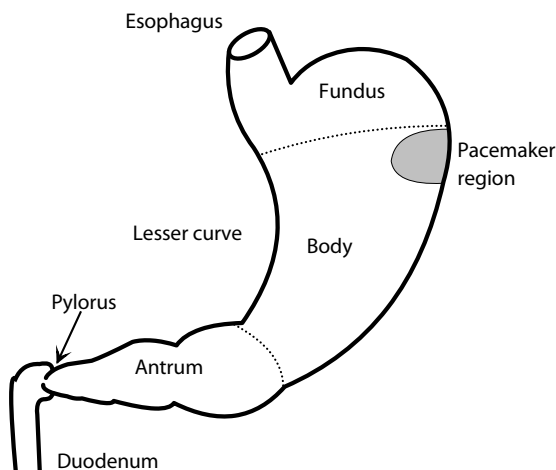


Figure 8–2 Regions of the stomach. The pacemaker region is the origin of mixing waves that sweep over the full stomach.

Stomach

The stomach is divided into four regions (Figure 8–2). They are the fundus, body, antrum, and pylorus. The fundus behaves like a reservoir in that it relaxes its tonic contraction and accommodates to the volume of incoming food. The distal stomach generates peristaltic waves that mix, disrupt, and propel the food.

The motile functions of the stomach arise from coordinated activity of three regionally distributed layers of smooth muscle: (1) an outermost **longitudinal layer** is present only in the distal two-thirds of the stomach and is in continuity with the pylorus; (2) a middle **circular layer** is found throughout the stomach, up to the distal antrum; and (3) an inner **oblique layer** is found immediately under the mucosa, but only along the lesser curve in the proximal half of the stomach.

Small Intestine

The lumen of the small intestine has a very large surface area by virtue of (1) projections from the walls toward the center of the lumen (**valvulae conniventes**) and (2) a dense covering of the walls and radial projections by the system of microvilli that forms the **brush border**.

Crypts and Villi

The epithelium of the small intestine is organized into villi. The **crypts of Lieberkühn** are interspersed among the villi. The crypts are subepithelial

tubular glands that secrete intestinal juice of regionally varying composition. They are lined by four types of cells (Figure 8–3): (1) **enterocytes** form the majority of cells. In the crypts, they perform secretory functions; (2) **enteroendocrine cells** constitute less than 1% of terminally differentiated cells. They are recognized by the presence of secretion granules and can be subdivided into more than a dozen subgroups. The largest of these is cells containing **serotonin**. Other subgroups secrete **gastrin**, **cholecystokinin (CCK)**, **gastric inhibitory peptide (GIP)**, **secretin**, **enteroglucagon**, **neurotensin**, **pancreatic polypeptide**, **neuropeptide Y (NPY)**, or **histamine**. These secretions act on other secretory cells or smooth muscle; (3) Goblet cells secrete mucus; and (4) Paneth cells are quiescent unless bacteria are present in the lumen. When they are active, they participate in antimicrobial defense by secreting lysozyme, immunoglobulin A, antimicrobial peptides, and other protein-digestive enzymes.

All cell types in crypts and villi originate from a small pool of stem cells that are located within the crypts and arise from a single progenitor cell.

During the time that these stem cells and their daughter cells line the crypts, they contain ion transport mechanisms that make them mostly secreting cells elaborating isotonic fluid into the intestinal lumen. They migrate in vertical bands up the villi and are shed from the villus tips about 5 days after leaving the crypt.

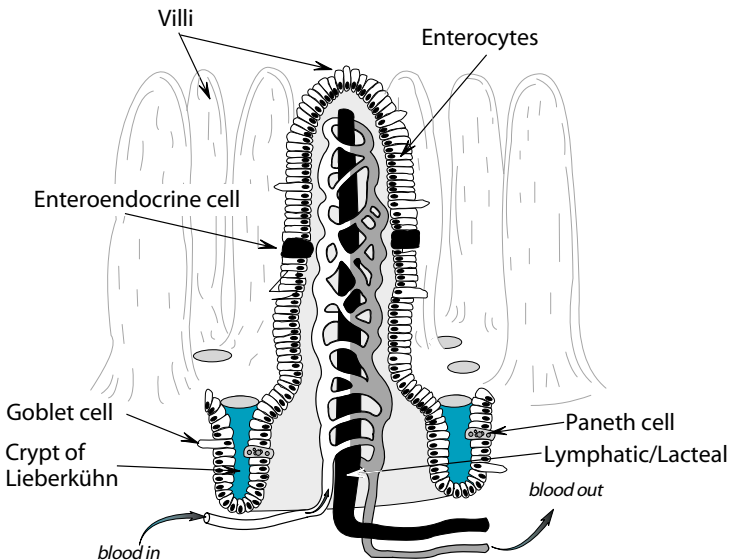


Figure 8–3 Structure of the wall of the small intestine. Any given villus has between 5 and 15 crypts at its base. Most of the villus surface is covered with enterocytes. There are a few enteroendocrine cells, mucus-secreting goblet cells, and Paneth cells.

As the enterocytes mature and migrate to the villus tip, they alter the type and distribution of membrane transporters and change from being secretory cells to absorbing cells. This involves increased expression of (1) transporters for glucose, galactose and fructose on the gut luminal side, (2) $\text{Na}^+\text{-K}^+\text{-ATPase}$ on the basolateral side, and (3) oligosaccharidases and oligopeptidases, whose respective function is to break down complex molecules into simpler molecules of sugars or peptides.

Large Intestine

There are no villi in the lumen of the large intestine. The secreting glands in this region are indentations in the mucosa, and they secrete mostly mucus, along with K^+ and HCO_3^- . The colon has a great capacity for absorbing Na^+ and water.

Innervation of the Gastrointestinal Tract

The GI tract is innervated by two networks: (1) intrinsic innervation is supplied by the **enteric nervous system**, and (2) extrinsic innervation derives from the **autonomic nervous system** (Figure 8–4).

Enteric Nervous System

The enteric nervous system contains all the neural elements required for complex integrative function and behaves like a “little brain” in the generation and modulation of phasic patterns of neuronal activity. It programs and regulates all GI functions. The two principal plexuses of the enteric nervous system are the **submucosal (Meissner’s) plexus**, located within the submucosa (see Figure 8–1), and the **myenteric (Auerbach’s) plexus**, located between the circular and outer longitudinal muscle layers. They extend along the length of the GI system, from the esophagus to the anus. The enteric nervous system receives modulating input from the parasympathetic system by way of the vagus or sacral nerves and the sympathetic nervous systems by way of the splanchnic network and innervates effector structures, such as epithelial cells, blood vessels, and smooth muscle.

Three morphologically different types of neurons make up the enteric nervous system, and they are named Dogiel type 1, 2, and 3.

Extrinsic Nerves

Parasympathetic fibers. Parasympathetic innervation is supplied by the vagus nerve and the pelvic nerves, which are of sacral origin. Parasymp-

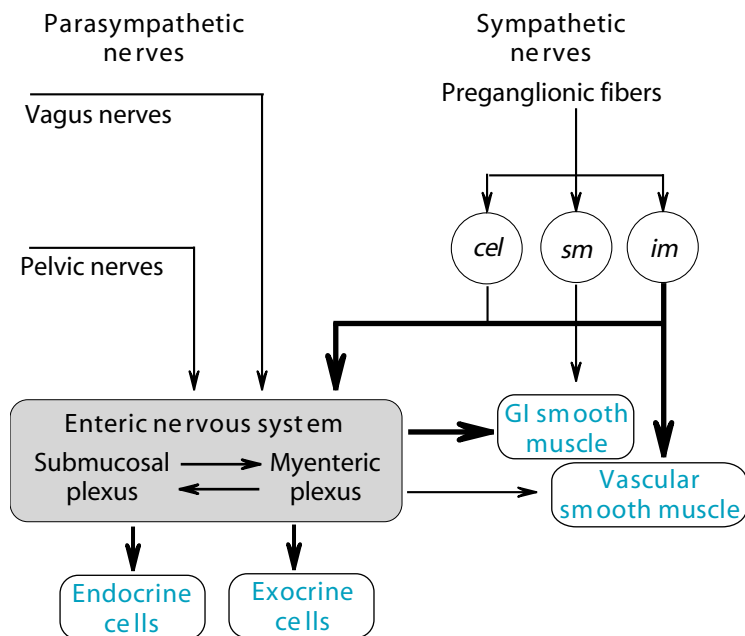


Figure 8–4 Innervation of the GI tract. Extrinsic innervation is supplied through the parasympathetic and sympathetic divisions of the autonomic nervous system and intrinsic innervation derives from the two plexuses of the enteric nervous system. Postganglionic sympathetic fibers originate mostly in three visceral ganglia. Most of these fibers modulate activity in the enteric nervous system. The smooth muscle of the GI vasculature is controlled mostly by postganglionic sympathetic fibers while the smooth muscle of the GI tract is innervated mostly by the enteric nervous system. Cel = celiac ganglion; sm = superior mesenteric ganglion; im = inferior mesenteric ganglion.

pathetic fibers are cholinergic and innervate both plexuses of the enteric nervous system. Increased parasympathetic activity generally increases intestinal smooth muscle activity.

Sympathetic fibers. The sympathetic innervation of the GI tract is noradrenergic postganglionic. Three types of termination occur: (1) in many cases, the target is postganglionic cholinergic neurons. Increased sympathetic discharge inhibits acetylcholine secretion from cholinergic neurons (a presynaptic α_2 -mediated mechanism), (2) some sympathetic fibers innervate smooth muscle cells directly, and (3) sympathetic fibers innervate splanchnic blood vessels and act to cause vasoconstriction.

GASTROINTESTINAL MOTILITY

The digestive and absorptive functions of the GI system require controlled progression of luminal contents so that each region may perform its spe-

cialized function in an optimal setting. This progression arises from motor activity that is (1) initiated by spontaneously generated smooth muscle action potentials, (2) coordinated by central and enteric nervous motor programs, and (3) modulated by local mechanical, chemical, or hormonal influences. As a result of the motor activity, ingested food is mixed with digestive secretions, digestible products are transported to absorptive sites, and indigestible products are transported to the rectum and evacuated.

There are two major patterns of motility:

1. During the fasting state, there are **migrating motor complexes**. They are all-encompassing peristaltic waves that begin in the stomach, move toward the colon, occur every 60 to 90 minutes, and last 10 to 20 minutes. During that time, there is irregular, intermittent contractile activity followed by short periods of uninterrupted, rhythmic contractions (Figure 8–5). Migrating motor complexes are initiated and propagated by the enteric nervous system.
2. During the fed state, there is continuous irregular activity. Migrating motor complexes are completely inhibited.

The central nervous system acts by way of extrinsic nerves to switch GI motor activity from the fasting state to the fed state.

Within these patterns, two types of contractions are observed in both the fasting and fed states: **peristalsis** and **mixing**.

Peristalsis

Peristalsis involves coordinated contraction and relaxation of the muscle layers and serves to propel contents along the tract. Such contractions are evoked by localized distension of the intestinal wall and consist of the following:

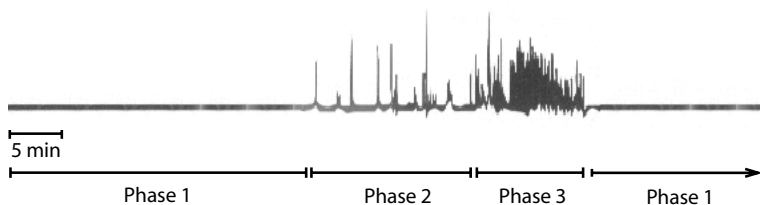


Figure 8–5 Pressure waves recorded in the proximal small intestine and showing the three phases in the sequence of a migrating motor complex. Phase 1 = quiescence; Phase 2 = phasic contractions begin to appear with increasing frequency; Phase 3 = a period of intense and repeated contractile activity.

- Ahead of the distending bolus, the circular muscle relaxes and the longitudinal muscle contracts. As a result, this segment receives the bolus that is moving from the mouth toward the anus.
- Behind the distending bolus, the circular muscle contracts, while the longitudinal muscle relaxes. These actions propel the bolus into the receiving segment.
- As the bolus moves forward, the receiving segment becomes a contracting segment because local relaxation is never enough to accommodate the bolus without some wall stretch.

Integrity of the enteric nervous system is vital for the peristaltic reflex. One of its major functions in all areas, except the esophagus and the colon (during mass movements), is to limit the number of segments that can be activated in any single peristaltic wave. In the esophagus, peristaltic waves travel along its whole length once they have been initiated.

Mixing Movements

These are nonpropagating segmental contractions of the circular muscle coat only. They produce local narrowings that divide the tract into discrete segments at regular intervals. The muscle then relaxes, and a new pattern of segmentation appears such that areas that were previously contracted are now relaxed and areas that were previously relaxed are now contracted. The effect is to move intestinal contents forward and backward so as to mix them with digestive enzymes and also to maximize contact with the absorbing endothelium.

Regional GI Motility

Mouth and Upper Esophagus

The movement of food through the GI tract begins with oral ingestion, chewing, and swallowing.

Chewing. Chewing accomplishes three outcomes. It (1) reduces food to smaller morsels to provide better exposure to digestive enzymes; (2) mixes food with saliva so that it moves more easily through more distal portions of the digestive tract and begins to be digested by salivary enzymes; and (3) forms the food into a bolus that is suitable for swallowing. Chewing is normally a voluntary act.

Swallowing. At suitable intervals during the process of chewing and in response to voluntary commands, the tongue presses against the hard

palate and separates a bolus and propels it into the oropharynx. Once there, it initiates the swallowing reflex. Its initial phase requires central nervous system coordination of respiration, speech, and upper esophageal sphincter relaxation. Subsequent transport of food toward the lower esophageal sphincter is due to the sweeping waves of peristalsis (Figure 8–6).

The **primary peristaltic wave**, a progressive, circular contraction that begins in the upper esophagus and moves distally, is induced as part of the swallowing reflex. It is initiated and coordinated in the brainstem and results from the sequential excitation of the intramural excitatory cholinergic neurons.

A **secondary peristaltic wave** is initiated when stretch sensors in the body of the esophagus are activated by the passing bolus. The lower

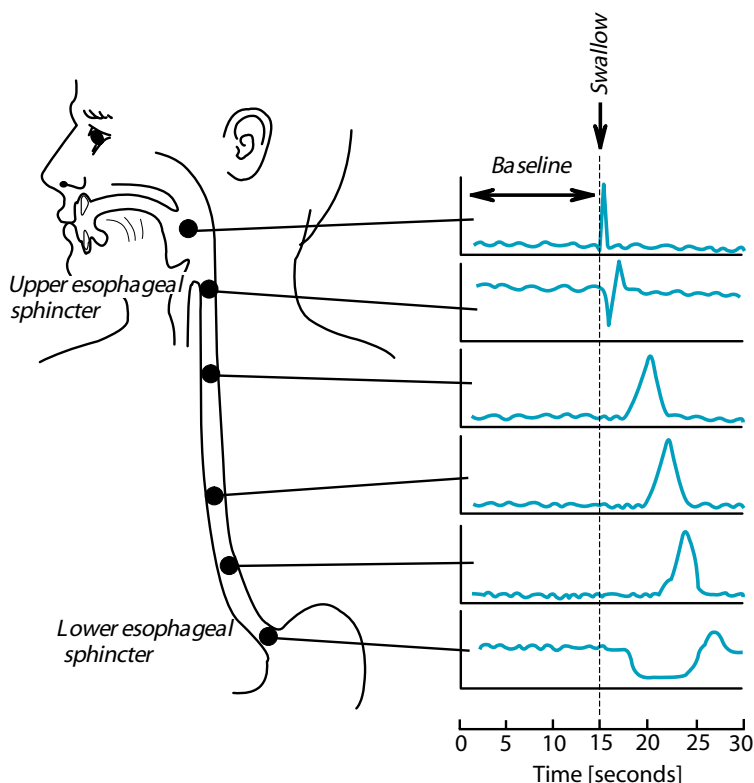


Figure 8–6 Timing of esophageal pressure waves during a swallow. More distal locations show pressure waves at a slightly later time than do proximal locations. The upper and lower sphincter each show a basal tone and a downward deflection (relaxation) before their respective contraction.

esophageal sphincter relaxes during swallowing so that the bolus can enter the stomach (see Figure 8–6). The mechanism of relaxation depends on non-adrenergic/noncholinergic (NANC) neurons that inhibit tonic sphincter contraction. Swallowing conveys food into the stomach within a few seconds.

Stomach

Reception and temporary storage of food. When food first enters the stomach, it is accommodated in the fundus portion. This region acts as a reservoir because it responds to local stretch with active smooth muscle relaxation. This reflex is also called **receptive relaxation**. Receptive relaxation is a vasovagal reflex in that both its afferents and efferents are vagal fibers. The efferents are NANC inhibitory fibers.

Receptive relaxation of the fundus is followed by **gastric accommodation**, which is a further relaxation that allows temporary storage of increasing volumes without increasing the pressure above a level that is just enough to move the stomach contents toward the antrum.

The third phase of food reception is a period of continuous tonic contractions that maintain a propulsive pressure gradient from the fundus to the pylorus.

Peristalsis and mixing. The fundus portion of the stomach is relatively quiescent and shows no mixing waves. In contrast, the distal half of the stomach shows regular waves of ring contractions (Figure 8–7). They are peristaltic and serve both mixing and propulsive functions.

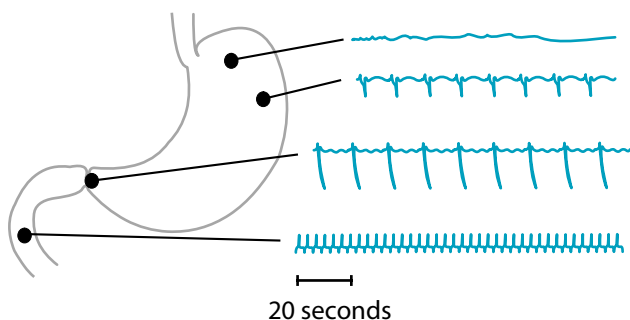


Figure 8–7 Myoelectrical activity in the stomach and early duodenum. The fundus portion of the stomach is electrically quiescent. Spontaneous electrical activity is first noted in the pacemaker region and increases in amplitude toward the pylorus. Electrical activity is generally absent in the small intestine between meals, except during a migrating motor complex, when high-frequency activity is observed.

Mixing waves arise from spontaneous electrical activity in the **interstitial cells of Cajal** in the stomach pacemaker region (see Figure 8–2) at about 3/min. They are modulated by extrinsic vagal and sympathetic influences. Their amplitude is almost imperceptible when the stomach is empty, but they show increasing intensity as the stomach fills.

The coupling of stomach filling to wave amplitude is a vagal mechanism because local application of acetylcholine increases peristaltic amplitude and duration. Increased sympathetic activity inhibits peristalsis.

Gastric emptying. A large meal can increase stomach contents by up to 1,500 mL and would typically take 3 hours to be emptied into the duodenum in peristaltic waves. Their amplitude, which determines the force and rate of gastric emptying, depends on stomach volume and both the physical state and chemical nature of the contents: (1) the greater the stomach volume the higher the rate of emptying; (2) liquids and small particles (≤ 1 mm) empty more rapidly; (3) carbohydrates pass through quickly, a meal high in fats passes through slowly, and proteins empty at an intermediate rate; and (4) contents that are high in osmolality or H^+ leave at a slow rate.

The control of gastric emptying includes duodenal and jejunal sensors of stretch or chemical composition (lipid content, glucose, osmolality, and $[H^+]$). When they are activated by one of these agents, they initiate reflex release of chemical factors, such as CCK, secretin, or GIP, that decrease the diameter of the pylorus. Other chemical agents can influence upstream motility. They include **gastrin**, which inhibits motility, and **motilin**, which stimulates motility.

Small Intestine

Motility patterns in the small intestine differ within different regions and with time since the last meal (Table 8–1).

Table 8–1
**Characteristics of Motility Patterns in the Small Intestine
(Applicable to Phase 3 of the Migrating Motor Complex)**

Location	Propagation Velocity [cm/min]	Max Contraction Frequency (Hz)	Duration [min]
Duodenum	5.0	12	9
Jejunum*	4.5 to 2.0	11.5 to 10.5	9 to 15
Ileum*	1.5 to 0.5	10.0 to 8.5	15.5 to 14
Cecum	0.5	6.0	

*From proximal to more distal sites.

- The duodenum receives semi-liquid chyme from the stomach and mixes it with bile and digestive secretions.
- The jejunum acts as a mixing and conduit segment.
- The ileum retains chyme until digestion and absorption are almost complete, and the terminal ileum controls emptying into the colon at a rate suitable to the absorptive capacity of the colon.

After a meal. Three types of contraction occur. They are **segmentation contractions**, **pendular contractions**, and **peristaltic contractions**.

Segmentation contractions. These are brief, localized events in circular muscle. They appear, disappear, and reappear regularly, forming contraction rings that involve only 1 to 4 cm of bowel at a time. They last less than 5 seconds and occur in sets that are spaced 5 to 10 seconds apart. Such contractions divide bowel contents into segments, and their primary purpose is local mixing. They are also propulsive and cause a slow but steady movement of bowel contents toward the colon.

Pendular contractions. Pendular contractions are rhythmic events in longitudinal muscle bundles. They occur over distances of a few centimeters and act to move the bowel over its contents. They serve, therefore, exclusively to propel food toward the colon. They can be coordinated along a considerable length of bowel, and when they are thus coordinated, they are called peristaltic contractions.

Peristaltic contractions. Peristaltic contractions are reflex in nature in that they are activated by the lumen content. Local stretch initiates the contractions, and their amplitude is modulated by the chemical nature of the bowel contents.

Between meals. During the interdigestive period, motor activity in the small intestine is characterized by the **migrating motor complex** (MMC) (see Figure 8–5). It occurs cyclically at 1- to 2-hour intervals at any single location in the fasting bowel, and the entire cycle migrates toward the colon. In addition to the MMC, the early portions of the fasting small intestine can show regular clusters of migrating contractions.

Small bowel interdigestive motor patterns show clear circadian rhythm. During the night (1) mean MMC cycle length is reduced to ~65 min from its daytime mean near 100 minutes, (2) phase 2 (intermittent activity) of the MMC diminishes or disappears in the ileum, and (3) phase 3 (periods of uninterrupted, rhythmic contractions) is longer and shows reduced propagation velocity.

Regulation of small intestine motility. The periodicity and cycle of the MMC are generated within the enteric nervous system (Figure 8–8). They are modulated by central nervous system mechanisms that superimpose the slower patterns characteristically seen in sleep or stress.

The presence of food inhibits the MMC by neural and chemical mechanisms: (1) intact vagal innervation is required for initiating and maintaining postprandial patterns; (2) when the vagus is blocked in the fed state, small bowel motility is regulated only by the enteric nervous system and chemical mechanisms and is characterized by irregular migrating bursts of activity; (3) regulatory peptides, such as gastrin, secretin, CCK, neurotensin, and enteroglucagon, can terminate the fasting motility patterns in the small intestine; and (4) in the fed state, different nutrients induce contractile patterns that differ with respect to amplitude, duration, and migration distance. Fat has the most potent effect, and protein has the least effect.

The ileocolonic sphincter is important for regulating the rate of transfer of bowel contents to the colon. Extrinsic nerves are not required for maintaining sphincter tone. However, its periodic relaxation, which permits transfer of bowel contents to the colon, is dependent on NANC nerves.

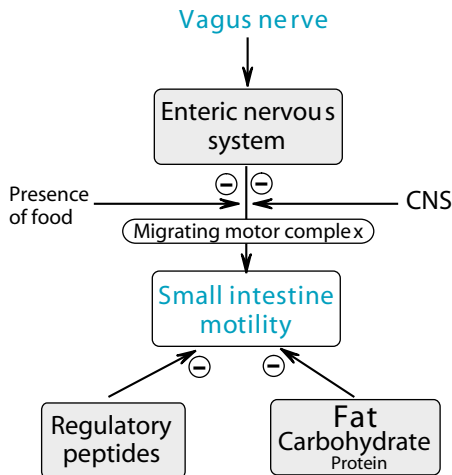


Figure 8–8 Motility in the small intestine is controlled by migrating motor complexes that originate in the enteric nervous system under the influence of vagal motor nerves. Modulating inputs derive from the central nervous system (CNS), mechanical and chemical sensors responding to the presence of food, regulatory peptides, and the chemical nature of bowel contents. Fat has the greatest inhibitory effect.

Colon

The colon consists of two storage reservoirs connected by a transport section. The cecum and ascending colon form the first reservoir, and the rectum forms the second. The remaining portions are the transverse, descending, and sigmoid portions of the colon, and they serve to propel colonic content at periodic intervals. The appearance of the colon is determined by the fact that its external muscles are collected into three longitudinal bands, called the **teniae coli**, that are shorter than the rest of the colon. This mismatch creates regularly spaced outpouchings that are called **haustra** (Figure 8–9).

Colonic slow wave activity originates in the midtransverse colon in an interconnected network of the interstitial cells of Cajal, located between the submucosa and the circular muscle layer. Spike bursts and oscillating activity (0.4 to 0.8 Hz) are superimposed on the slow waves.

The colon contracts at irregular intervals and shows two kinds of contractions: **phasic** and **giant migrating contractions**.

Phasic contractions. Phasic colonic contractions can be short (< 15 s) or long (~50 seconds) and are poorly coordinated along the length of the colon. Accordingly, they serve mainly a mixing function but can also propel contents, sometimes in a retrograde direction.

Giant migrating contractions. These contractions occur only once or twice per day, generally in the morning after waking, and form the major propulsive event in the colon.

Colon motor activity is stimulated within 10 minutes of eating a meal and continues for about an hour. The strongest stimulus is fat. Caloric load also has an influence in that a meal containing more calories will stimulate greater colonic motility. Although there is great variation among individuals, colonic contents require between 35 and 48 hours to traverse the length of the colon.

The colon, like the small intestine, shows circadian fluctuations in motor activity. It is greatly inhibited during sleep, increases after waking, and increases further after eating.

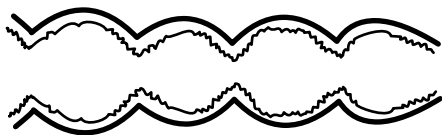


Figure 8–9 Haustra in the colon.

Regulation of colonic motility. The colon is innervated by excitatory and inhibitory neurons of mainly the **myenteric plexus** (Figure 8–10). Extrinsic innervation arises from vagal and pelvic nerve fibers that synapse with the enteric neurons at cholinergic, nicotinic, and NANC synapses.

Colonic activity is also modulated by reflexes whose adrenergic and somatostatinergic efferents arise from the **superior** and **inferior mesenteric ganglia**. These reflexes exert tonic inhibition of motor activity.

Central nervous system mechanisms are required for relaxation of the external sphincter in **defecation**, and they explain the increased motor activity in the sigmoid colon during short-term emotional or physical stress.

Rectum

The rectum consists of the internal and external anal sphincters (see Figure 8–10). The internal sphincter is a thickening of the circular smooth muscle layer. It is innervated by way of the pelvic plexus (cholinergic and adrenergic excitatory nerves as well as NANC inhibitory nerves) and adren-

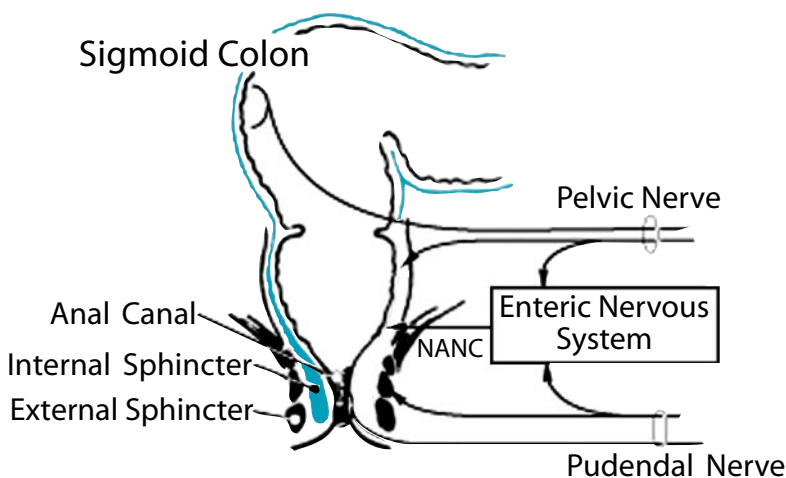


Figure 8–10 Sigmoid colon, muscle layers of the rectum, and schematic representation of the afferent and efferent nerves normally involved in their control. NANC = nonadrenergic noncholinergic.

ergic excitatory fibers in the pudendal nerve (see Figure 8–10). The external sphincter is formed by several bundles of striated muscle. They are innervated by α -motor neurons in the pudendal nerve and have no autonomic or enteric innervation.

Complex Motility Patterns

Defecation

Filling of the rectum. The rectum fills intermittently from the sigmoid colon by giant migrating contractions of the descending colon. As the rectum is distended with each incoming bolus, the internal sphincter relaxes reflexly (the reflex is governed by the enteric nervous system) so as to accommodate the bolus. Continence is maintained by reflex contraction of the external sphincter. The governing reflex is mostly independent of higher function and involves segmental afferents and efferents in the pudendal nerve (see Figure 8–10).

When the maximum tolerable volume is reached at about 2 L, the accommodative process fails, intrarectal pressure rises, and the associated stretch sensor activity leads to conscious perception of discomfort and an urge to defecate.

The first step is a transient relaxation of the internal anal sphincter (NANC inhibitory nerves) with simultaneous contraction of the external sphincter (α motor nerves). This reflex allows the rectal contents to come into contact with the mucosa of the proximal anal canal for the purpose of discriminating among gas (flatus) and solid or liquid stool.

If defecation is to be deferred, voluntary contraction of the external sphincter reinforces the reflex mechanisms, and the contents of the upper anal canal are forced back into the rectum.

Emptying of the rectum. At a suitable time, evacuation of the rectum is initiated by voluntary effort. This involves four components: (1) intra-abdominal and intrarectal pressure are increased by voluntary contraction of abdominal muscles; (2) rectal contents are moved distally by reflex contraction of longitudinal musculature in the colon and rectum. This increases intrarectal pressure further; (3) the internal sphincter relaxes as each pressure wave arrives in the rectum; and (4) the external sphincter is relaxed by voluntary effort.

At the end of defecation, the abdominal vasculature relaxes and the sphincter muscles are contracted.

Transection of the spinal cord above the sacral level abolishes the voluntary motor patterns that assist defecation. As a result, paraplegics must learn special techniques for relaxing the external anal sphincter.

Vomiting and Retching

Vomiting and retching are initiated by stimuli that include (1) activation of chemosensors, (2) conflicting visual and vestibular sensory inputs, and (3) emotional input from higher nervous centers.

During vomiting and retching, smooth muscle activity shows spastic contractions of the gastric antrum but complete relaxation of all structures headward from the gastric body to the upper esophagus; intraesophageal pressure is decreased by a switch to slow, deep inspirations; and skeletal muscle in the abdominal wall is contracted. This raises intra-abdominal pressure and creates a gradient between intra-abdominal pressure and esophageal pressure. The pressure gradient forces gastric contents upward into the relaxed esophagus.

The difference between vomiting and retching, once gastric contents have been pushed into the esophagus, is the state of the upper esophageal sphincter. If the upper esophageal sphincter is opened, evacuation into the mouth takes place (= vomiting). If the upper esophageal sphincter remains closed, distension of the esophagus will initiate a wave of secondary peristalsis that sweeps the gastric contents back from the esophagus into the stomach. This is perceived as retching.

GASTROINTESTINAL SECRETION

Gastrointestinal motor activity serves to mix and mill food and regulate its delivery toward the primary functions of the intestine. These are (1) secretion, (2) digestion, (3) absorption, and (4) elimination of indigestible remnants.

Electrolytes and Water

In healthy humans, the small intestine absorbs 8 to 9 L of water each day, and the large intestine absorbs an additional liter. Only 15% of this water comes from oral intake; the rest is provided by intestinal sources for the purposes of lubrication and optimization of environmental factors, such as osmolality and pH.

Control of Osmolality

Water reabsorption is along osmotic gradients and requires, therefore, that the mucosa be able to control the osmolality of intestinal contents. Luminal osmolality is the result of two processes:

1. Na^+ , Cl^- , and other osmotically active moieties are absorbed from the lumen by the enterocytes that line the villi and mucosa. The major mechanisms are shown in Figure 8–19.

2. Cl^- is secreted into the lumen by enterocytes lining the crypts. The driving mechanisms are a furosemide-sensitive, electroneutral co-transporter of Na^+ , K^+ , and 2Cl^- operating on the basolateral membrane and the Na^+ - K^+ pump that is located in the luminal membrane of these cells. The Na^+ , K^+ , and 2Cl^- co-transporter is driven by the Na^+ gradient, and both it and the Na^+ - K^+ pump move K^+ into the enterocyte. K^+ leaks out passively through a basolateral K^+ channel, Na^+ is removed by the luminal 3Na^+ -out, 2K^+ -in ATPase, and Cl^- leaves the enterocyte through a number of luminal Cl^- channels. One is strongly stimulated by cyclic adenosine monophosphate (cAMP), and one of them is the cystic fibrosis transmembrane regulator (CFTR) Cl^- channel that is also found in tracheal mucosa.

Optimization of pH

The digestive processes of the small and large intestine progress optimally at neutral pH and require, therefore, that the highly acidic ($\text{pH} < 3$) chyme entering from the stomach be neutralized in the upper duodenum by appropriately alkaline secretions. Such secretions derive from the exocrine pancreas, bile, **Brunner's glands** in the duodenal mucosa, and mucosal crypts in the small and large intestine.

Regulatory Peptides of the Gastrointestinal Tract

The GI system is regulated by an abundance of endocrine, neurocrine, and paracrine peptides, as summarized alphabetically in Table 8–2.

Nonpeptide Secretions of the Gastrointestinal Tract

Different portions of the GI tract secrete substances that have two basic functions: (1) digestion of food and (2) protection of the GI tract from its own destructive actions.

Saliva

The parotid, submandibular, and sublingual pairs of glands of the adult human produce about 500 mL of saliva each day. Saliva is a watery fluid whose components serve two major functions: lubrication and protection. Its contribution to digestion is small.

Salivary glands. Salivary glands are parallel arrangements of **secretory acini** and **mucus end pieces**. Secretory acini feed into **intercalated ducts**, and mucus end pieces feed into **mucus tubules**. Both the intercalated ducts

and the mucus tubules feed into larger **interlobular** (= **striated**) **ducts**, and the interlobular ducts feed salivary secretions into the mouth by way of **extralobular ducts**.

Contractile cells are found mostly as a thin layer surrounding the secretory acini and mucus end pieces.

Salivary glands are innervated by both sympathetic and parasympathetic nerves. Although they contain receptors for many neurotransmitters and other ligands, acetylcholine and norepinephrine are the major controllers.

Composition of saliva. Saliva is an electrolyte solution that contains electrolytes and two classes of proteins: **mucins** and **digestive enzymes**.

Electrolytes. The acini secrete **primary juice** that resembles plasma in composition. As the primary juice passes through the duct system, Na^+ and Cl^- are absorbed, while K^+ and HCO_3^- are secreted so that the final saliva has a higher concentration of K^+ and HCO_3^- than plasma and correspondingly lower concentrations of Na^+ and Cl^- . HCO_3^- serves a protective function against the acids that are constantly being produced by oral microorganisms.

Mucins. Mucin is synthesized by glands throughout the GI system. It is a glycoprotein that forms a highly viscous, protective gel layer. Its major functions in the mouth are (1) mechanical and chemical protection of the epithelium, (2) lubrication, (3) prevention of epithelial dehydration, and (4) trapping of microorganisms.

Digestive enzymes. In humans, the major salivary digestive enzyme is α -**amylase**. It is secreted mainly from the parotid glands. The daily secretion is enough to digest all the starch that is normally present in the diet. However, swallowing normally occurs so rapidly that salivary amylase is inactivated by stomach acidity before appreciable digestion has taken place. That makes pancreatic amylase the major starch-digesting enzyme in the body.

Regulation of salivary gland secretion. Significant volumes of saliva are produced only in response to autonomic nervous stimulation. The major mechanism is acetylcholine, acting through M_3 muscarinic receptors to activate phospholipase C and raising cytosolic Ca^{++} . In some instances, the sympathetic nervous system, acting through norepinephrine and α -adrenoreceptor activation of the phospholipase C pathway, is also important. The coupling from raised cytosolic $[\text{Ca}^{++}]$ to saliva production is not clear yet but appears to involve increased electrolyte permeability of the junctional membrane between adjacent acinar cells.

Table 8–2

Regulatory Peptides of the GI System

Peptide	Promoters	Major GI Actions
Bombesin (GRP)* Neurotransmitter in some fibers of the stomach enteric nervous system	Cholinergic agonists	Promotes gastrin release from “G” cells
CCK Synthesized in I cells of the epithelium in the duodenum and jejunum. Two forms exist: CCK-58 and CCK-33. (CCK-8 is a neurotransmitter in some nerve terminals.) The maximum activity is obtained from the last eight aa of the C-terminal. The last five aa are identical to those of gastrin.	<ul style="list-style-type: none"> Fatty acids, peptides, amino acids in the duodenal lumen Low levels of free trypsin in the duodenal lumen 	Receptor mediated by way of the phospholipase C pathway: <ul style="list-style-type: none"> Promotes secretion of enzyme-rich fluid from pancreatic acinar cells Potentiates action of secretin on pancreatic duct cells Stimulates release of pepsinogen from chief cells in gastric glands Inhibits gastric HCl secretion Stimulates gall bladder contraction Relaxes sphincter of Oddi Stimulates endocrine pancreas to release insulin, glucagon, PP, and somatostatin Promotes pancreatic growth
Gastrin Synthesized in G cells in the pylorus and duodenum. Gastrin exists in big (G-34) and little (G-17) forms, but the activity of both resides in their identical 4 aa C-terminal.	<ul style="list-style-type: none"> Peptides (plus Ca^{++}) in gastric lumen High catecholamines Bombesin (GRP) 	Receptor mediated by way of the phospholipase C pathway: <ul style="list-style-type: none"> Stimulates HCl secretion from parietal cells Increases force and frequency of peristalsis in distal stomach Promotes growth of gastric and duodenal mucosa
GIP Synthesized in K cells found mostly in the jejunum	<ul style="list-style-type: none"> Presence of glucose, fats, and amino acids in the lumen of the upper small intestine Elevated luminal $[\text{H}^+]$ 	<ul style="list-style-type: none"> Enhances insulin release from B cells in the endocrine pancreas Inhibits gastric HCl secretion Inhibits gastric motility Stimulates intestinal secretion

Continued

Table 8–2

Regulatory Peptides of the GI System—Continued

Peptide	Promoters	Major GI Actions
Glicentin Cleaved from proglucagon in epithelial L cells in the distal ileum and colon. GLP-1 and two additional peptides are produced simultaneously. (Proglucagon is derived from pre-proglucagon, which is synthesized in “A” cells of the endocrine pancreas and epithelial L cells in the distal ileum and colon.)	Presence of glucose and fats in the lumen of the lower ileum. Therefore, present in appreciable amounts only in cases of poor absorption from upper small intestine	<ul style="list-style-type: none"> • Inhibition of gastric and intestinal motility • Inhibition of gastric acid secretion
GLP-1 Produced along with glicentin by cleavage of proglucagon	Presence of glucose and fats in the lumen of the lower ileum	Biologically inactive, but can be modified to promote insulin release during carbohydrate ingestion (= incretin effect)
GRP Human equivalent of bombesin		
Histamine Synthesized from histidine in mast cells	Cholinergic agonists	Acts on H ₂ receptors on stomach parietal cells to promote HCl secretion and on chief cells to increase pepsinogen release
Motilin Synthesized in and secreted from M cells of the upper small intestine	<ul style="list-style-type: none"> • Migrating motor complex • Presence of acid, alkali, or fat in duodenum 	<ul style="list-style-type: none"> • Controls onset of MMC • Increases gastric motility • Relaxes pylorus • Increases resting pancreatic secretion
NPY Co-released with norepinephrine from sympathetic neurons during high rates of stimulation		Potentiates actions of noradrenaline

Continued

Table 8–2

Regulatory Peptides of the GI System—Continued

Peptide	Promoters	Major GI Actions
Oxyntomodulin Cleaved from glicentin in epithelial L cells in the distal ileum and colon. Oxyntomodulin and glicentin together are often called enteroglucagon .	Presence of glucose and fats in the lumen of the lower ileum	<ul style="list-style-type: none"> • Inhibition of gastric and intestinal motility • Inhibition of gastric acid secretion
Pancreatic Polypeptide Synthesized in and secreted from F cells in the endocrine pancreas	<ul style="list-style-type: none"> • Protein-rich food • Cholinergic agonists 	Inhibits pancreatic secretion of enzymes and HCO_3^-
Secretin Synthesized in and secreted from S cells of the epithelium in the duodenum and jejunum	$[\text{H}^+]$ or bile salts in the duodenum	Receptor mediated by way of the adenylate cyclase pathway: <ul style="list-style-type: none"> • Promotes alkaline secretions from pancreatic ducts (in synergy with CCK) • Stimulates bile ducts and Brunner's glands to form alkaline juice • Decreases rate of gastric emptying • Promotes somatostatin release
Serotonin <ul style="list-style-type: none"> • Formed from tryptophan in myenteric neurons or endocrine cells found in the stomach and small intestine • Often found in association with substance P 		Stimulates cholinergic enteric neurons to increase secretion of water and electrolytes

Continued

Table 8–2

Regulatory Peptides of the GI System—Continued

Peptide	Promoters	Major GI Actions
Somatostatin Synthesized in <ul style="list-style-type: none"> • enteric ganglion cells and nerve terminals • D cells of the stomach, endocrine, pancreas, and gut epithelium Two forms exist, SS-14 and SS-28	<ul style="list-style-type: none"> • Elevated luminal $[H^+]$ • Presence of glucose, protein, fat, or bile salts in the lumen of the small intestine 	SS-14 is an order of magnitude more potent than SS-28, but both have several inhibitory actions. They inhibit <ul style="list-style-type: none"> • secretion of gastric acid and pepsin, • gastrin release from G cells, • pancreatic enzyme secretion • actions of CCK • Release of acetylcholine from enteric nerves
Substance P A neurotransmitter, colocalized with several others		Stimulates <ul style="list-style-type: none"> • intestinal secretion, and • smooth muscle contraction.
VIP A neurotransmitter peptide of excitatory enteric ganglion cells.	Cholinergic agonists	<ul style="list-style-type: none"> • Mimics actions of secretin • Relaxes smooth muscle

*Bombesin is found in amphibians. Its human equivalent is gastrin-releasing peptide (GRP).

Gastric Secretion

Secretory activity of the gastric mucosa. The secretory activity of the stomach resides in both endothelial secretory cells and in **gastric glands**. Gastric glands are embedded in the mucosa and issue through pits in the epithelium. They are typed according to anatomic location and are named cardiac, oxyntic, or pyloric glands.

Cardiac glands. These glands are found only at the junction of the esophagus and the stomach. They are short and secrete mainly mucus.

Oxyntic glands. Oxyntic glands penetrate deep into the mucosa. They are found throughout the fundus and body of the stomach (see Figure 8–2) and are responsible for most of the gastric digestive juice. Each gland is a long tubule that is lined with four cell types (Figure 8–11).

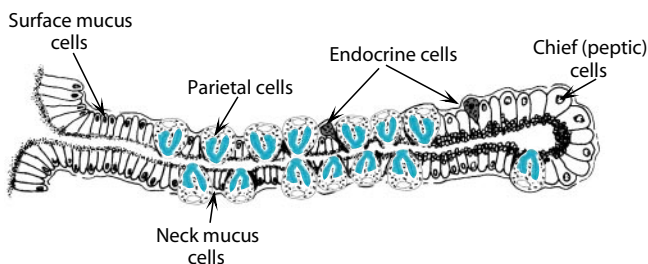


Figure 8–11 Oxyntic glands are long tubes at the bottom of epithelial pits. They contain neck mucus cells (secreting mostly mucins), parietal cells (secreting H^+ and intrinsic factor), chief cells (secreting pepsinogen, cathepsin, and gelatinase), and a variety of endocrine cells, including histamine-secreting enterochromaffin-like cells. The secretory canaliculi in parietal cells are shown in color.

1. Neck mucus cells: These cells elaborate mucus glycoproteins (mucins) and some pepsinogens. The mucus differs from that secreted by epithelial mucus cells in that the neck cells secrete soluble mucus, which mixes with chyme for the purpose of lubrication. Surface cells secrete **insoluble mucus** for the purpose of protecting the stomach mucosa from being digested itself. Mucus secretion is stimulated by cholinergic agonists.
2. Parietal cells: Parietal cells secrete H^+ and **intrinsic factor**. They are highly active cells, rich in mitochondria. Their distinctive features are (a) the presence, throughout the cell, of invaginated canals (**secretory canaliculi**) that open into the gland lumen and (b) a large number of vesicles that are localized within the cytoplasm when the cell is at rest and translocate to the canaliculi when the cell is stimulated. The vesicles are rich in $H^+-K^+ATPase$ and are the basis of H^+ secretion by the parietal cells against a million-fold concentration gradient.

In resting parietal cells, $H^+-K^+ATPase$ -containing vesicles are held within the cytoplasm. Their membrane is poorly permeable to K^+ , and, therefore, the active transport of K^+ -out and H^+ -in is halted when intravesicular K^+ is depleted. When parietal cells are stimulated (Figure 8–12), (a) the $H^+-K^+ATPase$ -containing vesicles migrate toward and fuse with the apical membrane in the secretory canaliculi and greatly expand the secretory surface area; (b) passive K^+ and Cl^- channels open in the vesicle membrane; and (c) H^+ is exchanged for K^+ across the vesicle membrane, and Cl^- exits passively because intracellular $[Cl^-]$ increases when the HCO_3^- that is left behind by each secreted H^+ is exchanged for Cl^- by the $HCO_3^-Cl^-$ exchanger in the basolateral membrane.

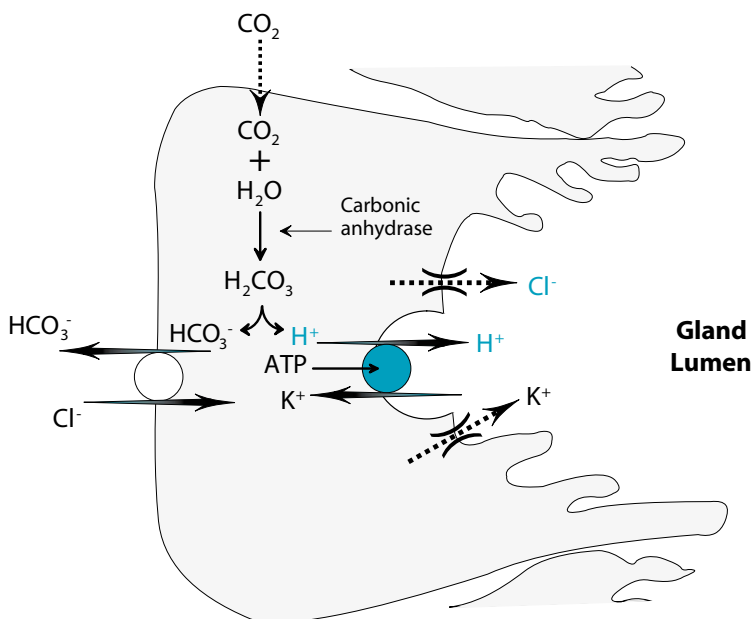


Figure 8-12 When a parietal cell is stimulated, a large number of $\text{H}^+\text{-K}^+$ ATPase-containing vesicles are translocated from the cytosol to the apical plasma membrane. The vesicle membrane also contains channels for K^+ and Cl^- , and these open on vesicle fusion with the apical membrane. Vesicle fusion makes K^+ available for countertransport and allows $\text{H}^+\text{-K}^+\text{-ATPase}$ to pump out H^+ . H^+ is generated from CO_2 at a high rate because parietal cells are rich in carbonic anhydrase. HCO_3^- is generated simultaneously and is exchanged for Cl^- on the basolateral side.

Intrinsic factor is obligatory for the absorption of vitamin B_{12} . It is a glycoprotein that is secreted from parietal cells in response to the same secretagogues that stimulate H^+ secretion. It binds to dietary vitamin B_{12} to form a digestion-resistant unit that is also a ligand for B_{12} -transporting receptors in the ilial epithelium. Lack of vitamin B_{12} prevents red blood cells from maturing and causes **anemia** that is characterized by the appearance in the blood of large, primitive red cell precursors (**megaloblasts**). However, the liver is capable of storing sufficient amounts to supply body needs for 3 to 6 years. Therefore, B_{12} deficiency anemias develop several years after intestinal absorption of the vitamin has stopped.

Acetylcholine and gastrin are the most important physiologic stimulants of parietal cell secretion. In addition, histamine acts through H_2 receptors to stimulate parietal cells and to potentiate the actions of other secretagogues.

3. Chief cells (peptic cells): Chief cells are found only at the base of the oxyntic gland (see Figure 8–11). They are the main source of **pepsinogen**, the precursor for the proteolytic enzyme **pepsin**, but also secrete a **gastric lipase**, **cathepsin**, and **gelatinase**. Pepsin is a heterogeneous group of proteolytic enzymes, derived from two broad classes of pepsinogens: PG I and PG II. They are activated by high $[H^+]$ and preferentially cleave peptide linkages between aromatic amino acids (tryptophan, tyrosine, and phenylalanine) and their neighbors. Because the pepsins have optimal activity at pH 1 to 3, they are inactivated soon after chyme reaches the small intestine and, therefore, account for only about 10 to 15% of total protein digestion.

Acetylcholine from enteric or vagal nerve terminals and acting on M_3 muscarinic receptors is the strongest stimulant for chief cells. Its release may be initiated centrally or by a local reflex. Cholecystokinin and gastrin, both activating the CCK-B receptor, are also stimuli for pepsinogen secretion, and both the M_3 and CCK-B receptor activate the phospholipase C pathway. Secretin can also stimulate pepsinogen secretion. Its intracellular pathway is elevated cAMP. Chief cells have no histamine H_2 receptors.

Pyloric glands. These glands are found in the antrum region of the stomach (see Figure 8–2). Their most important cell is the G cell, which synthesizes and secretes the hormone gastrin.

Regulation of gastric secretion. The main regulators of secretory activity are (1) acetylcholine (M_3 receptor) and gastrin (CCK-B receptor), operating by way of the phospholipase C pathway to increase cytosolic $[Ca^{++}]$ and diacylglycerol (DAG), and (2) somatostatin and histamine (H_2 receptor), operating by the adenylate cyclase pathway to increase cytosolic $[cAMP]$. Acetylcholine, gastrin, and histamine promote secretion. Somatostatin activates an inhibitory G protein and, therefore, decreases cytosolic $[cAMP]$ and inhibits secretion.

Basal secretion. Between meals and in the absence of other stimuli, there is a basal secretory rate that amounts to less than 10% of the maximally stimulated rate. It is lightly driven by vagal nervous activity and histamine because it can be reduced by the muscarinic receptor antagonist atropine as well as by H_2 receptor antagonists. Absence of food from the stomach means that the gastric juices are not buffered and that the $[H^+]$ is very high (near 150 mmol/L). This is a strong stimulus for somatostatin release from

the D cells in the mucosa of the body and antral regions of the stomach. Somatostatin inhibits gastrin release from G cells and has an inhibitory effect on parietal cells, which are the source of gastric acid.

Sight and ingestion of food stimulate secretion in three phases, which are identified by the location of the major stimulus as **cephalic**, **gastric**, or **intestinal**.

Cephalic phase of gastric secretion. The sight and smell of food elicit conditioned reflexes that account for about 30% of the secretory response to food intake (Figure 8–13). They operate through increased efferent vagal nervous activity to (1) stimulate H^+ secretion from parietal cells, (2) stimulate histamine release from enterochromaffin-like cells in the oxyntic glands, and (3) increase release of gastrin-releasing peptide (GRP) from enteric neurons in the antrum. Histamine is a strong paracrine stimulus for H^+ secretion from parietal cells. Bombesin stimulates gastrin release from G cells, and gastrin is an endocrine stimulus for secretion from parietal and chief cells.

Gastric phase of gastric secretion. This phase provides most of the secretory output and is governed by mechanical and chemical signals from the

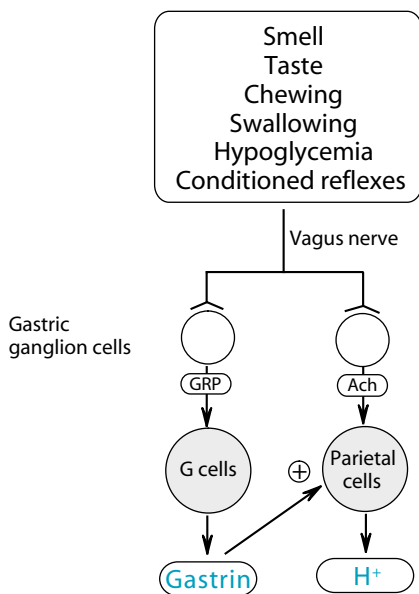


Figure 8–13 The cephalic phase of gastric secretion. The major influence on G cells and parietal cells in the gastric mucosa derives from the vagus nerve. Secretion of gastrin and H^+ involves neurons that secrete GRP or acetylcholine.

stomach wall to either the midbrain centers or the local enteric nervous system (Figure 8–14). Mechanical information derives from stretch sensors, and chemical input derives mostly from dietary peptides.

Stomach distension causes release of acetylcholine around parietal cells, enterochromaffin-like cells, and G cells mostly by a long vago-vagal loop (see Figure 8–14) and a little through a shorter enteric loop. It also causes continued GRP release around G cells. Amino acids, peptides (from partially digested proteins), GRP, and acetylcholine act on G cells to increase gastrin secretion. Carbohydrate, fat, and undigested protein have no direct chemical effect but do act by contributing to distension. Gastrin, histamine, and acetylcholine each promote secretion from parietal and chief cells.

The gastric phase of secretion is inhibited if $[H^+]$ is sufficiently high to promote somatostatin release from gastric mucosal D cells.

Intestinal phase of gastric secretion. This phase accounts for less than 10% of the secretory response to a meal and probably derives from the few G cells that are located diffusely through the pylorus and duodenum. The most important aspect of the intestinal phase is inhibition of gastric emptying and secretion. The main inhibitory stimuli are the arrival in the duodenum of chyme that is high in acidity, fat content, or osmolality.

High acidity in the duodenum releases **secretin** from S cells. Secretin inhibits gastric emptying and promotes the secretion of **somatostatin**. Somatostatin inhibits gastrin release and the secretion of gastric acid and

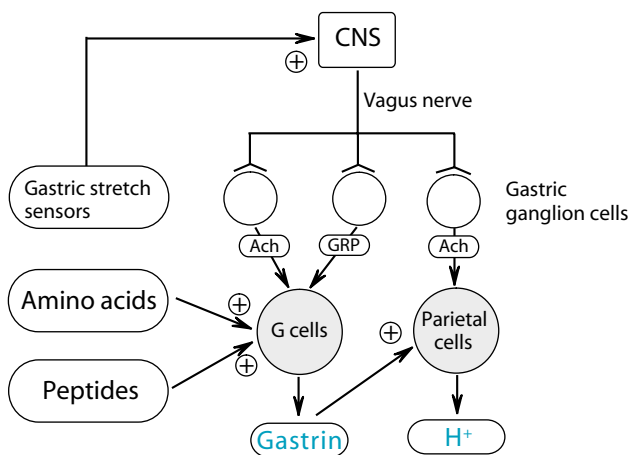


Figure 8–14 During the gastric phase of gastric secretion, the dominant influences on secreting cells arise from mechanosensors that respond to stretch of the stomach wall and stimulatory influences of peptides, amino acids, and gastrin-releasing peptide (GRP) on G cells. Ach = acetylcholine.

pepsinogens. High fat content (fatty acids and monoglycerides) in the duodenum promotes release of somatostatin, CCK, and GIP.

Pancreatic Secretion

Anatomy of pancreatic acini and ducts. The **exocrine pancreas** is organized into **lobules**, each lobule consisting of secretory sacs (acini), each of which drains into an intralobular (intercalated) duct. Interlobular ducts converge into extralobular (interlobar) ducts, and they, in turn, converge into the main pancreatic duct, which opens into the duodenum.

The acini secrete a Cl^- -rich fluid that contains a variety of digestive enzymes to break down protein, fat, starch, or nucleotides. Cells in the extralobular ducts secrete an HCO_3^- -enriched fluid.

Unless the pancreas is stimulated, the secretory rate from the acini predominates, and pancreatic juice is high in Cl^- (about 110 mmol/L). When the pancreas is stimulated, especially with secretin, $[\text{HCO}_3^-]$ rises to near 120 mmol/L while $[\text{Cl}^-]$ falls to about 40 mmol/L.

Pancreatic acinar and duct cells are richly supplied with membrane receptors. Most activate the phospholipase C pathway of DAG, IP_3 , and Ca^{++} (see Figure 1–14 in Chapter 1, “General Physiologic Processes”), and this group includes CCK-A, M_4 muscarinic, and substance P receptors. Some operate by way of activating adenylate cyclase to raise cytosolic cAMP, and these include secretin, vasoactive intestinal polypeptide (VIP), and the VIP-associated co-transmitters PHM* (in humans) or PHI* in other species.

Enzymatic secretions of the exocrine pancreas. Each day about 1 L of pancreatic fluid is secreted and it contains four classes of enzymes or inactive precursors (**zymogens**) (Table 8–3):

Nonenzymatic secretions of the exocrine pancreas.

Protein products. Digestive enzymes form the major fraction of protein secretions from the pancreas. However, **pancreatic secretory trypsin inhibitor (PSTI)**, **lithostathine**, and **mucin** are important nonenzymatic proteins. Pancreatic secretory trypsin inhibitor is an endogenous trypsin inhibitor. It functions to delay trypsin activation until the pancreatic secretions have been delivered into the duodenal lumen. Lithostathine acts to prevent stone formation by preventing precipitation of CaCO_3 . Mucin is the gel-forming glycoprotein constituent of mucus.

Electrolyte solutions. The cellular mechanisms by which fluid rich in HCO_3^- is secreted from cells in the extralobular ducts and fluid rich in Cl^-

*PHM = peptide histidine methionine amide (a neurotransmitter co-released with VIP in humans; PHI = peptide histidine isoleucine amide (co-released with VIP in non-humans).

Table 8–3

Enzymatic Secretions of the Exocrine Pancreas

Enzyme Class	Action	Examples
Proteolytic	<ul style="list-style-type: none"> • All are secreted as inactive precursors • Split peptide bonds that tend to be on the C-terminus of polypeptides and they differ with respect to the specificity of amino acids attacked 	Trypsinogen* Procarboxypeptidase A and B Chymotrypsinogen A and B Pro-elastase-2 and pro-protease E.
Lipolytic	Hydrolyze bonds within fatty acids and cholesterol esters	Pancreatic lipase† Phospholipase A ₂ Nonspecific carboxylesterase
Amylolytic	Break down starch	Pancreatic α -amylase
Nucleolytic	Hydrolyze phosphate bonds in RNA or DNA	Ribonuclease Deoxyribonuclease I and II

*Trypsinogen yields *trypsin* when the duodenal enzyme *enteropeptidase* (a.k.a. enterokinase) splits the peptide bond between lysine and isoleucine at the N-terminal of trypsinogen. Trypsin activates each of the other proteolytic zymogens.

†Activation and stabilization of pancreatic lipase requires the presence of *colipase*, which is secreted by pancreatic acini as pro-colipase and is activated by trypsin.

is secreted from acinar cells depend on the presence of cytosolic carbonic anhydrase, an $\text{Na}^+\text{-H}^+$ exchanger in the basolateral membrane (facing the interstitium), a $\text{Cl}^-\text{-HCO}_3^-$ exchanger in the apical membrane (facing the lumen of the duct), and a variety of Cl^- channels in the apical membrane, including the CFTR channel. The actions and interactions of these components are similar to those described earlier for H^+ production in the parietal cells of the gastric mucosa (see Figure 8–12) except that pancreatic acinar cells secrete HCO_3^- .

Regulation of exocrine pancreatic secretion. The presence of HCO_3^- -rich pancreatic juice is important for moving the acidity of chyme that has left the stomach with high $[\text{H}^+]$ toward the alkaline optima that are required by pancreatic enzymes, particularly lipase.

Resting pancreatic secretion rates. In western societies, waking humans eat or snack frequently, and resting pancreatic secretion prevails only during sleep.

Then pancreatic secretion is correlated with the migrating motor complex (see Figure 8–5), each phase 2 of increased motility being associated with increased motilin-mediated pancreatic secretion that is inhibited during phase 3 by pancreatic polypeptide (PP) receptor–dependent mechanisms.

Stimulated pancreatic secretion rates. Pancreatic secretion rates, like gastric secretion rates, can be grouped into cephalic, gastric, and intestinal phases.

Cephalic phase: Vagal efferent activity, initiated by the sight, smell, or taste of food and the chewing of food, can modulate pancreatic enteric nervous activity so as to elicit up to 55% of maximal secretory activity from the pancreas (Figure 8–15). Acetylcholine, acting on M_4 muscarinic receptors and activating the phospholipase C pathway, is the main mechanism. Additional secretory activity can be elicited when acid chyme is delivered into the duodenum during the cephalic phase and releases secretin from S cells. Secretin operates through a stimulatory G protein–coupled receptor to increase cytosolic cAMP and secretion.

Gastric phase: Vaso-vagal reflexes, initiated mainly by gastric distension, cause a slight increase in pancreatic secretion.

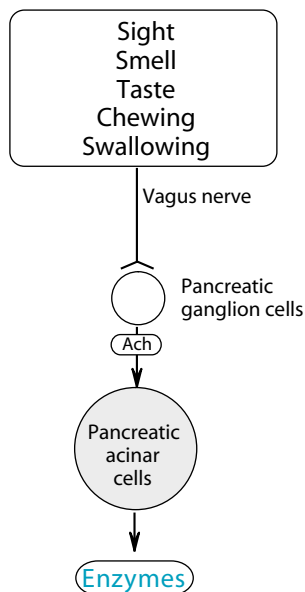


Figure 8–15 Cephalic phase of pancreatic secretion. During this phase, inputs from central nervous nuclei are transmitted by way of the vagus and cause acinar cells to secrete digestive enzymes in anticipation of the arrival of intestinal chyme. Ach = acetylcholine.

Intestinal phase: Pancreatic HCO_3^- secretion is strongly stimulated by the arrival of H^+ and fatty acids in the duodenum. They promote pancreatic HCO_3^- secretion by means of secretin (Figure 8–16). Pancreatic enzyme secretion is stimulated simultaneously with electrolyte secretion by the presence of fatty acids, peptides, amino acids, high osmolality, high $[\text{Ca}^{++}]$, or high $[\text{Mg}^{++}]$ in the duodenal lumen.* These agents exert their effects mostly by way of CCK. During the intestinal phase, inhibitory peptides, such as PP and somatostatin, are released as well.

Secretions from the Liver and Gallbladder

Most circulating plasma proteins, except immunoglobulins, are synthesized and secreted by the liver. These range from clotting factors with a half-life of a few hours to albumin with a half-life of almost 2 weeks. With respect to digestive functions, the most important secretions from the liver are contained in **bile**, an aqueous solution of electrolytes and other inorganic and organic compounds, including **bile acids** and the hemoglobin breakdown product **bilirubin**.

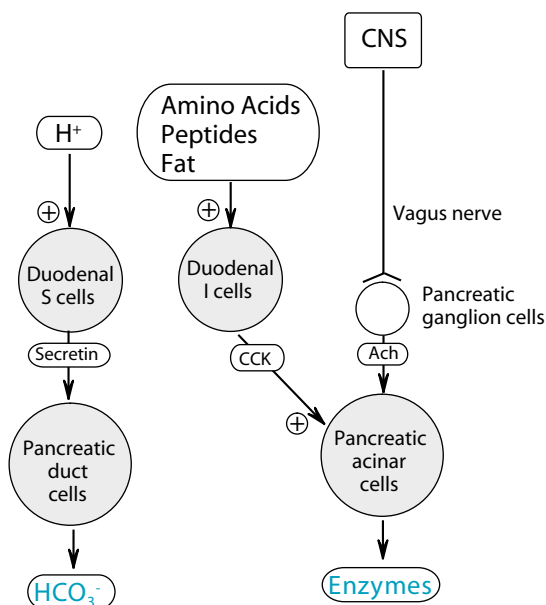


Figure 8–16 Intestinal phase of pancreatic secretion. The presence of H^+ in duodenal chyme induces S cells to release secretin while amino acids, peptides, and fat act on I cells to promote CCK release. Secretin stimulates pancreatic duct cells to secrete a fluid that is rich in HCO_3^- . CCK promotes enzyme secretion from pancreatic acinar cells.

* H^+ in the lumen has only a slight stimulatory effect.

Anatomy of the biliary system. The liver is composed of microcirculatory units, the acini, that are arranged like tubes, each around a central vein that is perfused by a branch of the portal vein. Hepatocytes and a system of sinusoids radiate from each central vein in such a way that each hepatocyte is perfused on two of its sides by sinusoidal fluid (Figure 8–17).

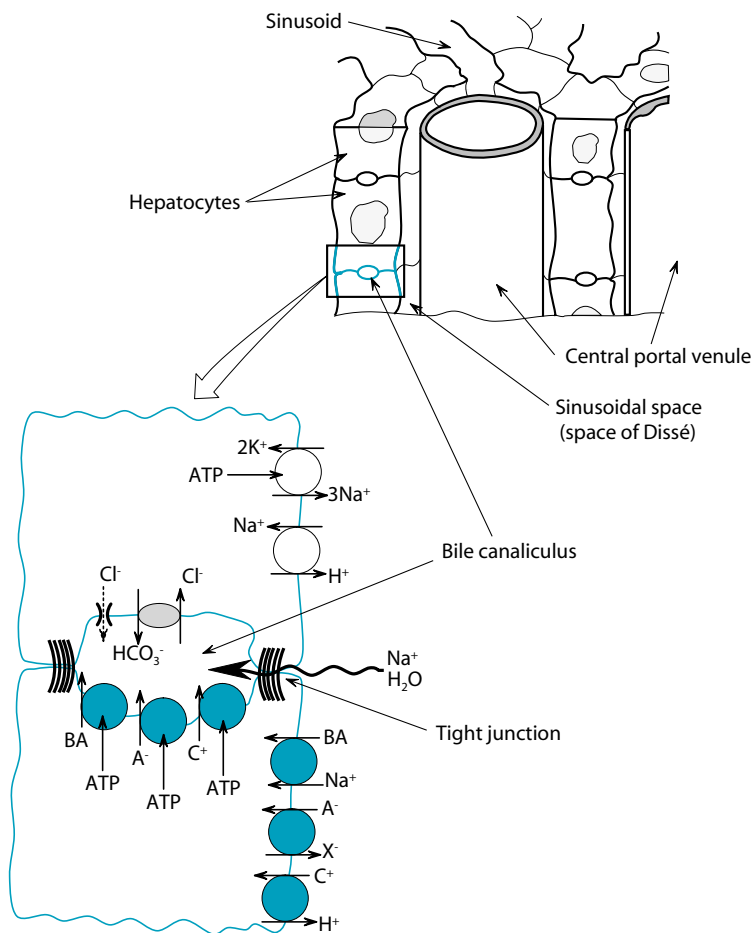


Figure 8–17 Anatomy of the biliary system. Hepatocytes are arranged so as to form sinusoids that radiate from a central portal venule. Bile canaliculi lie between adjacent liver parenchymal cells (hepatocytes). Bile formation is dependent on three types of ATPases in the canalicular membrane. Two of them are organic anion (A⁻) or cation (C⁺) transporters, and one transports bile acids (BA). Each of them also transports a variety of drugs or hormones. The sinusoidal membrane also has three types of carriers, identified as BA-Na⁺, A⁻-X⁻, and C⁺-H⁺. The Na⁺-dependent bile acid carrier (BA-Na⁺) transports conjugated bile acids and a number of hormones and drugs. A⁻-X⁻ is a Na⁺-independent anion exchanger system that will also transport unconjugated bile acids, bilirubin, the dye indocyanine green, and others. C⁺-H⁺ is a cation exchanger.

The other two sides each enclose a system of canaliculi that connects to a system of ducts leading into the gallbladder. The canaliculi are the site of bile acid secretion from hepatocytes.

Secretion of bile.

Bile acids. Bile acids are the main metabolites of cholesterol. Cholesterol is either synthesized *de novo* from acetyl-CoA in hepatocytes (see Figure 10–3 in Chapter 10, “Metabolism and Nutrition”) or recycled from dietary cholesterol that enters hepatocytes mainly by endocytosis of chylomicron remnants (see Fat Digestion and Absorption below).

The liver continuously produces the primary bile acids **cholic acid** and **chenodeoxycholic acid**.^{*} They are secreted into the bile canaliculi (see Figure 8–17) by specific, ATP-dependent transporters, and the secreted fluid is modified in the ducts by epithelial absorption and secretion as well as by conjugation with amino acids (taurine and glycine), sulfate, or glucuronic acid. Conjugation not only forms bile salts but decreases bile acid toxicity and increases both water solubility and resistance to precipitation in acid media. Even in the conjugated form, the bile salts will precipitate out of solution at pH < 4. The pH in bile ducts is maintained above that level by secretion of HCO_3^- from epithelial cells (see Figure 8–17).

When primary bile acids are exposed to intestinal bacteria, the secondary bile acids **deoxycholic acid** and **lithocholic acid** are formed. Bile acids differ from one another by the placing of OH or H groups at positions 3, 7, or 12 in the steroid nucleus of cholesterol (see Figure 9–22). Only a small fraction of all circulating bile is synthesized *de novo* in hepatocytes. The majority is absorbed from the small intestine[†] and returns to the hepatocytes by way of the portal vein, entering the liver sinusoids through the epithelium of the central venules (see Figure 8–17). This loop for recycling and conserving bile acids is called the **enterohepatic circulation**. It requires reabsorptive mechanisms in the intestinal wall as well as specific transporters in the sinusoidal membrane of hepatocytes (see Figure 8–17).

Bilirubin. Bilirubin is a breakdown product of hemoglobin. Hepatocytes conjugate bilirubin to glucuronic acid to form water-soluble **bilirubin glucuronide** (Figure 8–18) and secrete it into the bile canaliculi. Its yellow color is partly responsible for the color of bile and also of stool because it is not reabsorbed from the intestine. When hepatocytes are unable to clear suffi-

^{*}Bile acids are produced from cholesterol by reactions that alter bonding to H or OH groups at positions 3, 7, or 12 of the cyclopentano-perhydrophenanthrene nucleus of the cholesterol molecule (see Figure 9–22).

[†]Conjugated and unconjugated bile acids are passively absorbed along the entire gut. In addition, conjugated bile acids are actively transported from the lumen of the distal ileum.

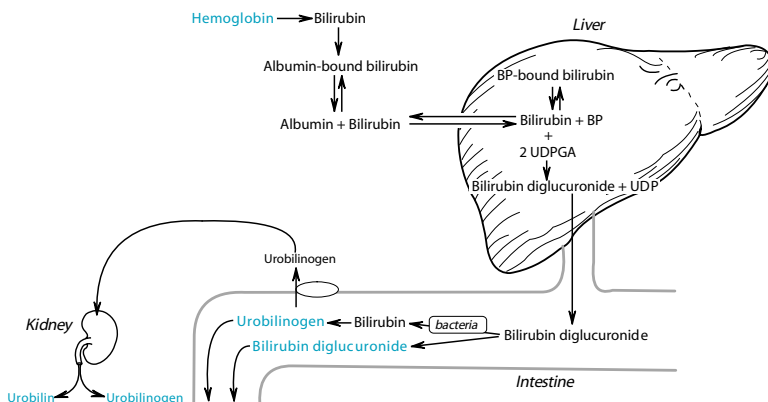


Figure 8-18 The tissue macrophage system destroys aging red cells, breaks down hemoglobin, and produces bilirubin. It is bound mostly to albumin. Free bilirubin enters hepatocytes and exists there in the cytosol in equilibrium with binding protein-associated bilirubin. Conjugation with uridine diphosphoglucuronic acid (UDPGA) yields bilirubin diglucuronide, which is secreted into the bile duct. Intestinal bacterial action yields urobilinogen. Some urobilinogen is absorbed from the intestine and it, as well as its oxidized form, urobilin, are excreted in urine. BP = binding protein; UDP = uridine diphosphate.

cient bilirubin from the blood, the skin assumes the characteristic color of **jaundice**.

Intestinal bacteria degrade bilirubin to form **urobilinogen**, which is reabsorbed from the intestine and is partly excreted in urine. The yellow color of urine is due to the color of oxidized urobilinogen (= **urobilin**).

Storage and release of bile: the gallbladder. Between meals, bile is stored and concentrated in the gallbladder, a distensible, muscular organ. Concentration occurs by virtue of H_2O and $NaCl$ absorption across the gallbladder epithelium. The driving mechanisms are located in the apical epithelium and involve (1) Na^+-H^+ exchange, (2) $Cl^- - HCO_3^-$ exchange, and (3) Na^+-Cl^- co-transport. During meals, when bile is required for the digestion and absorption of fats, it is expelled into the lumen of the duodenum. The controlling mechanisms are CCK and acetylcholine, both of which cause gallbladder contraction. Cholecystokinin also relaxes the **sphincter of Oddi** in the common bile duct near its junction with the duodenum.

Regulation of bile flow. Canalicular bile formation is driven by active transport of organic and inorganic anions into the canalicular lumen (see Figure 8-17). The carriers are located both in the canalicular membrane and

in the sinusoidal membrane. This arrangement allows the transport of newly synthesized bile acids out of hepatocytes as well as recycling of constituents that have returned to the liver by way of the enterohepatic circulation. Tight junctions between adjacent hepatocytes (see Figure 8–17) prevent secreted ions from diffusing back into the sinusoids but do not offer appreciable hindrance to the passage of Na^+ or water, which is drawn into the canaliculi by electrical or osmotic gradients. As a result, bile flow increases linearly with the amount of osmotically active particles secreted into the canaliculi. Some of them are bile acids, and they determine the **bile acid–dependent flow**. **Bile acid–independent flow** is created by the osmotic force created within canaliculi by a variety of compounds, including glutathione, HCO_3^- , and bilirubin; all of them are actively secreted by ATPases in the canalicular membrane.

Regulation of bile synthesis and secretion. The rate of primary bile acid synthesis in hepatocytes depends inversely on the amount of bile acid returned to the liver via the enterohepatic circulation. The controlling mechanism is feedback inhibition by bile acids of **7- α -hydroxylase**, the rate-limiting enzyme in the formation of primary bile acids from cholesterol.

Secretion of recycled and newly synthesized bile acids is regulated, in part, by the state of hepatocyte hydration and, in part, by chemically mediated alterations in second-messenger systems.

Cell swelling induces bile acid secretion by a cytoskeletal mechanism of inserting active transporters into the canalicular membrane. Chemical control over bile secretion is exerted by secretin, which acts by a cAMP-dependent mechanism to stimulate HCO_3^- secretion.

INTESTINAL DIGESTION AND ABSORPTION OF SPECIFIC SUBSTANCES

Most of the nutrients absorbed by the enterocytes lining the intestinal lumen are small, chemically simple degradation products that derive from complex dietary molecules (polysaccharides, proteins, and triacylglycerols). This requires not only a range of digestive enzymes but also an aqueous medium of appropriate electrolyte composition.

Water Absorption

Water is transported by osmotic forces.

Electrolyte Absorption

Electrolyte absorption occurs actively and passively by way of symports, antiports, or channels (Figure 8–19).

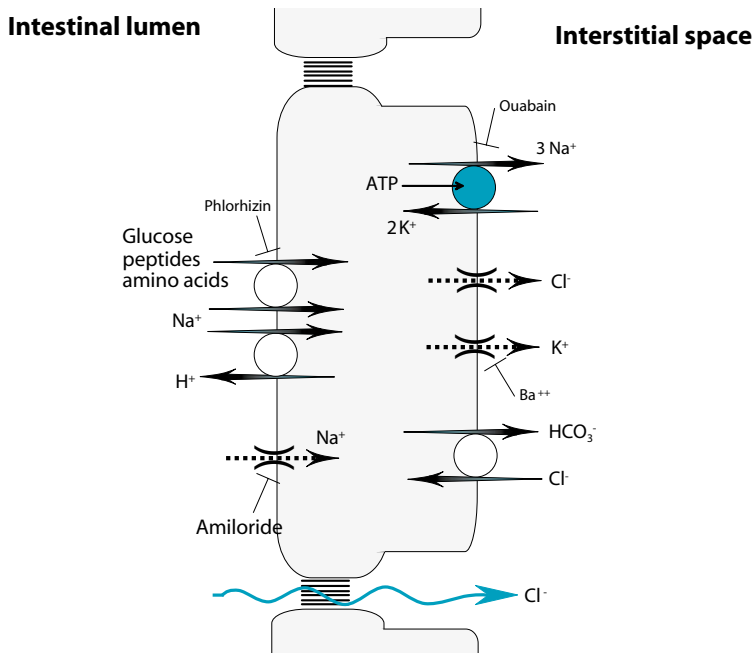


Figure 8–19 The major mechanisms for intestinal electrolyte absorption. Na⁺ enters on the luminal side partly co-transported with a variety of noncharged moieties, partly through a Na⁺-H⁺ antiporter and partly through an amiloride-sensitive channel. Cl⁻ is mostly absorbed through the paracellular pathway. The basolateral portion of the cell membrane contains Na⁺-K⁺-ATPase, passive channels for Cl⁻ and K⁺, as well as a HCO₃⁻-Cl⁻ antiporter. The H⁺ transported in exchange for Na⁺ on the luminal side and the HCO₃⁻ exchanged for Cl⁻ on the basolateral side both derive from intracellular H₂CO₃, which is formed when metabolically produced CO₂ is combined with H₂O.

Sodium

Na⁺ absorption on the luminal side occurs by (1) co-transport with glucose or other nutrients, (2) in exchange for H⁺, and (3) passively through an amiloride-sensitive Na⁺ channel. Na⁺ leaves the enterocyte actively by way of Na⁺-K⁺-ATPase on the basolateral side (see Figure 8–19).

Potassium

K⁺ is reabsorbed passively on the luminal side in response to concentration gradients resulting from Na⁺- and water reabsorption. It also enters the enterocyte through the basolateral Na⁺-K⁺-ATPase. It leaves passively through a barium- (or tetraethyl ammonium-) sensitive K⁺ channel. The epithelium of the colon also contains a K⁺-in/H⁺-out K⁺-H⁺-ATPase in the luminal membrane.

Chloride

Cl^- is absorbed mainly by a paracellular path, down an electrical gradient.* Several Cl^- channels are present in the basolateral membrane. They transport mainly ions that have entered the cell by Cl^- - HCO_3^- exchangers, also located in the basolateral membrane. The main function of this exchanger is to remove from the enterocyte a part of the HCO_3^- that is left behind when H^+ is extruded in exchange for Na^+ .

Not all reabsorptive mechanisms are represented equally along the intestine.

- In the jejunum, the dominant mechanisms are Na^+ co-transport with glucose or other nutrients and Na^+ - H^+ exchange.
- In the ileum and proximal colon, the dominant mechanism is paired exchange of Na^+ - H^+ and Cl^- - HCO_3^- .
- Throughout the colon, K^+ - H^+ -ATPase is a prominent mechanism, and amiloride-sensitive Na^+ channels are present mostly in the distal colon.

Carbohydrate Digestion and Absorption

Carbohydrates in the human diet consist of complex polysaccharides like starch (65% of the diet), disaccharides, such as sucrose (25%) or lactose (7%), and monosaccharides, such as fructose (3%). Their composition is such that digestive breakdown would yield three types of monosaccharides: glucose (80%), fructose (15%), and galactose (5%) (Figure 8–20).

Polysaccharides

Starch. Dietary starch consists of covalently linked chains of mostly glucose arranged in two forms: **amylopectin** (75%) and **amylose**. The covalent bonds linking glucose in amylopectin and amylose are broken by salivary and pancreatic **α -amylase**, yielding **maltose**, **maltotriose**, and **α -limit dextrins**. These oligosaccharide products are then broken down to glucose monomers by brush border enzymes (see Figure 8–20).

Cellulose. Cellulose is the major storage form of glucose in plants. Like starch, it is a glucose polymer, but the neighboring glucose molecules are linked in a configuration that differs from that seen in starch and is not susceptible to breakdown by α -amylase. It is excreted in the feces and is commonly called “bulk” or “fiber.”

*Some regions of the small intestine also have luminal Cl^- - HCO_3^- exchangers.

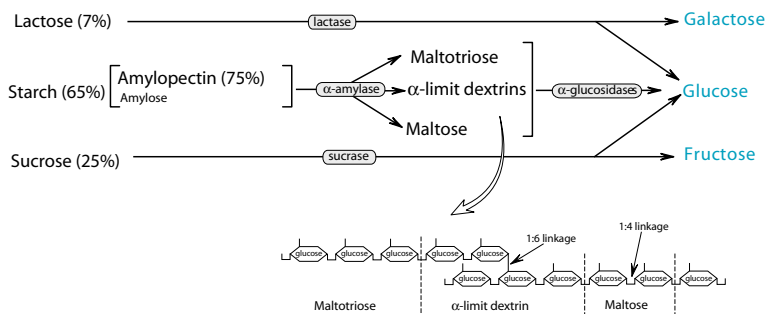


Figure 8–20 Dietary carbohydrate intake is mostly in the form of starch (65%) and disaccharides like sucrose and lactose. Starch is predominantly amylopectin and to some extent animal starch, amylose. Salivary and mostly pancreatic amylase breaks starch at interior 1:4 α linkages to yield the glucose polymers maltotriose, α –limit dextrins and maltose. These, as well as disaccharides like lactose and sucrose, are hydrolyzed by enzymes located at the wall of the intestinal lumen. The final monosaccharide products, galactose, glucose, and fructose, are absorbed, mostly in exchange for Na^+ . The important α -glucosidases are isomaltase, glucoamylase, α -dextrinase, and sucrase.

Glycogen. Glycogen is a dietary polysaccharide of animal origin. Its chemical configuration resembles that of starch and is broken by α -amylase.

Disaccharides

Sucrose is composed of glucose and fructose, whereas **lactose** consists of galactose and glucose. They are broken down to their respective monosaccharides by the brush border enzymes **sucrase** and **lactase**.*

Monosaccharides

The monosaccharides glucose, fructose, and galactose have already been absorbed by the time chyme has traveled 20 cm into the jejunum. Two classes of Na^+ -linked transporters in the brush border membrane of intestinal villi are responsible: (1) glucose and galactose compete for the SGLT-1 transporter that is inhibited by phlorhizin (see Figure 8–19), and (2) fructose is absorbed by an electroneutral transporter.

The monosaccharides diffuse across the enterocyte and leave from the basolateral side by a variety of transporters, including GLUT-2, to enter the portal blood.

*Congenital lack of lactase causes **lactose intolerance**. In this disorder, undigested dietary lactose (from milk products) holds water in the intestine by osmotic forces and causes diarrhea. In addition, some of the ingested lactose is degraded by intestinal bacteria to organic acids and CO_2 . These cause the symptoms of bloating, belching, flatulence, and cramping.

Protein Digestion and Absorption

Dietary protein constitutes the major fraction of protein in the intestinal lumen. Its digestion begins in the stomach because of pepsins that are derived from chief cell pepsinogens. Protein digestion continues and is completed in the small intestine because of the actions of (1) pancreatic proteases, (2) brush border peptidases, and (3) intracellular peptidases that are found in the cytosol of villus epithelial cells.

Pancreatic Proteases

Pancreatic enzyme secretion is stimulated partly by vagal mechanisms but mostly by CCK. **Trypsin** is of greatest significance because it activates each of the other proteolytic zymogens.

The action of pancreatic proteases results in oligopeptides that are further broken down by brush border peptidases, such as the aminopeptidases, folate conjugase, enterokinase, and others (Figure 8–21). The resulting free amino acids and short-chain peptides are then absorbed into the villus epithelial cells by specific carrier proteins and subjected to further breakdown by cytosolic di- and tripeptidases. There are separate Na^+ -coupled and Na^+ -independent carrier systems for neutral, basic, acidic, or secondary amino acids.

Fat Digestion and Absorption

The major form of dietary fat derived from animal products is triglycerides. Their chemical formulation is a glycerol group bound to three fatty acid chains of up to 16 or 18 carbon atoms. They are classified as **saturated**, when their carbon chain contains no double bonds, and **unsaturated**, when double bonds are present.

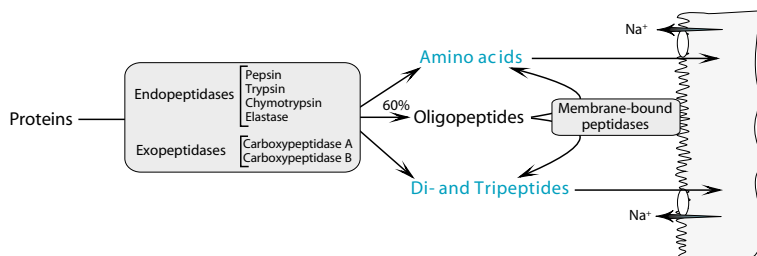


Figure 8–21 Digestion and absorption of protein. Two classes of pancreatic proteases break down proteins into amino acids, di- or tripeptides, and oligopeptides. Endopeptidases hydrolyze interior peptide bonds whereas exopeptidases hydrolyze peptide bonds of amino acids at the C-terminus. Oligopeptides are further broken down into reabsorbable units by peptidases that are bound to the brush border membrane. Reabsorption happens mostly in exchange with Na^+ .

Fats are used as energy sources or chemical substrates for many cell types in the body. However, triglycerides cannot be used directly and must be broken down. This involves **emulsification**, **micelle formation** in the lumen of the duodenum, and formation of **chylomicra** within mucosal epithelial cells (Figure 8–22).

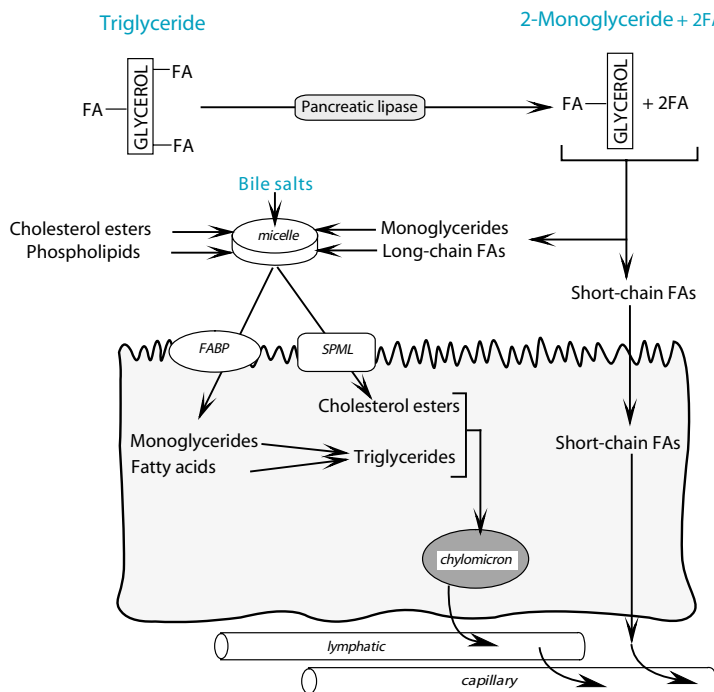


Figure 8–22 Digestion of fat. Triglycerides are the major chemical constituent of dietary fats. Pancreatic lipase breaks each triglyceride molecule into 2 fatty acids and a 2-monoglyceride. Short-chain fatty acids are readily absorbed by the enterocyte, but long-chain fatty acids and monoglycerides are not. They are incorporated into mixed micelles, which are formed spontaneously when the concentration of bile salts rises above a critical concentration. The mixed micelle is the dominant form of transport for triglycerides, monoglycerides, fatty acids, cholesterol esters, and phospholipids to the enterocytes lining the villi in the intestine. Fatty acid binding proteins regulate the uptake of fatty acids and monoglycerides. Sphingomyelinase aids transport of cholesterol esters. Absorbed constituents and endogenously synthesized components are reassembled to form triglycerides and they, along with absorbed cholesterol esters, are formed into chylomicra, which are released into the central lacteal of the villus. FA = fatty acid.

Emulsification

The churning action of the stomach creates large fat drops within the aqueous chyme. They are reduced to smaller droplets by mechanical activity in the duodenum, and their suspension in aqueous chyme forms an emulsion.

Micelle Formation

Pancreatic lipases act on the duodenal emulsion droplets and break up the triglycerides, forming free fatty acids (FFAs), 2-monoglyceride, and glycerol (see Figure 8–22). Long-chain fatty acids and 2-monoglyceride are poorly soluble in water and, therefore, difficult to absorb. They are brought into solution by a special property of bile salts:

Bile salts have a hydrophilic portion because of the presence of carboxyl and hydroxyl groups and a hydrophobic portion. When their concentration in a solution rises above a critical level (called the **critical micelle concentration**), they spontaneously form disk-shaped **micelles** in which the hydrophilic portion of each molecule faces outward, while the hydrophobic portion faces inward.

Lipids are incorporated into the micelles. Triglycerides and dietary cholesterol esters reside in the hydrophobic center, whereas phospholipids and 2-monoglycerides reside in the perimeter, their hydrophilic heads facing out. Such micelles, containing triglycerides, cholesterol esters, and phospholipids, are called **mixed micelles**. They are packages of 2-monoglyceride, long-chain FFAs, and cholesterol in water-soluble form, and they diffuse to the unstirred layer near the brush border of the villus mucosal cells (see Figure 8–22). Once there, the FFAs, triglycerides, and cholesterol esters diffuse out and are taken up by enterocytes. **Sphingomyelin** in the brush border membrane regulates cholesterol uptake and **fatty acid binding proteins** (FABPs), including FABP_{PM}, are necessary for the uptake and cytosolic transport of fatty acids.

Chylomicron Formation

Within the endoplasmic reticulum of the enterocyte, absorbed fatty acids and 2-monoglycerides are reassembled with endogenously synthesized glycerol to form triglycerides again. These and dietary cholesterol are formed into **chylomicra** (droplets coated with phospholipid and apoprotein), released into the central lacteals of the brush border villi, and are delivered in that form to the intestinal lymphatic system and from there to the blood (see Figure 8–22). Absorption of dietary fat and cholesterol by chylomicra is only a small aspect of the biology of **lipoproteins**, a highly selective transport system for lipids and cholesterol.

Lipoproteins

Lipoproteins are lipid-protein emulsion droplets. They are classified into six groups on the basis of size, mobility, density, lipid species, and associated proteins. The outer coating of these emulsion droplets is characterized by the presence of different **apoproteins** (Table 8–4).

Chylomicra. Chylomicra contain triglycerides and cholesterol esters, both from dietary sources. Their outer coat contains several apoproteins, including apo A's, C's, apo E, and, most importantly, apo B₄₈, which can serve as a marker (Figure 8–23). Chylomicra are 80 to 500 nm in diameter, originate in intestinal enterocytes, and serve to transport triglycerides in blood. In tissues that contain lipoprotein lipase (adipose tissue and striated muscle are most significant), that enzyme is activated by apo C₂, which is found in the shell of chylomicra and very-low-density lipoprotein (VLDL). It acts rapidly to release and hydrolyze triglycerides from chylomicra.

Chylomicron remnants. Remnants are smaller than chylomicra (40 to 100 nm) but contain the same apoproteins in the outer coat as their parent particles. They originate from chylomicra by lipoprotein lipase activity and serve to transport dietary cholesterol esters to the liver (see Figure 8–23).

Very-low-density lipoproteins. Very-low-density lipoproteins originate in the liver (see Figure 10–3 in Chapter 10, “Metabolism and Nutrition”). They are 30 to 80 nm in diameter and serve to transport triglycerides (formed in the liver) and cholesterol esters to the peripheral capillaries, where the triglycerides are released by lipoprotein lipase. Their outer coating contains apo C's, apo E, and apo B₁₀₀.

Intermediate-density lipoproteins. Intermediate-density lipoproteins (IDLs) are 25 to 40 nm in diameter. They are what remains of VLDL after most triglycerides have been removed by the action of lipoprotein lipase. Therefore, they contain mostly cholesterol esters. Some IDL are taken up by the liver, whereas the remainder are converted to LDL. They are also in exchange equilibrium with HDL₂, transferring cholesterol esters from HDL₂ to IDL and triglycerides from IDL to HDL₂ (see Figure 8–23).

Low-density lipoproteins. Low-density lipoproteins (LDLs) derive from IDL by processes that remove phospholipids and apoproteins. They contain mostly cholesterol esters, are about 20 nm in diameter, and contain apo B₁₀₀ as the dominant apoprotein. Low-density lipoproteins are the major source of cholesterol for peripheral tissues and are also taken up by hepatocytes. The uptake is mediated by LDL receptors that recognize apo B₁₀₀, but not apo B₄₈, which is the dominant apoprotein in chylomicra and their remnants. When a cell requires cholesterol, it synthesizes receptors for LDL

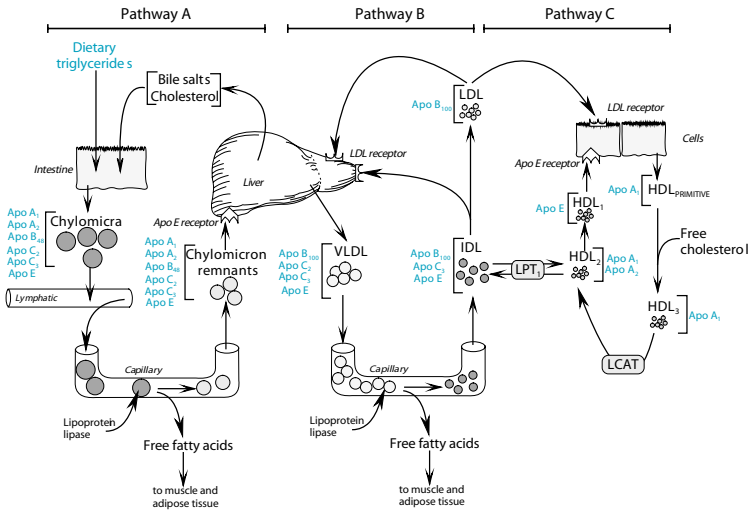


Figure 8–23 Lipoproteins in lipid metabolism. Important apoproteins associated with each of the particles are shown in color. Three pathways, A, B, C, can be recognized. *A*, Dietary fat and cholesterol esters are transported from the intestine to the blood by chylomicra. The presence of apo B₄₈ facilitates chylomicron entry into the lymphatics and apo C₂ activates lipoprotein lipase. Chylomicron remnants are taken up into hepatocytes by way of apo E receptors. *B*, Triglycerides that have been synthesized in the liver are released as VLDL. The release process is facilitated by apo B₁₀₀. VLDL are transferred to blood and apo C₂ activates lipoprotein lipase. The VLDL remnants form IDL. IDL can (1) engage in exchange processes with HDL₂, (2) be taken up by hepatocytes or other cells containing LDL (apo B₁₀₀) receptors, or (3) be converted to LDL. *C*, HDL originate in enterocytes and other cells. They take up free cholesterol, which is esterified by LCAT and then transferred to IDL with the help of lipid transfer protein-1 (LPT₁). HDL₃ are converted to HDL₂ while transferring cholesterol esters to IDL, acquiring triglycerides from IDL and also adding apo A₂ to the HDL outer coating. Apo A₂ prevents further esterification of cholesterol. HDL₂ then acquire apo E and become HDL₁. Apo E allows HDL₁ to be taken up by hepatocytes and other cells that contain apo E receptors. HDL = high-density lipoprotein; IDL = intermediate density lipoprotein; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

and inserts them into the plasma membrane within specialized surface pits. Such pits and their receptor-ligand complexes are pinched off to form a vesicle. H⁺ transporters raise the intravesicular [H⁺] and cause release of the LDL receptor for recycling to the plasma membrane and conversion (by the action of acid lipases) of the cholesterol esters to cholesterol. The cholesterol thus formed is used for the needs of the cell as well as for feedback inhibition of **HMG-CoA reductase**, an enzyme that is required for intracellular synthesis of cholesterol. Low-density lipoproteins are also taken up by **scavenger receptors** on macrophages. Thus, when the plasma concentration of LDL is high, macrophages become loaded with cholesterol esters and form **foam cells** that are associated with atherosclerosis (see

Table 8–4

Apoprotein Locations and Functions

Apoprotein	Location	Function
Apo A ₁	Structural component of HDL	Coenzyme for LCAT in promotion of receptor-mediated cholesterol uptake by HDL
Apo A ₂	Structural component of HDL	Blocks LCAT-mediated cholesterol esterification in HDL
Apo B ₄₈	Characteristic structural component of chylomicra	Facilitates chylomicron entry into central lacteals in brush border villi
Apo B ₁₀₀	Structural component of LDL and IDL	Ligand for LDL receptor
Apo C ₂	Structural component of chylomicra and VLDL	Activates lipoprotein lipase but not hepatic lipase
Apo C ₃	Structural component of chylomicron remnants	Inhibits lipoprotein lipase
Apo E	Structural component of chylomicra, remnants, VLDL, IDL, and HDL	Ligand for LDL receptors

LCAT = lecithin-cholesterol acyltransferase.

“Endothelial Role in Lipid Metabolism” in Chapter 6, “Cardiovascular Physiology”).

The human LDL receptor is a large (about 850 amino acids) membrane-spanning glycoprotein that recognizes apo B₁₀₀, but not apo B₄₈. Its rate of synthesis is inversely related to intracellular levels of cholesterol or its metabolites.

High-density lipoproteins. High-density lipoproteins (HDLs) are small (5 to 12 nm in diameter), and three types are recognized. Their origin is uncertain, but it may be the enterocytes lining intestinal villi. High-density lipoproteins-3 are primitive HDLs that have taken up free cholesterol from peripheral tissues, and this might be their major function. The acquired cholesterol is esterified and then either transferred to IDL (by way of lipid transfer protein-1, LPT₁) or conveyed to other cells by way of HDL₁ (see Figure 8–23).

There is a strong negative correlation between serum HDL levels and ischemic heart disease.

Enzymes in lipoprotein metabolism.

Hepatic lipase. Hepatic lipase is synthesized in hepatocytes and distributed only to the capillary endothelial cells in the liver. It acts specifically on HDL and IDL, not on chylomicra or VLDL. Its function is to hydrolyze triglycerides to form FFAs and 2-monoglyceride.

Lecithin-cholesterol acyltransferase. This is a plasma-borne enzyme that transfers fatty acids from lecithin (a component of the surface of HDL) to cholesterol, which is also a component of the HDL surface coat. The resulting cholesterol esters are more hydrophobic than their substrates and, therefore, move to the core of the particles and cause them to increase in size from HDL₃ to HDL₂ to HDL₁ to IDL to LDL.

Lipoprotein lipase. Lipoprotein lipase is found in the capillary endothelium in adipose tissue, heart, red skeletal muscle, adrenal cortex, ovary, and lactating mammary gland. It is synthesized in tissue cells that surround the capillaries and acts specifically on chylomicra and VLDL because these lipoproteins contain apo C₂. Its action is to hydrolyze triglycerides to form FFAs and 2-monoglyceride.

Lipid transfer protein-1 (LPT₁). This protein is also known as cholesterol ester transfer protein. It transfers cholesterol esters from HDL₂ to IDL and triacylglycerols in the opposite direction.

Regulation of Intestinal Absorption

Absorption occurs at a steady rate that is determined mostly by load. Nevertheless, short-term increases in absorption are caused by norepinephrine (α -adrenoreceptor mediated) and somatostatin. Long-term control is exerted by glucocorticoids and mineralocorticoids. These substances increase absorption of water and electrolytes by promoting active Na⁺-K⁺ transport.

VITAMINS AND TRACE ELEMENTS

Vitamins are essential dietary constituents that maintain health and growth by mechanisms other than the supply of energy. Their dietary sources and biologic functions are described in Chapter 10, "Metabolism and Nutrition," but summarized in Table 8–5.

Table 8–5
Vitamins, Their Dietary Sources, and Mechanisms of Absorption

Vitamin	Dietary Sources	Mechanism of Absorption
Water-Soluble Vitamins		Readily absorbed in early portions of small intestine
Thiamine (B ₁) Niacin Pantothenic Acid Biotin	Cereal grains	Co-transported with Na ⁺ in duodenum and jejunum
Riboflavin (B ₂)	Dairy products	Facilitated transport in duodenum
Pyridoxine (B ₆)	Yeast, wheat, and corn	Diffusion down concentration gradient
Folic acid and derivatives	Leafy green vegetables	Carrier mediated
Cyanocobalamin (B ₁₂)	Meat, dairy products, and eggs	Released from food by gastric digestion. Then bound to R proteins and intrinsic factor. Pancreatic enzymes break down R proteins but not intrinsic factor. Intrinsic factor is the ligand for brush border absorption of intrinsic factor-B ₁₂ complex.
Fat-Soluble Vitamins		Require bile salts and pancreatic lipase
Retinol (A)	Mostly yellow vegetables or fruit	Solubilized by micelles, absorbed into enterocytes, cleaved into 2 molecules of retinal, esterified with palmitic acid, and carried in the core of chylomicra. Transported in plasma by way of a transporting protein.

Continued

Table 8–5

Vitamins, Their Dietary Sources, and Mechanisms of Absorption—Continued

Vitamin	Dietary Sources	Mechanism of Absorption
Cholecalciferol (D)	Fish liver	Carried in chylomicra and delivered to the liver in chylomicron remnants. Hepatic hydroxylation to form inactive precursor that is used by mitochondria in renal tubular cells to form the active vitamin.
Tocopherol (E)	Meat, eggs, dairy products, and leafy vegetables	Solubilized in micelles Absorbed passively and enters intestinal lymph
K	K ₁ in leafy green vegetables	Solubilized in micelles Absorbed by an active carrier
	K ₂ is formed by bacteria in the colon	Diffusion down a concentration gradient

FUNCTIONS OF THE LIVER

The liver is the first organ that is reached by substances absorbed into the intestinal microcirculation. They enter the working units (**acini**) of the liver by way of terminal portal venules (see Figure 8–17) and diffuse into the sinusoids that extend from the central portal venule to a terminal hepatic venule. The intestinal absorbate may also contain drugs or intestinal microorganisms. Therefore, liver cells have several functions in addition to those related to metabolism. They include (1) protein synthesis, (2) bile formation and recirculation, (3) circulatory functions, and (4) secretion, as well as (5) detoxification and excretion (Table 8–6).

One of the excreted products is urea, which is produced by the liver from nitrogen-containing waste products.

Table 8–6
Summary of Liver Functions

Function	Details
Metabolic Functions	
Carbohydrate Metabolism	<p>When plasma glucose concentration is high:</p> <p>Glucose is broken down to form (1) <i>glycogen</i> (glycogenesis) for energy storage and (2) <i>pyruvate</i> (glycolysis) plus 2 molecules of ATP. Pyruvate then follows one of 3 possible pathways:</p> <ol style="list-style-type: none">(1) The Krebs cycle to release further ATP by oxidative phosphorylation(2) Conversion to fatty acid or ketone bodies. When there is excess ATP within the hepatocyte, then the rate of the Krebs cycle decreases and accumulating acetyl-CoA is used for synthesis of fatty acid or ketone bodies.(3) Conversion to lactate. During glycolysis, NAD⁺ is required for the formation of 1,3-bisphosphoglycerate from glyceraldehyde 3-phosphate. When there is not enough O₂ present, then reoxidation of NADH to NAD⁺ by the electron transport chain is insufficient to maintain glycolysis. In that setting, NAD⁺ is regenerated by conversion of pyruvate to lactate with the help of lactate dehydrogenase. <p>When plasma glucose concentration is low:</p> <p>New glucose is formed by (1) breaking down glycogen stores (glycogenolysis) or (2) the processes of <i>gluconeogenesis</i>, forming new glucose from lactate, pyruvate, amino acids, or glycerol.</p>
Fat Metabolism	<p>Dietary fat is solubilized with the help of bile salts, which are synthesized in the liver.</p> <p>Dietary fat and cholesterol reach the liver in chylomicron remnants and are metabolized.</p> <p>Triglycerides and cholesterol are formed for export in the lipoprotein particles, VLDL.</p>
Amino Acid Metabolism	<p>When plasma amino acid concentration is high:</p> <p>The liver is a buffer in the control of the plasma pool of free amino acids.</p> <p>In the postprandial state, amino acids derived from intestinal absorption are delivered in the portal blood and most are extracted and metabolized to pyruvate and ketone bodies*.</p>

Continued

Table 8–6

Summary of Liver Functions—Continued

Function	Details
Protein Synthesis[†]	<p>When plasma amino acid concentration is low: Amino acids are formed by hepatic proteolysis.</p> <p>Most plasma proteins are synthesized by the liver. The immunoglobulins are the major exception.</p>
Circulatory Functions	<p>Synthesis of clotting factors ensures that blood remains in a fluid state.</p> <p>The hepatic vascular bed is large, spongy, and highly compliant. This permits storage of blood volume.</p>
Secretion	
Bile Salts	Bile acids are the major breakdown product of cholesterol. The liver continuously produces the primary bile acids, <i>cholic acid</i> and <i>chenodeoxycholic acid</i> .
Cholesterol	Cholesterol is synthesized from acetyl-CoA and is either secreted within VLDL or broken down to form bile salts.
Lecithins	Lecithins are phospholipids that are associated with bile salts and also form a part of the outer shell of VLDL.
Bilirubin	Bilirubin, an end product of hemoglobin degradation, is conjugated to glucuronic acid to form water-soluble <i>bilirubin diglucuronide</i> and secreted into the bile canaliculi.
Detoxification and Excretion	Many of the enzymes that operate to detoxify and excrete drugs and other substances are found in the liver. They are responsible for the processes of <i>biotransformation</i> that modify some toxins in a way that permits excretion in water-soluble form in urine or in lipid-soluble form in bile.
Urea	Excess nitrogenous compounds are converted to urea.

*The branched chain amino acids, isoleucine, leucine, and valine are not catabolized and are used only for hepatic protein synthesis.

[†]Disorders of hepatic protein synthesis will be revealed first by clotting disorders because of the short half-lives of clotting factors (a few hours) compared with the half-life of albumin and other proteins (10–14 days).

Urea and the Urea Cycle

There is no body store for nitrogen-containing compounds, such as amino acids, as there is for carbohydrates (stored as glycogen) or lipids (stored as

triglycerides). As a result, nitrogen ingested in excess of requirements has to be excreted. The pathway is that it is first converted to **ammonia** (NH_3). Some ammonia is excreted by the kidney, but most of it is converted to **urea** before being excreted. Synthesis of urea occurs in the liver by the **urea cycle** (Figure 8–24).

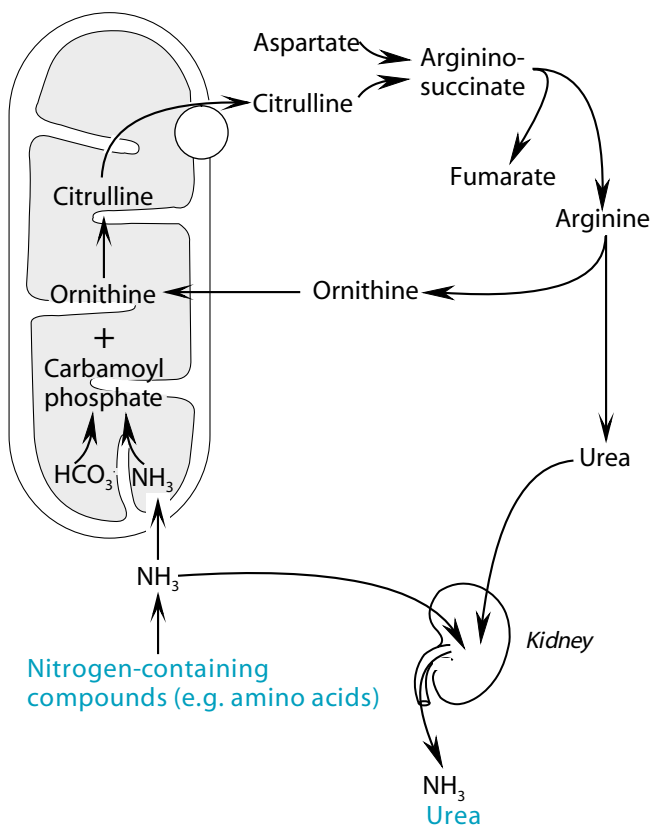


Figure 8–24 Excess amino acids are transaminated to form glutamate, which is deaminated to form NH_3 . NH_3 is partly excreted in urine, but mostly converted to **urea** before being excreted. Six steps are involved: (1) Hydrolysis of two ATP permits NH_3 and CO_2 (in the form of HCO_3^-) to be condensed and activated in the mitochondria to form **carbamoyl phosphate**. (2) The carbamoyl group is transferred within mitochondria to ornithine and this forms **citrulline**. (3) Citrulline is transported out of the mitochondria. Within the cytosol, (4) citrulline is condensed with aspartate to form **argininosuccinate**; (5) arginino-succinate is split into **fumarate** and **arginine** and (6) urea is formed from arginine and ornithine is regenerated in this step. Ornithine is transported back into the mitochondria and urea is excreted by the kidneys.

Endocrine System

PRINCIPLES OF CHEMICAL CONTROL

Transfer of chemicals is the most common form of exchange among cells. Such transfer serves to carry nutrients, waste products, energy, and information. Endocrine physiology is concerned with the study of information transfer and communication among cells. Its general principle is that a molecular effector is produced by a **secreting cell** and delivered to a **target cell**, where it binds to a receptor protein. Such binding alters the tertiary structure of the protein with the consequences of (1) changing the function of a distal site on the protein and (2) causing a biologic effect in the target cell.

The nature of the physical relationship between secreting cells and target cells and the mode in which the chemical agent is delivered from one to the other determine whether the communication between the two classes of cells is **autocrine**, **endocrine**, **neurocrine**, or **paracrine** (Table 9–1).

Table 9–1

Forms of Chemical Communication

Interaction	Relationship of Secreting Cell to Target Cell	Delivery of Message
Autocrine	They are one and the same	Exocytosis to membrane receptors
Endocrine	Physically separated	By the vascular system
Neurocrine	Physically separated; the secreting cell is a neuron	By the vascular system
Paracrine	Physically separated, but contiguous	Exocytosis and diffusion

Feedback Control in Endocrinology

One of the effects of chemical action on target cells is that the secreting cell is notified of the success of its chemical communication. In most instances, the secretory rate of the target cell is inversely related to the magnitude of the target cell response. This is termed **negative feedback**.

There are also examples of **positive feedback**, whereby an effect that is induced in the target cell induces the signaling cell to amplify its signal further.

Biorhythms

Most endocrine functions show both circadian (approximately 24 hours) and ultradian rhythms. The dominant pacemakers for many of these rhythms are in the **suprachiasmatic nuclei**, which are located in the anterior hypothalamus, on both sides of the third cerebral ventricle and just above the optic chiasm. Neurons in these nuclei show an intrinsic 24-hour rhythmical pattern in both their metabolic and electrical activities. This pattern is modulated by inputs from many brain regions as well as from the retina; it can be reset by neuropeptide Y or **melatonin**.

Ultradian rhythms are found within a circadian rhythm in the release of a variety of hormones. For example, cortisol shows pulsatile release every 4 hours. In most cases, the origin of these rhythms is not yet known.

Cellular Mechanisms of Hormone Action

Hormonal interaction with target cells begins with reversible binding to highly specific receptors. Such receptors are located in the plasma membrane, the cytosol, or the cell nucleus.

Interactions with Plasma Membrane Receptors

As described in detail in Chapter 1, five classes of receptors (Figure 9–1) lead to four general sequences after a ligand-receptor complex has formed:

1. Allosteric activation of an intracellular receptor domain followed by phosphorylation (tyrosine kinase) or dephosphorylation (tyrosine phosphatase) of intracellular proteins to cause a biologic effect.
2. Activation of a G protein to trigger a catalytic enzyme (**adenylate cyclase** or **phospholipase C**) and transform a precursor into a second messenger [cAMP, inositol 1,4, 5-trisphosphate (IP_3), Ca^{++} , and diacylglycerol (DAG)]. The second messenger, in turn, activates an intracellular effector (commonly a kinase).

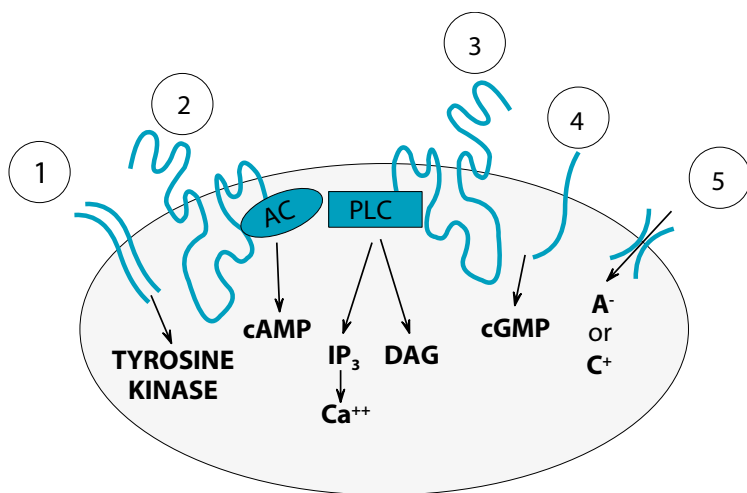


Figure 9–1 There are five classes of plasma membrane receptors, each responsive to a class of ligand. Those belonging to the tyrosine kinase class respond to ligand binding with autophosphorylation and subsequent binding to a cytosolic adaptor protein. The adaptor protein is then phosphorylated by the activated tyrosine kinase and initiates an intracellular cascade that leads to biologic action. Receptors identified as 2, 3, or 4 lead, upon receptor activation, to formation of a second messenger. The fifth class leads, upon activation, to a change in conductivity of an ion channel. AC = adenylate cyclase; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DAG = diacylglycerol; PLC = phospholipase C.

3. Allosteric activation of an intracellular guanylate cyclase domain of the receptor. Activated guanylate cyclase produces the second messenger cyclic guanosine monophosphate (cGMP) from the precursor GTP. Cyclic guanosine monophosphate then acts on protein kinase G to lead to biologic effects.
4. When the receptor complex is an ion channel, its activation causes a change in channel conductivity and subsequent alteration in membrane potential.

Interactions with Cytosolic or Nuclear Receptors

Some ligands penetrate the plasma membrane and form ligand-receptor complexes either within the cytosol (glucocorticoid receptors) or within the nucleus (estrogen or tri-iodothyronine). In the absence of ligand, the receptor's DNA-binding domain is blocked, often by a 90-kDa heat shock protein, HSP₉₀. When ligand has bound, HSP₉₀ dissociates, and the DNA-binding domain is exposed (Figure 9–2), the ligand-receptor complex binds to DNA and increases transcription of messenger ribonucleic acids (mRNAs) that are

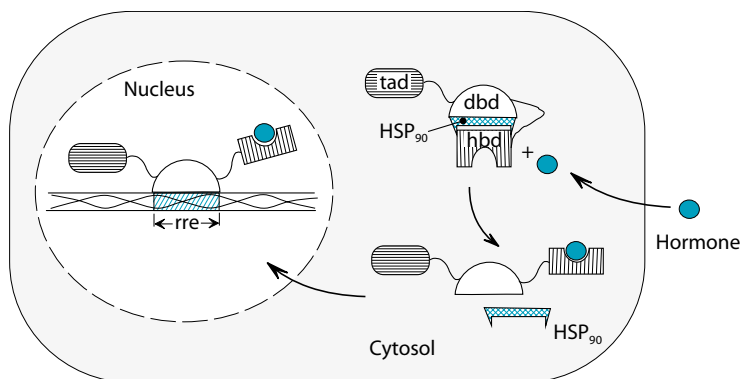


Figure 9-2 Cytosolic and nuclear receptors have three functional domains: a hormone-binding domain (hbd), a DNA-binding domain (dbd), and a transcription-activation domain (tad). When ligand such as a glucocorticoid penetrates the plasma membrane, it forms a ligand-receptor complex within the cytosol and simultaneously displaces heat shock protein (HSP₉₀), which has been blocking the DNA-binding domain (dbd). Formation of the complex (1) changes the conformation of the receptor protein so as to expose dbd and (2) releases the receptor from its cytosolic anchor so that the hormone-receptor complex may be translocated into the nucleus. There the DNA-binding domain of the complex binds the receptor response element (rre) of a gene and permits the transcription activation domain (tad) to stimulate transcription of the target gene. hbd = hormone-binding domain.

encoded by the receiving gene. The mRNAs are subsequently translated in the ribosomes and form proteins that alter cell function.

The time scale of action of hormones with cytosolic or nuclear receptors is in the range of a few days rather than in the range of several minutes.

Molecular biology of nuclear and cytosolic receptors. These receptors each have a unique N-terminal region of variable length (100 to 500 amino acids) and contain regions that function as transcription-activation domains. Their DNA-binding domain is centrally located, has the C₄ **zinc finger** motif,* contains about 68 amino acids, and displays a great deal of homology among different receptors. The ligand-binding domain is near the C-terminal of the receptor protein and contains a ligand-dependent activation domain that sometimes functions as a suppression domain when ligand is absent.

The DNA of cells containing nuclear or cytosolic receptors has characteristic nucleotide sequences that bind nuclear receptors. These sequences

*A zinc finger has the property that enables it to insert its α -helix into the major groove of DNA.

are called the **receptor response element**. Once the hormone-receptor complex interacts with a response element on the target gene, transcription is activated.

Control of gene transcription. Gene **transcription** is the first step toward **gene expression**, and it involves (1) binding of RNA polymerase to DNA to initiate transcription, (2) splitting of the DNA strand, (3) formation of an RNA strand by base-pairing with the DNA, and (4) termination of transcription.

Whether or not a specific gene is expressed in a particular cell at a particular time is a consequence of the binding and activity of **transcription factors** that interact with the regulatory sequences of that gene. Lipid-soluble ligands that bind to cytosolic or nuclear receptors provide a mechanism for regulating transcription factor activity.*

HYPOTHALAMUS AND ANTERIOR PITUITARY

A portion of the anterior diencephalon forms the nuclei of the hypothalamus. The pituitary gland (hypophysis) lies close to the basal portion of the medial hypothalamus and is connected to it through the **pituitary stalk**. The stalk carries both nerve fibers and a portal system[†] of blood vessels.

The pituitary gland consists of three lobes: anterior (adenohypophysis), posterior (neurohypophysis), and intermediate (pars intermedia). In human adults, the intermediate lobe is rudimentary only.

Hypothalamic control over pituitary function is accomplished through nervous as well as circulatory pathways.

Relevant Embryology and Anatomy of the Hypothalamus-Anterior Pituitary Unit

The embryonic origin of the anterior and intermediate lobes of the pituitary is an evagination of the roof of the pharynx, named **Rathke's pouch**. These lobes are innervated by sympathetic and parasympathetic fibers, but there are hardly any hypothalamic fibers that continue past the median eminence to provide a direct connection between the hypothalamus and the anterior and intermediate pituitary lobes. The posterior pituitary, on the other hand, does receive such fibers.

*The kinds of transcription factors expressed in a particular cell type are determined by transcription factor genes and their control during differentiation and development of the cell type.

[†]A portal circulatory system is characterized by an upstream capillary network that exists for the purpose of collecting substances from the interstitial space so that they may be transported to a second, downstream capillary network.

Special secretory neurons in the arcuate and other nuclei of the hypothalamus synthesize agents that are transported down their axons and released by exocytosis from the axon terminals into a portal system that links the **median eminence** at the head of the pituitary stalk to the anterior pituitary (Figure 9–3). The immediate cause for their release is action potentials from the neuron cell bodies. The portal vascular system is formed by capillaries of the superior hypophyseal artery, the hypophyseal portal veins, and the capillary network of the anterior pituitary. The anterior pituitary effluent then drains into the **anterior intercavernous venous sinus**.

The capillaries of the median eminence are fenestrated and are not part of the blood-brain barrier. The capillary network of the anterior pituitary bathes secretory cells belonging mostly to one of the following five types:

1. Somatotropes, which secrete growth hormone
2. Lactotropes (mammotropes), which secrete prolactin
3. Thyrotropes, which secrete thyroid-stimulating hormone (TSH)
4. Gonadotropes, which secrete the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH)
5. Corticotropes, which secrete adrenocorticotrophic hormone (ACTH), β -lipotropic hormone (LPH), and some γ -melanocyte-stimulating hormone (MSH)

In addition to these five one-product cell types, certain cells contain the secretory apparatus for more than one peptide.

Anterior Pituitary Hormones and Their Control by the Hypothalamus

The hypothalamic agents that reach the anterior pituitary by way of the portal vascular system act as release-promoting or release-inhibiting factors for a variety of anterior pituitary hormones. For that reason, they are called **trophic factors**. Their physiologic roles are summarized in Table 9–2.

Features that are common to all the hormones of the hypothalamic-pituitary axis are (1) pulsatility of release, (2) superposition of circadian and ultradian rhythms on the pulsatile release, and (3) feedback control by both short and long loops.

Pulsatile release arises from periodic burst firing that is a feature of the hypothalamic peptidergic neurons. Experiments have shown that such pulsatility maintains the sensitivity of anterior pituitary target cells.

Growth Hormone

Structure of growth hormone. The human growth hormones (hGH) are single polypeptide chains. The dominant form (75%) has 191 amino acids

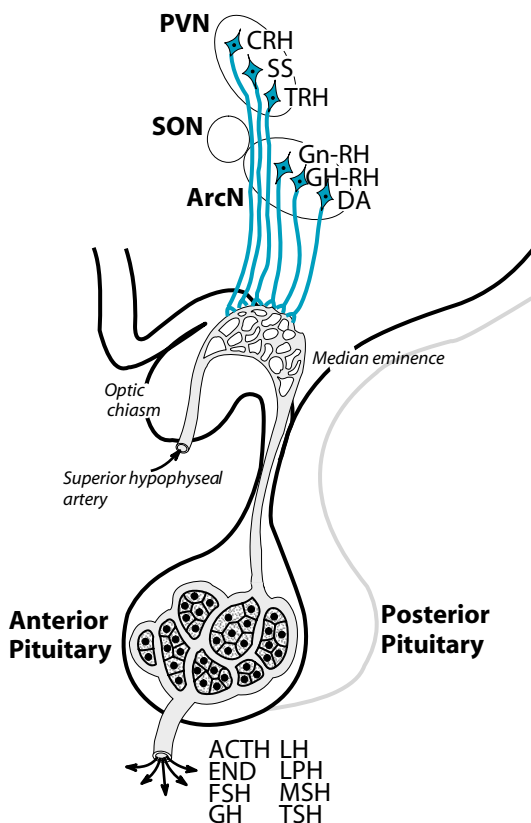


Figure 9-3 Secretory neurons located in the paraventricular, arcuate, and other nuclei of the hypothalamus send their axons to the portal circulation in the median eminence and release their release-promoting or -inhibiting factors in response to action potentials in the axons of the secretory neurons. The factors are transported to and exert their effects on cells in the anterior and intermediate lobes of the pituitary. They drain from there through a number of short veins into the adjacent cavernous sinuses. ArcN = arcuate nucleus; ACTH = adrenocorticotrophic hormone; CRH = corticotropin-releasing hormone; DA = dopamine; END = endorphins; FSH = follicle-stimulating hormone; GH = growth hormone; GH-RH = growth hormone-releasing hormone; Gn-RH = gonadotropin-releasing hormone; LH = luteinizing hormone; LPH = lipotropic hormone; MSH = melanocyte stimulating hormones; PVN = paraventricular nucleus; SON = supraoptic nucleus; SS = somatostatin; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone (= thyrotropin).

and a molecular weight of 22,000. It is named 22K hGH. The next most prominent form (10%) is 15 amino acids smaller, is also biologically active, and is named 20K hGH. A 191-residue form that differs from the normal form by only 13 amino acids appears during pregnancy, as does **human chorionic somatomammotropin** (hCS), which also has 191 amino acids but differs from hGH by 29 residues.

Table 9–2
Summary of the Actions of Hypothalamic Trophic Factors

Hypothalamic Trophic Factor	Target Releasing Factor in Ant. Pituitary	Target	Controlled Hormone
GH-RH (+)	Growth Hormone	Circulating Precursors	Somatomedins
SS (-)	Growth Hormone	Muscles and Adipocytes	↑ Lipolysis
TRH (+)	TSH	Thyroid	Thyroxine (T ₄)
PIFs (mostly DA) (-)	Prolactin	Lacteals	Lactation
PRFs (TRH, VIP) (+)	Prolactin		
CRH (+)	ACTH	Adrenal Cortex	Cortisol
	γ-MSH	Anterior Pituitary & Intermediate Lobe	γ-LPH, β-END
	β-LPH		
GnRH (+)	FSH/LH	Ovaries/Testes	Estrogen, Progesterone/Testosterone

Synthesis and release of growth hormone. More than half of the anterior pituitary cells are somatotropes. They secrete growth hormone in a pulsatile manner every 4 hours, peaking within 2 hours of falling asleep. GH secretion is controlled by **growth hormone–releasing hormone** (GH-RH) and **somatostatin** (SS), both synthesized in the hypothalamus and released in pulsatile patterns that are phase-shifted 180 degrees relative to each other.

Growth hormone secretion is stimulated by three classes of physiologic challenges: (1) decreased availability of energy substrates for cells (for example, fasting), (2) increased plasma levels of certain amino acids, and (3) stress. The final common pathway for each is the hypothalamic peptides GH-RH and SS.* Peptides like TRH and vasopressin can play a minor role.

Growth hormone secretion is feedback inhibited by GH itself, by insulin-like growth factor-1 (IGF-1) (Figure 9–4), or by an abundance of plasma glucose or free fatty acids.

Growth hormone–releasing hormone. Growth hormone–releasing hormone is a 44 amino acid peptide, produced mostly in neurons that project to the median eminence from the arcuate nucleus and the ventromedial hypothalamus (see Figure 9–3). It promotes (1) GH synthesis by enhancing gene transcription in somatotropes and (2) GH release by receptor-mediated activation of adenylate cyclase and subsequent increase in the conductivity of a Ca⁺⁺ channel.

Somatostatin. Somatostatin exists as both a 14 and a 28 amino acid peptide. The 28 amino acid form is the more potent inhibitor of GH and

*Somatostatin is also synthesized in cells of the gastrointestinal mucosa, where it serves a variety of inhibitory functions, and in D cells of the pancreas, where it is a paracrine modulator of insulin and glucagon secretion.

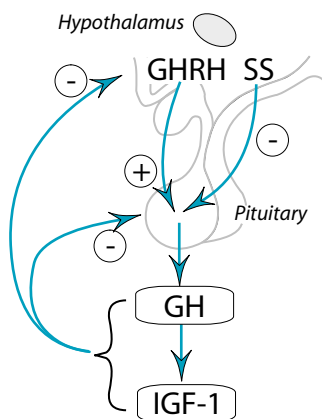


Figure 9-4 Growth hormone synthesis in pituitary somatotropes is stimulated by hypothalamic growth hormone–releasing hormone (GH-RH) and inhibited by somatostatin (SS) as well as by negative feedback from the products. GH = growth hormone; IGF-1 = insulin-like growth factor-1.

TSH. Somatostatin-secreting neurons that are capable of inhibiting somatotropes or thyrotropes are located mainly in the anterior paraventricular nucleus and anterior region of the periventricular nuclei (see Figure 9-3). Somatostatin has no effect on GH mRNA but inhibits GH secretion. The effects of SS are mediated by the SS₂ receptor, which operates by inhibition of adenylate cyclase.

Transport and metabolism of growth hormone. Growth hormone is bound to two kinds of plasma proteins. The high-affinity carrier is a fragment of the GH receptor. The basal GH plasma level is near 3 ng/mL and its half-life in plasma is 6 to 20 minutes. It is metabolized at least partly in the liver.

Actions of growth hormone. Some effects are due to GH directly; many are caused by the **somatomedins**, whose release is promoted by GH.

Growth hormone actions that do not require somatomedins: Somatomedin-independent effects of GH are triggered by a membrane receptor of the cytokine class. The receptor includes specific cytoplasmic domains that mediate (1) tyrosine kinase activation,* (2) metabolic actions, (3) activation of **STAT[†] proteins**, and (4) Ca⁺⁺ influx. Subsequent biologic effects of GH vary widely and include actions on electrolytes, energy metabolism, and somatomedins (Table 9-3).

*Although the GH receptor does not include a tyrosine kinase domain, its activation initiates the nonreceptor, cytoplasmic tyrosine kinase, **Jak2**. Activation of Jak2 leads to mitogenic proliferation, phosphorylation of intracellular proteins, MAP kinase activation, activation of STAT-1, -3, and -5, and induction of target gene expression.

[†]STAT = signal transducers and activators of transcription.

Growth hormone actions that require somatomedins: The effects of GH on growth and protein metabolism (Table 9–4) are not due to GH directly but to an interaction with somatomedins.

The somatomedins are polypeptides. They are produced in the liver, cartilage, and other tissues in response to stimulation by GH and a variety of other factors, including insulin. Glucocorticoids, estrogen, and protein deficiency depress somatomedin activity. In humans, the principal somatomedin is IGF-1 (also called somatomedin C). It circulates, bound to IGF-binding proteins. Such binding increases its half-life by up to 20 hours. One outcome of this prolongation of half-life is a relatively constant biologic effect of GH, even in the face of pulsatile release. Insulin-like growth factor-2 is less affected by GH, appears to have a role only in prenatal development, and shows very limited distribution in human adults.

Thyroid-Stimulating Hormone (Thyrotropin)

Structure of thyroid-stimulating hormone. Human TSH is a glycoprotein of 211 amino acids. Its two subunits are designated α and β , are encoded by genes on separate chromosomes, and are linked in the pituitary thyrotropes. The α -subunit is identical to that found in LH, FSH, and human chorionic gonadotropin (hCG). The β -subunit is the locus of specific TSH responses.

Synthesis and release of thyroid-stimulating hormone. Glycosylation of α and β polypeptides and subsequent modification of the attached carbohydrate side chains are important aspects of TSH synthesis because

Table 9–3
GH Actions Independent of Somatomedins

Electrolyte metabolism	↑ Ca^{++} absorption from the GI tract
	↓ Ca^{++} reabsorption in nephrons
	↓ Na^{+} reabsorption in nephrons*
Energy metabolism	↑ Number of insulin receptors
	↓ Glucose uptake and utilization in muscle
	↑ Hepatic gluconeogenesis
	↑ Mobilization of FFA from adipocytes
Somatomedins	↑ Production and release of somatomedins

*This action does not involve the mineralocorticoids.
GI = gastrointestinal; FFA = free fatty acids.

Table 9–4

GH Actions Dependent on Somatomedins

Growth*	↑ Cell size
	↑ Rate of cell division
	↑ Longitudinal growth of cartilage and bone [†]
	↑ Bone circumference ^{‡§}
Metabolism	↑ Protein synthesis
	↑ Lean body mass

*All tissues that are capable of growing are positively affected in cell size and rate of cell division by increased levels of IGF-1.

[†] Before puberty, while androgen levels are low and the epiphyses have not yet fused with the long bones, the major effects are on the longitudinal growth of cartilage and bone.

[‡] After puberty, when androgens have caused ossification and closure of the epiphyseal growth plates of the long bones, longitudinal growth is no longer possible in them. However, IGF-1 promotes longitudinal growth in membranous bones, which have no epiphyses and circumferential growth in all bones.

[§] In adults, prolonged administration of GH will cause **acromegaly**, a syndrome of characteristic deformities in bone and soft tissues.

they permit linking of the two subunits, expression of its full biologic activity, and prolonged half-life in plasma. Glycosylation and modification take place in the rough endoplasmic reticulum and Golgi apparatus of the pituitary thyrotropes, which constitute about 5% of the cells in the anterior pituitary.

Secretion of TSH from the anterior pituitary is pulsatile, with peaks occurring every 2 to 4 hours. The mean output is lowest in the morning, rises from about 21:00 onward, and reaches a peak near midnight. The secretion rate is increased by direct action of hypothalamic TRH and decreased by somatostatin as well as by negative feedback that is exerted on the pituitary and hypothalamus by the thyroid hormones T₃ and T₄ (Figure 9–5).

Thyrotropin-releasing hormone (TRH). This hormone consists of only three amino acids and is secreted mostly from the medial parvocellular portion of the paraventricular nucleus (see Figure 9–3) and from the ventromedial nucleus. Its rate of secretion is increased by cold temperatures and decreased by stress and warmth.

Although TRH-containing fibers are widely distributed in the hypothalamus, those controlling pituitary function project directly to the median eminence (see Figure 9–3). The principal target of TRH is the pituitary thyrotrope, where it stimulates TSH synthesis and secretion by a receptor-mediated mechanism involving primarily the IP₃ pathway of increasing cytosolic Ca⁺⁺ and secondarily increased conductivity of voltage-gated Ca⁺⁺

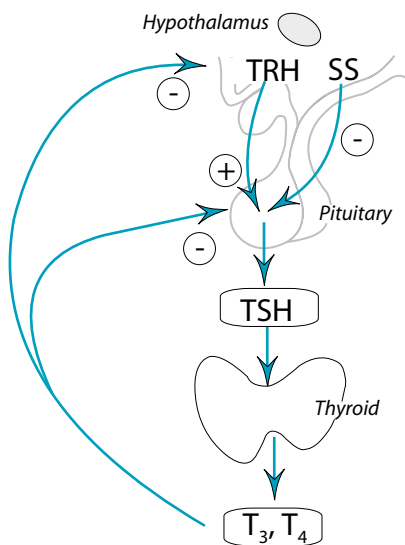


Figure 9–5 Hypothalamic thyroid-releasing hormone (TRH) stimulates and somatostatin (SS) inhibits pituitary thyroid-stimulating hormone (TSH) synthesis and secretion. TSH acts on the thyroid to promote thyroid hormone (T_3 and T_4) production and release. The thyroid hormones, in turn, exert negative feedback on both the pituitary and the hypothalamus. TSH = thyroid stimulating hormone (= thyrotropin); T_3 = tri-iodothyronine; T_4 = thyroxine.

channels. Thyroid-releasing hormone also stimulates prolactin release from lactotropes, but the physiologic significance of this to lactation is not clear.

Thyroid-releasing hormone is found outside the hypothalamus. Its action there is as a modulator of nerve function.

Somatostatin. The SS_2 receptor inhibits adenylate cyclase and, thereby, lowers cytosolic cAMP and phosphorylation of protein kinase A. The associated decrease in conductivity of voltage-gated Ca^{++} channels opposes the effect of TRH on those channels.

Transport and metabolism of thyroid-stimulating hormone. Human TSH has a biologic half-life of 60 minutes. It is degraded by the kidneys and liver.

Actions of thyroid-stimulating hormone. The TSH is the major regulator of thyroid function and thyroid size. It rapidly stimulates the thyroid to increase iodide trapping and binding, to secrete thyroglobulin into the colloid, and to synthesize T_3 and T_4 . Prolonged action of TSH enlarges the

thyroid, and this condition is called **goiter**. The actions of TSH are mediated by a serpentine membrane receptor that activates adenylate cyclase through a G protein.

Prolactin

Structure of prolactin. Human prolactin is a peptide of 199 amino acids, folded into loops by three disulfide bridges linking neighboring cysteine residues.

Synthesis and release of prolactin. Prolactin is synthesized in lactotrope cells of the anterior pituitary. They constitute 15 to 20% of the normal pituitary cell mass and increase to 70% during pregnancy.

The major hypothalamic influence on lactotrope cells is constitutive inhibition by **prolactin-inhibiting factors**, mostly **dopamine** (Figure 9-6). Dopamine derives primarily from cells in the dorsal part of the arcuate nucleus. Dopaminergic inhibition of prolactin release is exerted by way of D_2 receptors. Their predominant effector mechanism is inhibition of adenylate cyclase with consequent inhibition of voltage-gated Ca^{++} channels. Dopaminergic inhibition of prolactin release is feedback-promoted by prolactin itself (see Figure 9-6).

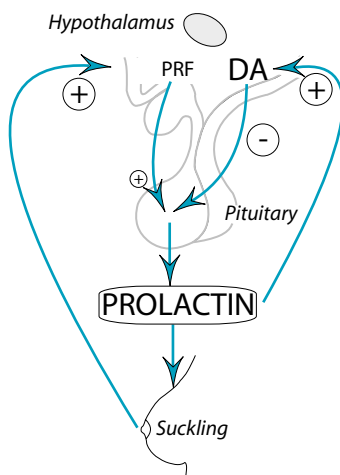


Figure 9-6 The major hypothalamic influence on prolactin synthesis in pituitary lactotrope cells is inhibition by **dopamine** (DA). Prolactin release is increased mainly by mechanical stimulation of the breast and is released in direct proportion to the strength of the suckling stimulus. This stimulus may operate by way of prolactin-releasing factors (PRF) like thyroid-releasing hormone, vasoactive intestinal peptide, or serotonin.

Prolactin release is increased mainly by breast suckling and also by mechanical stimulation of the cervix. The presence of afferents from the nipples or the cervix is essential for this increase, as are **prolactin-releasing factors**. Thyroid-releasing hormone, serotonin, and vasoactive intestinal peptide (VIP) may act as releasing factors.

Actions of prolactin. Prolactin effects are membrane receptor mediated. The receptor belongs to the superfamily of class 1 cytokine receptors whose function is mediated by two classes of signaling molecules: (1) **Janus kinases** and (2) transducers and activators of transcription.

Prolactin is found in the plasma of both women (8 ng/mL) and men (5 ng/mL).

Prolactin is absolutely required for milk secretion and exerts its action in three ways:

1. It acts on the mammary gland to promote growth and milk secretion. The secretory action involves increasing the local production of casein and lactalbumin* and is inhibited by agents that disrupt microtubules. It is also critically dependent on estrogen levels.†
2. It increases lipoprotein lipase activity in the mammary gland, and this promotes high fat content in human milk.
3. It inhibits Gn-RH secretion from the hypothalamus as well as Gn-RH effects on pituitary gonadotropes. It also antagonizes the effects of gonadotropins on the ovaries. These mechanisms, in concert, inhibit ovulation while a woman is breast-feeding. This inhibition is called **lactation amenorrhea**.

The actions of prolactin in men are uncertain. However, excess prolactin causes hypogonadism and impotence.

Pro-opiomelanocortin, Adrenocorticotrophic Hormone, Lipotropic Hormone, and Melanocyte-Stimulating Hormones

Corticotropes, which constitute about 15% of the anterior pituitary cells, synthesize **pro-opiomelanocortin** (POMC), a protein that is cleaved to yield a family of hormones.

Synthesis and Processing of Pro-opiomelanocortin. Cells in the anterior and intermediate pituitary lobes as well as in the hypothalamus,

*Lactalbumin is a regulatory protein of the lactose synthetase enzyme system. This system is essential for the formation of lactose, the principal carbohydrate in human milk.

†The breasts enlarge during pregnancy because of high circulating levels of prolactin, estrogen, and progesterone. The levels of estrogens and progesterone decrease suddenly when the placenta is expelled after birth. The decrease in estrogen levels permits lactation to begin. Thereafter, any rise in estrogen will antagonize the milk-producing effect of prolactin.

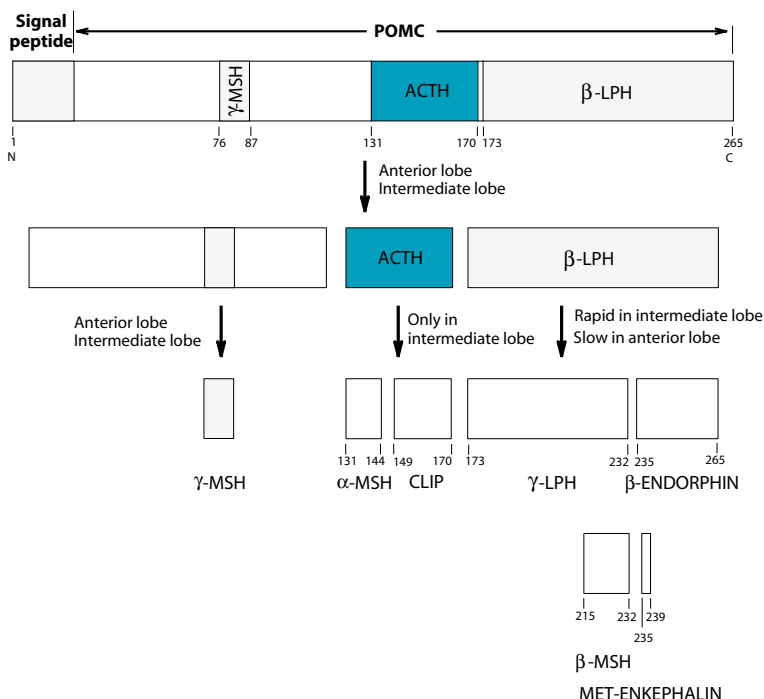


Figure 9-7 Cleavage of POMC to produce ACTH and other peptides in the anterior and intermediate lobes of the pituitary. The N-terminal is numbered 1 and the C-terminal is numbered 265. Successively smaller fragments are produced by proteolytic cleavage, mostly at Lys-Arg pairings, but occasionally at Lys-Lys or Arg-Arg pairings. The intermediate lobe is well defined in the human fetus but is at best rudimentary in adults. Therefore, α -MSH and CLIP may not be secreted in appreciable amounts. The biologic functions of CLIP and γ -LPH are unknown. ACTH = adrenocorticotrophic hormone; CLIP = corticotropin-like intermediate lobe peptide; LPH = lipotropic hormone; MSH = melanocyte-stimulating hormone; POMC = pro-opiomelanocortin.

lungs, gastrointestinal (GI) tract, and placenta synthesize a 265-amino acid preprohormone that includes a signal peptide and the prohormone POMC (Figure 9-7). It can be processed in both the anterior and intermediate lobes* to yield **ACTH**, **β-LPH**, and an N-terminal fragment. β -Lipotrophic hormone and the N-terminal fragment can be further processed in either the anterior or intermediate lobes to yield γ -MSH, γ -LPH, and β -endorphin (see Figure 9-7).

Adrenocorticotrophic hormone: Adrenocorticotrophic hormone contains 39 amino acids, of which the first 23 are identical in all species. It

*The intermediate lobe is well defined in the human fetus but is, at best, rudimentary in adults.

has a plasma half-life near 10 minutes and appears to be metabolized mostly in the kidneys.

Adrenocorticotrophic hormone controls the adrenal cortex by membrane receptor-mediated mechanisms that activate adenylate cyclase by way of a G protein and, thereby, increase cytosolic [cAMP]. Such an increase has some short-term effects but mostly long-term transcription consequences.

Short-term actions of ACTH: Elevated cAMP promotes phosphorylation of protein kinase A, which, in turn, catalyzes phosphorylation of **cholesteryl ester hydrolase** and increases its activity. Cholesteryl ester hydrolase breaks down the storage form of cholesterol in the lipid droplets of adrenal cortical cells, makes more free cholesterol available, and, thereby, increases synthesis of adrenocortical steroids. This is a weak effect of ACTH.

Long-term actions of ACTH: Elevated cAMP leads to up-regulation of mRNA for adrenocortical steroid hydroxylases and related enzymes. This affects particularly the enzymes of the **cytochrome P₄₅₀ superfamily**, which are crucial for adrenal function.

Beta-lipotropic hormone: Beta-LPH is a linear polypeptide of 91 amino acids and undetermined physiologic function.

Gamma-melanocyte-stimulating hormone (γ -MSH): Gamma-MSH and the other MSHs act to disperse pigment granules in **melanophores**, which are melanin-containing cells in the skin of fishes, reptiles, and amphibians. Melanins are pigments of black, brown, yellow, or red hue. Humans do not have melanophores, but they do have **melanocytes**, which synthesize melanins that determine the color of skin and hair. Although injection of MSHs into humans leads to darkening of the skin, the physiologic role of human MSHs is not yet known.

Endogenous opioid peptides: The opioid peptides include **endorphins**, **enkephalins**, and **dynorphins**. They are chemically related but are produced by different biosynthetic pathways. The anterior pituitary cleaves endorphins from POMC, and β -endorphin is the most abundant form (see Figure 9–7).

The endogenous opioid peptides may play a role in a variety of complex physiologic patterns associated with pain perception, learning, behavior, and addiction.

Regulation of POMC synthesis. The major regulator of POMC synthesis, cleavage, and release of products is corticotropin-releasing hormone (CRH; Figure 9–8).

Corticotropin-Releasing Hormone

Corticotropin-releasing hormone is a 41-amino acid, single-chain polypeptide that is produced mostly by neurons in the parvocellular division of the paraventricular nucleus of the hypothalamus but also by other areas of the brain and the viscera. The placenta has the highest concentration of CRH outside the nervous system.

Corticotropin-releasing hormone increases mRNA for POMC and promotes ACTH release by a receptor-mediated, cAMP- and Ca^{++} -dependent mechanism.

Corticotropin-releasing hormone neurons receive afferent signals from a variety of central nervous and peripheral sensory sources. They appear to be most strongly stimulated by the complex inputs generated by physical or emotional stress and are a significant component in the mechanisms that allow us to deal with stress. They are inhibited by negative feedback (see Figure 9–8) from ACTH (short loop) and glucocorticoids (long loop). Corticotropin-releasing hormone is released in bursts throughout the day but shows a diurnal variation. The highest level occurs about 1 hour before waking, and the lowest level is found in the late evening.

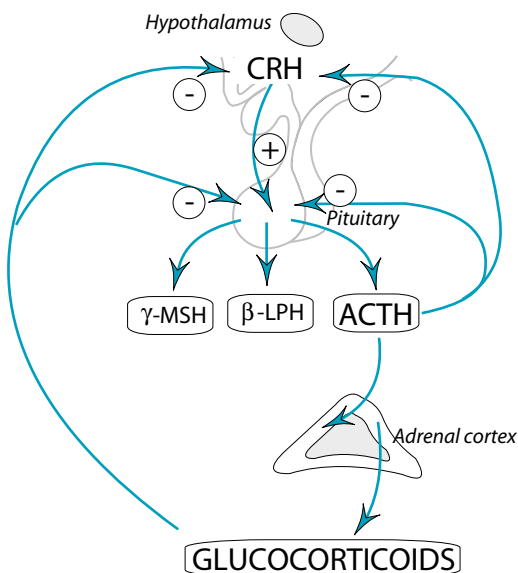


Figure 9–8 Synthesis of ACTH and glucocorticoids is driven by corticotropin-releasing hormone (CRH). CRH acts on pituitary corticotropes and causes them to synthesize POMC, which is split into γ -MSH, β -LPH, and ACTH. The target organ for ACTH is the adrenal cortex. Glucocorticoids synthesized there provide negative feedback on both the pituitary and the hypothalamus. ACTH = adrenocorticotrophic hormone; LPH = lipotropic hormone; MSH = melanocyte-stimulating hormone; POMC = pro-opiomelanocortin.

Gonadotropins

Gonadotropes make up approximately 10% of all cells in the anterior pituitary, and they produce FSH and LH in proportions that vary with conditions. The two gonadotropins are mostly secreted by separate cells, but a small proportion of gonadotropes secretes both hormones. Follicle-stimulating hormone and LH regulate ovarian and testicular function.

Structures of gonadotropins. Like TSH, FSH and LH are glycoproteins, each is made up of an α - and β -subunit, and the α -subunits of each are identical.

Follicle-stimulating hormone. In women, FSH induces growth of ovarian follicles in preparation for the next ovulation cycle. It also stimulates granulosa cells of the follicle to grow and synthesize estradiol.

In men, FSH stimulates secretory activity in **Sertoli's cells** and, thereby, helps maintain the spermatogenic epithelium.

Luteinizing hormone. In women, LH stimulates the ovarian theca cells to produce androgens, which then diffuse to the granulosa cells, where they are converted to estrogens. A surge in LH secretion at about day 10 to 12 of the menstrual cycle triggers ovulation from the dominant follicle. Thereafter, LH is responsible for initial formation of the **corpus luteum** and secretion of progesterone, the major steroid product of the corpus luteum.

In men, LH is primarily responsible for controlling testosterone synthesis in the Leydig cells of the testes.

Regulation of gonadotropin secretion. Gonadotropin secretion is promoted by Gn-RH and inhibited by negative feedback from the gonadal steroids, estrogens, progesterones, and androgens (Figure 9–9). This inhibition is exerted both at the pituitary and hypothalamic levels. It is pronounced during the prepubertal period, and the onset of **puberty** coincides with a reduction in the tonic gonadal inhibition of Gn-RH release.

Gonadotropin-releasing hormone: Gonadotropin-releasing hormone-containing neurons that project to the median eminence are distributed around the septal, preoptic, and basal regions of the hypothalamus. They are controlled by a variety of olfactory, visual, auditory, limbic system, and brainstem inputs and secrete their product, which is a linear 10-amino acid peptide, at intervals of 60 to 90 minutes unless it is slowed by increased levels of testosterone or progesterone.

The gonadotropic function of Gn-RH is dependent on membrane receptors that cause activation of cytosolic $[Ca^{++}]$. Gonadotropin-releasing hormone also regulates both receptor number and affinity in its target cells.

Gonadotropin-releasing hormone is present in various regions of the limbic system and appears to be involved there in modulating emotional aspects of sexual behavior.

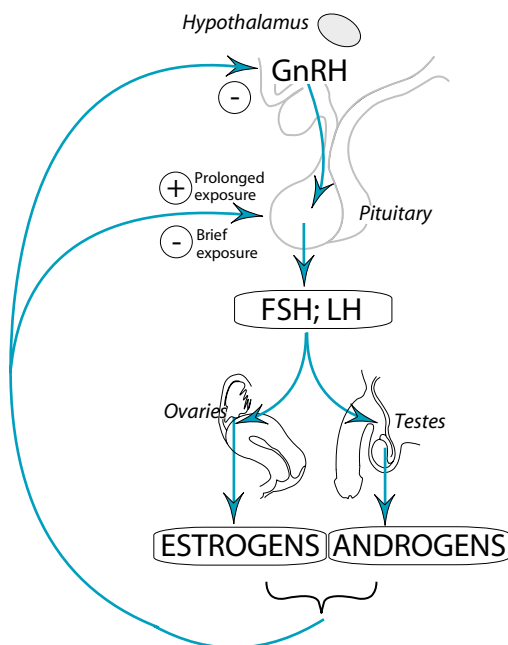


Figure 9–9 Regulation of gonadotropin synthesis. Gn-RH stimulates pituitary gonadotropes to synthesize FSH and LH. They, in turn, stimulate the ovaries and testes to produce estrogens and androgens. Feedback inhibition on the hypothalamus and pituitary gonadotropes is provided by estrogens and androgens under normal circumstances. However, all female mammals have the ability to provide positive feedback on pituitary gonadotropes after they have been exposed to estrogens for half of the menstrual cycle. FSH = follicle-stimulating hormone; GnRH = gonadotropin releasing hormone; LH = luteinizing hormone.

Estrogens in the control of gonadotropin secretion: Estrogens exert two modes of feedback control on gonadotropins: (1) brief exposure of the pituitary to estrogens decreases its sensitivity to Gn-RH, and (2) prolonged exposure of the pituitary to estrogens increases its sensitivity to Gn-RH.

THE HYPOTHALAMUS AND POSTERIOR PITUITARY

Relevant Embryology and Anatomy of the Hypothalamus-Posterior Pituitary Unit

The posterior pituitary develops from a loop in the floor of the third cerebral ventricle. It is made up mostly of unmyelinated nerve endings from the supraoptic and paraventricular nuclei of the hypothalamus (Figure 9–10). In addition, there are **pituicytes**, which are modified astroglial cells and contain fat globules. They have no secretory function. The axons from supraoptic and paraventricular neurons terminate near capillaries of the **inferior hypophy-**

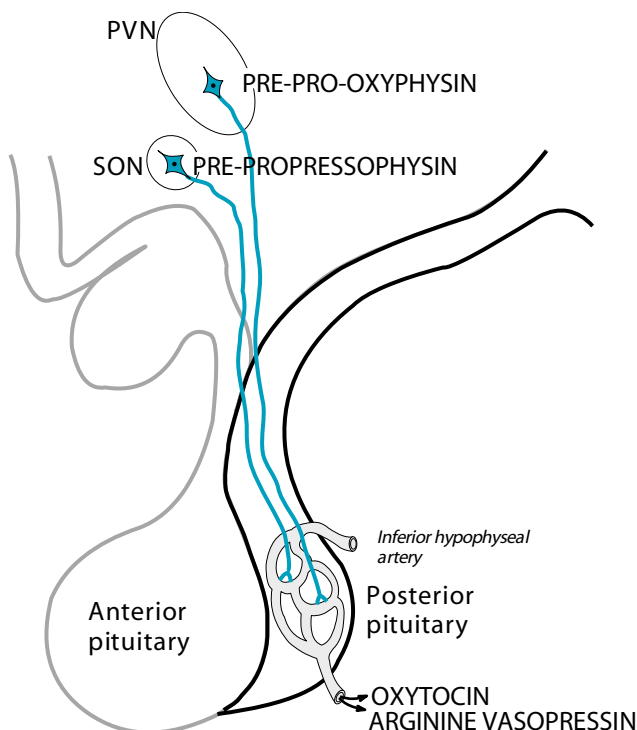


Figure 9–10 Oxytocin and vasopressin are derived, respectively, from pre-pro-oxyphysin and pre-pro-pressophysin. The capillary network of the posterior pituitary serves as a way station for the transfer of oxytocin and vasopressin to the vascular system for transport to peripheral target organs.

seal artery (see Figure 9–10). This capillary bed is a vital anatomic feature because it allows neurosecretions to be transferred to the vascular system.

Posterior Pituitary Hormones

The posterior lobe of the pituitary gland produces no biologic responses to hypothalamic agents. Therefore, it is not controlled by the hypothalamus; it acts as a way station for transferring two hypothalamic neurosecretions, **arginine vasopressin (AVP)*** and **oxytocin**, to the bloodstream for transport to peripheral target organs (see Figure 9–10).

*Arginine vasopressin differs by one amino acid from lysine vasopressin, which is secreted by some animals.

Structure of Posterior Pituitary Hormones

Vasopressin and oxytocin are small peptides (9 amino acids), formed into a loop by a disulfide bridge.

Synthesis and Release of Posterior Pituitary Hormones

Vasopressin and oxytocin are synthesized as part of larger precursors in cells of the magnocellular divisions of the supraoptic and paraventricular nuclei of the hypothalamus.

- Most of the cells in the supraoptic nucleus contain the vasopressin precursor **pre-pro-pressophysin** and some contain the oxytocin precursor **pre-pro-oxyphysin**.
- In the paraventricular nucleus, a greater proportion of cells contain oxytocin precursor than vasopressin precursor.

Each of the posterior pituitary hormones is associated with a characteristic **neurophysin** and is packaged in that form into secretory granules in the Golgi apparatus of the synthesizing neurons. Oxytocin is attached to neurophysin-I (93 amino acids) while AVP is attached to neurophysin-II (95 amino acids). The neurophysins are cleaved from their respective hormone at a glycine residue while they are being transported along the axons toward the pituitary. Both products are released by exocytosis in response to action potentials in the magnocellular neurons that contain the hormones. It is not known whether the neurophysins have a biologic role after their release.

Vasopressin

Vasopressin has two major actions, both mediated by G protein-coupled receptors:

1. V_1 receptors are located mostly in the brain and in vascular smooth muscle. Their activation in the brain leads to increased drinking (possibly in synergy with angiotensin II), and in vascular smooth muscle, V_1 activation causes vasoconstriction (by an IP_3 -mediated increase in cytosolic Ca^{++}).
2. V_2 receptors are found on the basolateral side of cells in the renal collecting tubule. When they are activated, they cause insertion of water channels (**aggrephores**) into the luminal side of these cells by a cAMP-dependent mechanism. This increases water permeability of such cells, increases free-water* reabsorption at this site, and, thereby, regulates body fluid osmolarity and body fluid volume.

*Free water is water that is not accompanied by osmolites. Reabsorption of such water is capable of diluting osmolites and, thereby, of decreasing extracellular osmolarity.

Regulation of vasopressin secretion. Basal plasma vasopressin concentration is 1 to 3 ng/L. Two separate systems provide afferent information that leads to vasopressin release, **osmosensors** and **stretch sensors** (Figure 9–11).

Osmosensors: Changes in extracellular osmolarity are the more sensitive of the two stimuli for increased vasopressin release. A change of as little as 2% will cause detectable vasopressin release. The region of highest sensor concentration is the AV3V region of the hypothalamus, but areas within the

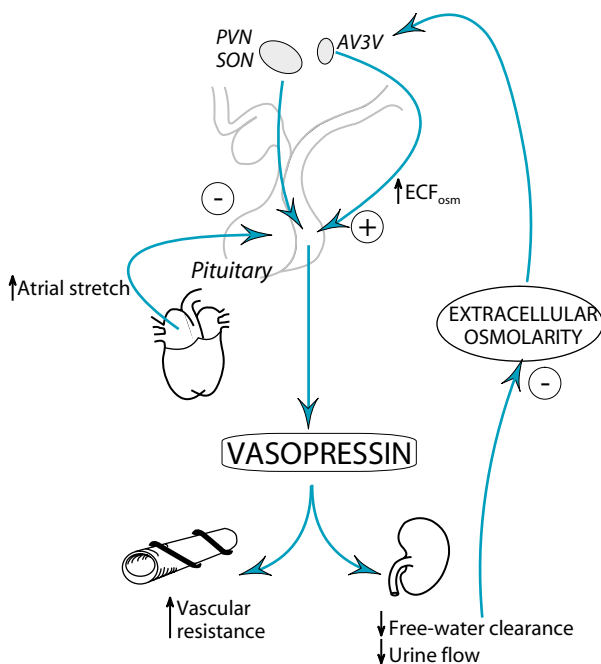


Figure 9–11 Vasopressin secretion changes in response to blood volume or extracellular osmolarity. Increased atrial stretch (increased blood volume) inhibits vasopressin while increased extracellular osmolarity (ECF_{osc}) promotes vasopressin release. ECF_{osc} is detected by osmolarity-sensitive neurons in the AV3V region of the hypothalamus. Vasopressin acts by receptor-mediated mechanisms to increase constriction of vascular smooth muscle and to decrease renal excretion of water without accompanying osmolites (= free water). Decreased excretion of free water both decreases urine flow and decreases ECF_{osc} . AV3V = anteroventral region of the third cerebral ventricle; PVN = paraventricular nucleus; SON = supraoptic nucleus.

portal venous vascular bed in the GI tract are also capable of eliciting vasopressin secretion.

Stretch sensors: Sensors for blood volume are located near the junctions of the great veins with the left or right cardiac atria. Atrial stretch and vasopressin release are inversely related. This relationship forms the basis of a blood volume regulatory mechanism by which renal water excretion is correlated with blood volume.

Alcohol: Alcohol inhibits vasopressin secretion. This causes increased urine flow and is responsible for the dehydration that is part of a morning hangover.

Oxytocin

Oxytocin has two main physiologic functions: (1) it is a strong stimulant for the contraction of smooth muscle in the uterus and the distal portion of the mammary gland duct system, and (2) it promotes maternal behavior toward the newborn. The smooth muscle effects are mediated by a G protein–coupled membrane receptor that activates phospholipase C and causes increases in cytosolic $[Ca^{++}]$ and $[DAG]$.

- Responsiveness of the uterus to oxytocin is dependent on many factors including the presence of estrogen (which enhances contraction) and progesterone (which inhibits contraction). The sensitivity of the uterus to oxytocin increases in late pregnancy as a result of an increase in the number of oxytocin receptors. Oxytocin-induced uterine contractions are powerful and may be essential for the birth process.
- Oxytocin-mediated contractions of the uterus (in women) and the vas deferens (in men) are also observed during orgasm. The biologic purpose of such contractions may be facilitation of sperm transport.
- Smooth muscle contractions in the mammary glands result in transport of milk to the lactiferous sinuses and subsequent milk ejection. Such contractions are vital for lactation because, in their absence, no milk can be obtained by suckling.

Regulation of oxytocin secretion. Oxytocin release (Figure 9–12) is stimulated by (1) mechanical stimulation of the breast nipple, such as occurs in suckling, or of the vagina and uterus, and (2) emotional correlates of human reactions to sexual excitement or the crying of a baby.

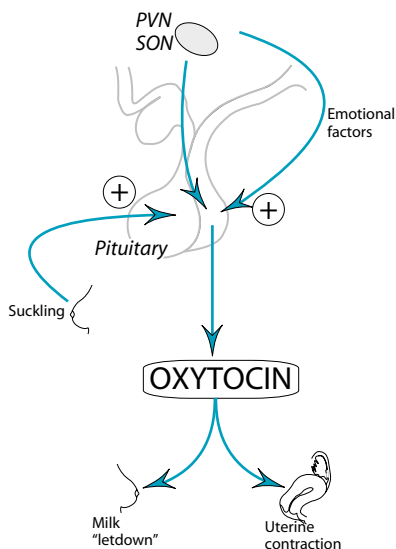


Figure 9–12 Oxytocin secretion is stimulated by emotional factors as well as mechanical stimulation of the nipple area or the cervix. Oxytocin acts on the breast to expel milk, provided that the breast has been primed by elevated estrogen levels. It also causes strong contractions of the uterus. PVN = paraventricular nucleus; SON = supraoptic nucleus.

THE PINEAL GLAND

Relevant Embryology and Anatomy of the Pineal Gland

The pineal gland is a pea-sized organ situated at the roof of the third cerebral ventricle under the posterior end of the corpus callosum (Figure 9–13). A stalk connects it to the posterior and habenular commissures. In addition to neuroglia, it contains secretory cells in close approximation to fenestrated capillaries. These cells secrete **melatonin**, which they form from **serotonin** (Figure 9–14). The pineal is large in infants and begins, in puberty, to diminish in size and to be filled with radiopaque calcium salts.

Melatonin

Synthesis of Melatonin

Melatonin is formed in the pineal gland and to some extent in the retina from the neurotransmitter serotonin, which is formed from the essential amino acid **tryptophan** (see Figure 9–14). There is a day/night rhythm in melatonin synthesis, peak levels occurring during the period of darkness. For this reason, melatonin has been called the **darkness hormone**.

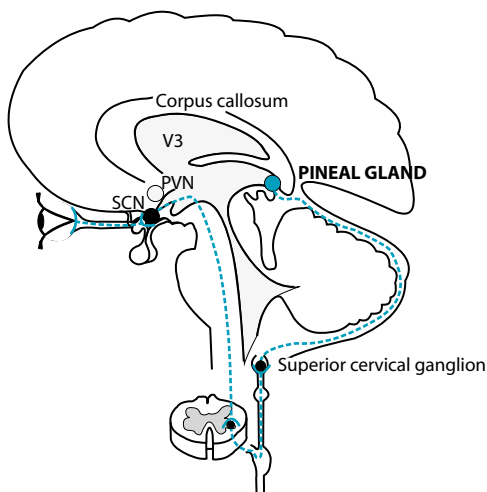


Figure 9–13 Location of the pineal gland and its innervation by autonomic nerves. PVN = paraventricular nucleus; SCN = suprachiasmatic nucleus; V3 = third cerebral ventricle.

Mechanism of diurnal variation in melatonin synthesis. The light/dark cycle of melatonin synthesis is driven by sympathetic nerves from the superior cervical ganglion (see Figure 9–13). Autonomic input derives from the retina by way of the suprachiasmatic nucleus. The effect of sympathetic nerve activity on the pineal is to increase cytosolic cAMP and that leads to increased activity of the enzyme *N*-acetyltransferase (see Figure 9–14).

Actions of Melatonin

Popular mythology ascribes wondrous effects to melatonin in (1) the cure of diseases such as cancer, high blood pressure, Alzheimer's disease, acquired immunodeficiency syndrome (AIDS), or coronary heart disease; and (2) the improvement of sleep, sexual performance, and life span. However, the only firmly established roles for melatonin are (1) its involvement in organization of daily (circadian) patterns and (2) its scavenging of free radicals.

Melatonin and biorhythms. Administration of melatonin can shift a person's sleep-wake cycle but rarely affects other biorhythms. However, the ability of melatonin to produce advances or delays in the timing of sleep patterns depends upon its time of administration.

Melatonin brings on feelings of tiredness earlier when it is administered in the late afternoon or early evening and delays sleepiness to a later time

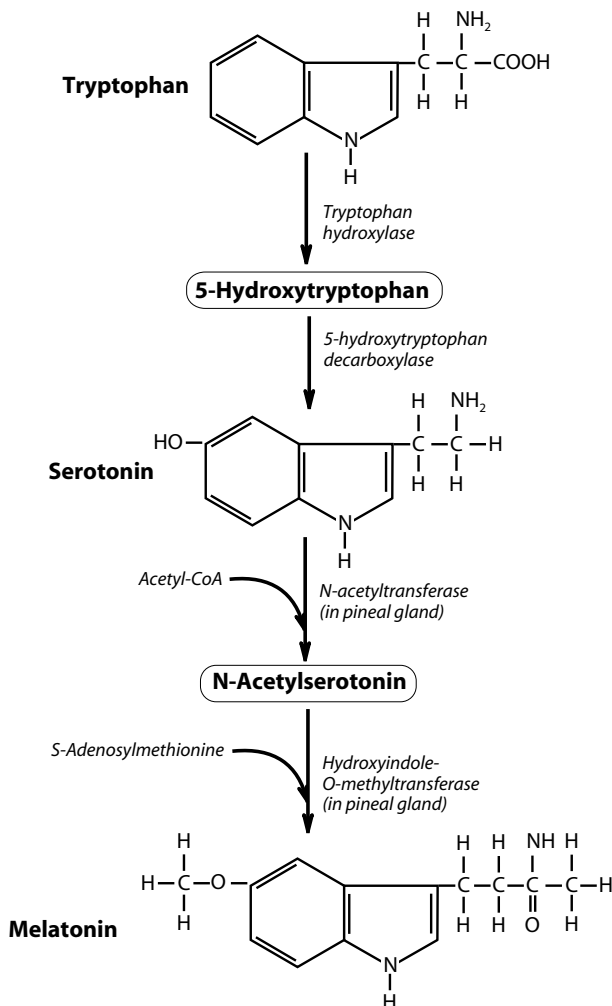


Figure 9–14 Synthesis and structure of melatonin. The pineal gland contains the enzymes *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase that are required to synthesize melatonin from serotonin. Serotonin is produced in several cells, including brain cells, from the amino acid tryptophan.

when it is administered between early morning and noon. The ability of melatonin to “reset” the body clock is the basis for its use by jet travelers, shift workers, or blind people.*

*The usual reported effects are improved sleep quality, reduced time taken to fall asleep, better daytime alertness, and quicker rate of resynchronization of melatonin and cortisol rhythms to the ambient day/night cycle.

When melatonin (at 2 to 5 mg/d) moves the sleep-wake cycle forward, then it will sometimes, but not always, advance the timing of its own internal rhythm, the timing of prolactin, and cortisol rhythms.

The biorhythm effects of melatonin are receptor mediated* and result from a change in the timing of neuronal activity in the suprachiasmatic nuclei, which are the dominant pacemakers for many biologic rhythms.

Melatonin and free radicals. Free radicals are highly reactive molecules with an unpaired valence electron. Many free radicals derive from oxygen, specifically from that small portion (less than 5%) of O₂ that is not used in mitochondrial oxidative phosphorylation but becomes semireduced species and reactive oxygen intermediates. Such free radicals are highly toxic because they inactivate or destroy cellular molecules. Melatonin can detoxify free radicals, including the most toxic member of the family, the hydroxyl radical (•OH), which is produced from hydrogen peroxide in the presence of Fe⁺⁺.

THYROID GLAND

Relevant Anatomy and Embryology of the Thyroid Gland

The thyroid gland consists of two lobes that are joined by an isthmus. It is located on the anterior surface of the trachea, at the base of the laryngeal cartilage. It is made up of irregular lobules, and each of them is made up of many **follicles**, which are the functional units of the gland. Follicles have a spheroid form (Figure 9–15) and range in diameter from 50 to 500 μm. They are lined by specialized epithelial cells, the **thyrocytes**, which synthesize **thyroglobulin** and the **thyroid hormones**. They are flat when they are inactive or large and cuboidal when they have been stimulated to activity.

Follicles constitute about 70% of the normal human thyroid gland. The remainder is connective tissue, capillaries, lymphatics, and autonomic nerves, all of which surround the follicles. Arterial blood supply derives from the upper and lower thyroid arteries and the vasculature drains into the internal jugular veins.

The thyroid contains a second endocrine system in the form of **C cells** (**parafollicular cells**). C cells are arranged around and in contact with thyrocytes (see Figure 9–15), but they do not contact the follicle lumen. C cells synthesize the hormone **calcitonin**.

*Two subtypes of melatonin receptors have been described in mammals: MEL-1A and MEL-1B. The molecular mechanisms of receptor activation may involve at least two parallel transduction pathways, one inhibiting adenylate cyclase and the other inhibiting phospholipase C. In many cases, its effect is inhibitory and requires previous activation of the cell by a stimulatory agent. Melatonin also regulates transcription factors, such as expression of c-Fos.

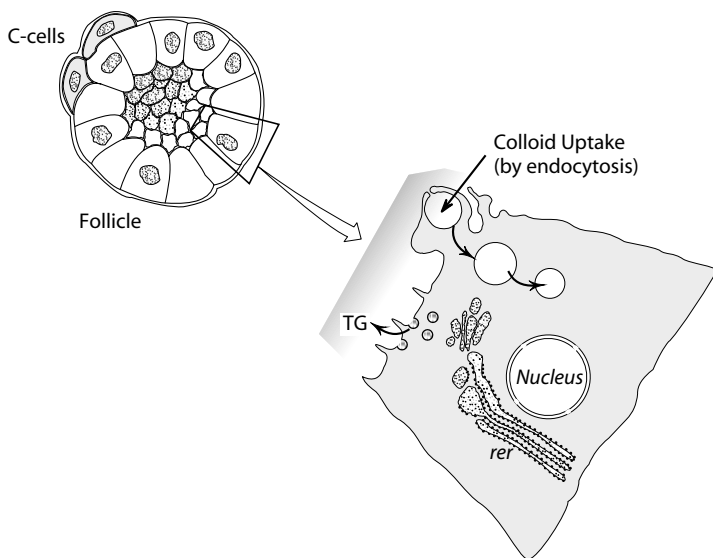


Figure 9-15 Cross-section through a spheroidal follicle in the thyroid gland. Each follicle is lined by thyrocytes. They enclose a core that is filled with colloid, a substance that is made up mostly of thyroglobulin (TG), which is secreted by the thyrocytes. Some of the thyroglobulin is iodinated to produce thyroid hormones. When thyroid hormone is needed, then thyrocytes take up colloid in droplets and process it to release free thyroid hormones.

C cells are attached to thyrocytes on the outside of follicles. C cells synthesize and release the hormone calcitonin. rer = rough endoplasmic reticulum.

The Thyroid Hormones Thyroxine (T_4) and Tri-iodothyronine (T_3)

The main secretory product of the thyroid is L-thyroxine (T_4). Some of the biologically more potent L-3,5,3'-tri-iodothyronine (T_3) is secreted as well, but most of the circulating T_3 is produced in nonthyroid tissue.

Structure of Thyroid Hormones

Thyroid hormones are iodinated forms of a molecule that consists of two residues of the amino acid tyrosine, linked by an oxygen molecule.

Synthesis, Storage, and Release of Thyroid Hormones

Thyroid hormone synthesis involves (1) uptake of iodide, (2) synthesis of thyroglobulin, and (3) assembly of iodinated tyrosine residues on the thyroglobulin backbone. A summary of these processes is shown in Figure 9-16.

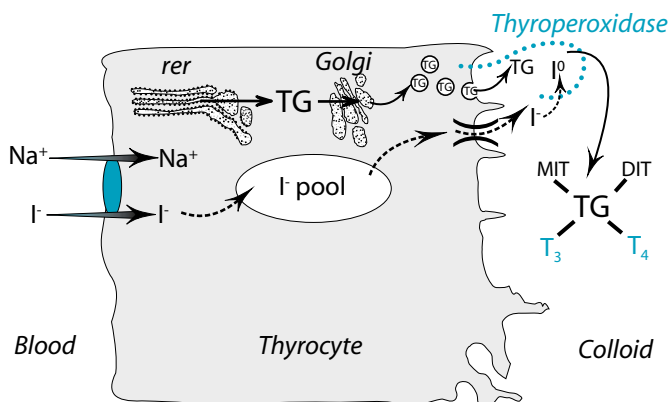


Figure 9–16 Synthesis and storage of thyroid hormone includes thyroglobulin (TG) synthesis, iodide (I^-) transport, and iodination of thyroglobulin. TG is synthesized in the rough endoplasmic reticulum (rer) and packaged within the Golgi apparatus into secretory vesicles. Iodide is co-transported with Na^+ into the thyrocyte at the basolateral membrane, enters the intracellular I^- pool, and leaves passively, down an electrochemical gradient mostly through a selective I^- channel in the apical membrane. The enzyme thyroperoxidase directs oxidation of I^- , tyrosine iodination to form MIT and DIT and oxidative condensation of either DIT pairs to form $TG-T_4$, MIT plus DIT to form $TG-T_3$ or DIT plus MIT to form TG -(reverse- T_3). Iodinated tyrosine residues remain attached to thyroglobulin by peptide linkage and are stored in that form in the colloid. DIT = di-iodotyrosine; I^- = iodide; I^0 = oxidized iodide; MIT = mono-iodotyrosine.

Iodine metabolism. Availability of iodine, an essential dietary component, is the rate-limiting step in the formation of thyroid hormones. Ingested iodine is converted to iodide (I^-) in the GI tract and enters the body iodide pool, which includes the extracellular fluid. The external membrane of thyrocytes absorbs iodide (I^-) by secondarily active Na^+ -co-transport (Figure 9–16). This process is called **iodide trapping**. It adds I^- to an intracellular pool that also receives I^- liberated during thyroid hormone secretion (Figure 9–17). I^- leaves on the apical side to enter the colloid by passive mechanisms generally through a high-affinity selective I^- channel (see Figure 9–16) and to some extent through a low-affinity, nonselective anion channel.

Thyroglobulin synthesis. Thyroglobulin is synthesized in thyrocytes under direction of a gene located on chromosome 8. Its mRNA production is stimulated by TSH and inhibited by **epidermal growth factor**. Insulin and several thyroid transcription factors regulate expression of the TG gene. The finished, glycosylated, folded, and vesicle-enclosed protein is secreted into the colloid by exocytosis (see Figure 9–16).

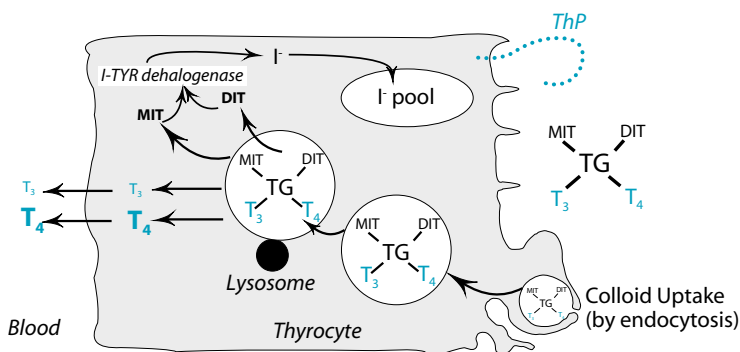


Figure 9-17 Upon stimulation by thyroid-stimulating hormone, the thyrocyte takes up vesicular droplets of colloid by endocytosis. These colloidal vesicles establish contact with lysosomes so that lysosomal enzymes can break the peptide linkages to release T_4 , T_3 , $r-T_3$, MIT, and DIT. The iodinated tyrosines MIT and DIT are deiodinated so that liberated iodine can be recycled. T_4 , T_3 , and $r-T_3$ are released into the circulation, T_4 being the dominant secretory product. DIT = di-iodotyrosine; I-TYR dehalogenase = iodotyrosine dehalogenase; MIT = mono-iodotyrosine; T_3 = L-3,5,3'-tri-iodothyronine; T_4 = L-thyroxine; TG = thyroglobulin; ThP = thyroperoxidase.

Thyroglobulin is rich in tyrosine residues, and many of them are exposed at the surface of the molecule and available for iodination. However, only four iodinated tyrosine residues, located at the ends of the TG molecule in the form of mono-iodotyrosine (MIT) or di-iodotyrosine (DIT), contribute to the formation of thyroid hormones, T_3 and T_4 . T_3 , T_4 , DIT, and MIT are all attached to thyroglobulin, and this complex is stored as colloid in the core of the thyroid follicles.

Thyroglobulin iodination: Once I^- has diffused to the follicular side of the thyrocyte apical membrane, it is oxidized to **iodine** (I^0) and I^+ by means of hydrogen peroxide (H_2O_2), which is produced with the help of membrane-bound **NADPH* oxidase**. Within seconds of being formed, I^0 is transferred to the 3 position (see Figure 9-18) of a tyrosine residue in **thyroglobulin** to form MIT under the control of another membrane-bound colloidal enzyme, **thyroperoxidase**. These processes of I^- oxidation and binding to tyrosine are called **I^- organification** and are sketched in Figure 9-16.

Mono-iodotyrosine remains bound, by peptide linkage, to a thyroglobulin molecule and is then iodinated in the 5 position to form DIT, and it also remains bound to thyroglobulin. This step is followed by an oxidative con-

*NADPH = reduced nicotinamide adenine dinucleotide phosphate.

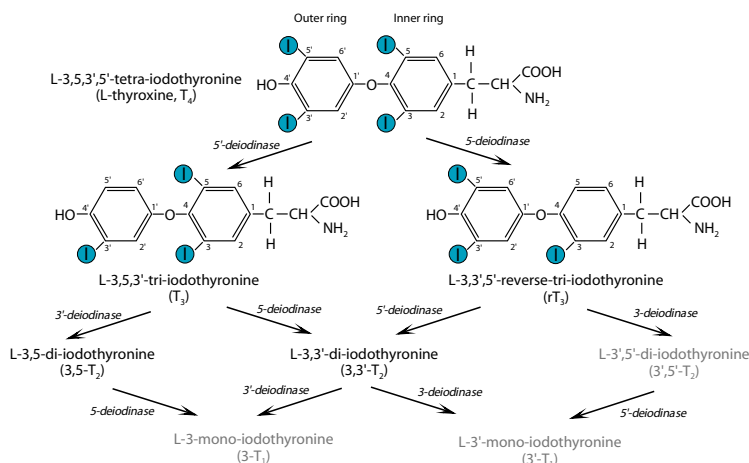


Figure 9-18 Structure and metabolism of T_4 (L-3,5,3',5'-tetraiodothyronine). It is derived from a pair of tyrosine residues that are linked by oxygen. T_4 is deiodinated mostly in peripheral target cells to T_3 or reverse- T_3 (rT_3). T_3 is 5 to 10 times more potent than T_4 . Reverse- T_3 , 3,5- T_2 and 3,3'- T_2 have 1/100th to 1/10th the biologic potency of T_4 , and the de-iodination products 3',5'- T_2 , 3- T_1 , and 3'- T_1 have no biologic activity.

densation of two DIT molecules to form alanine plus TG- T_4 .^{*} Iodide oxidation and all subsequent steps to DIT condensation are under the control of **thyroperoxidase**. Condensation of MIT and DIT also occur, but to a much lesser extent, and this forms TG- T_3 and TG-(reverse- T_3) to an even lesser extent.

Thyroperoxidase: This enzyme is shaped like a question mark (see Figure 9-17). Its carboxyl terminal is located in the thyrocyte cytoplasm and almost all of its 933 amino acids protrude into the follicular lumen. It is found only in thyrocytes and controls (1) oxidation of I^- , (2) tyrosine iodination, and (3) oxidative condensation of DIT pairs to form TG- T_4 , MIT plus DIT to form TG- T_3 , or DIT plus MIT to form TG-(reverse- T_3).

Thyroxine (T_4) and tri-iodothyronine (T_3). TG- T_4 and the little TG- T_3 that has been formed are released into the follicular lumen and are stored as **colloid** until secretion is stimulated by TSH. Such stimulation causes colloid that is in immediate contact with the thyrocyte apical membrane to be ingested by endocytosis (see Figure 9-17). The colloid-filled vesicles merge and fuse with lysosomes and are digested by proteolytic enzymes. This yields MIT, DIT, T_4 , T_3 , and a remnant of amino acids (see Figure 9-17). Mono-

^{*}An alternative process has been proposed, namely, that one DIT molecule is detached from TG and undergoes a cascade of reactions before being attached to a second DIT that is still attached to TG.

iodotyrosine and DIT are deiodinated by iodotyrosine dehalogenase, which does not attack T_3 or T_4 . The resultant I^- and tyrosine as well as other amino acid remnants are recycled.

Regulation of Thyroid Hormone Synthesis and Secretion

An overview of thyrocyte regulation is shown in Figure 9–5.

Regulation by thyroid-stimulating hormone. Thyroid-stimulating hormone is the primary regulator of thyroid function and growth. Its effects are mediated by an adenylate cyclase–activating serpentine membrane receptor. This receptor is expressed mostly in thyrocytes but has been found in adipocytes and retro-orbital tissue of patients suffering from **Graves’ disease**. Thyroid-stimulating hormone stimulation of thyrocytes has a variety of effects. They include the following:

1. An immediate increase in passive I^- transport into the colloid
2. Increased synthesis and insertion of Na^+I^- co-transporters into the basolateral thyrocyte membrane
3. Increased thyroperoxidase synthesis and increased I^- organification
4. Increased exocytosis of thyroglobulin and increased endocytosis of colloid (see Figures 9–16 and 9–17)
5. Increased lysosomal degradation of colloid droplets (see Figure 9–17) and, hence, increased secretion of T_3 and T_4
6. Increased thyroid growth

Regulation by thyrotropin-releasing hormone. Although TRH is found diffusely throughout the brain and may function as a neurotransmitter, its highest concentrations are found in the hypothalamus and the median eminence. It is delivered from the median eminence to the anterior pituitary, where it interacts primarily with high-affinity receptors that are G protein coupled to the phospholipase C system. Such interaction causes an increase in cytosolic $[Ca^{++}]$. Thyroid-stimulating hormone stimulation of thyrotropes increases TSH synthesis and secretion in inverse proportion to cytosolic levels of I^- .*

Transport and Metabolism of Thyroid Hormones

Transport of thyroid hormones in blood. T_4 and T_3 are secreted to the extracellular space in a ratio of 9:1. Once in the circulation, most thyroid hormone is reversibly bound to four carrier proteins (Table 9–5).

*This feedback inhibition is named the Wolff-Chaikoff effect.

Table 9–5

Forms of Thyroid Hormones in Plasma

Form	Bound to	Biologic Half-Life (days)	Plasma Concentration (nmol/L)		Percent of Circulating Hormone	
			T ₃	T ₄	T ₃	T ₄
Free	—		0.004	0.02	0.2	0.02
Protein bound	TBG	5			70–75	70–75
	TTR	2	2.3*	103*	<1	15–20
	Albumin	13			25–30	5–10
	Lipoproteins				<6	<3

TBG = thyroxine-binding globulin; TTR = transthyretin, also known as thyroxine-binding prealbumin (TBPA).

*total for all protein bound

Free T₃ and T₄: Free T₃ and T₄ are the active forms of thyroid hormone. They are regulated by TSH and peripheral metabolism and are in equilibrium with the pools of bound T₃ and T₄. T₃ is 5 to 10 times more potent than T₄. Most of it is produced in the periphery by deiodination of T₄ (see Figure 9–18).

Thyroxine-binding globulin (TBG): Thyroxine-binding globulin is synthesized in the liver. Its plasma levels are increased physiologically by estrogens and decreased by androgens and glucocorticoids. It has high binding affinity for both T₃ and T₄.

Transthyretin (TTR): This protein, formerly called **thyroxine-binding prealbumin** (TBPA), is synthesized mostly in the liver but is also found in the cerebrospinal fluid because of synthesis in the **choroid plexus**. It binds T₄ much more effectively than it binds T₃. It also binds retinol-binding protein.*

Albumin: Although albumin has low binding affinity for thyroid hormones, it has high carrying capacity by virtue of its high plasma concentration.

Lipoproteins: Some thyroid hormones are carried in association with lipoproteins, mostly high-density lipoprotein, and T₄ uptake into target cells may be in association with lipoproteins.

*The retinols are the A vitamins.

Thyroid hormone activation and deactivation. The daily hormone output of the thyroid gland is 93% T_4 . Only 5% is in the form of the biologically more potent T_3 and 2% is as the minimally active reverse- T_3 (see Figure 9–18). Only a small fraction of the secreted T_4 is used in endocrine reactions. Most of it follows one of three pathways:

1. Twenty percent is deactivated in the liver or kidney and the products are excreted in bile or urine.
2. Thirty-three percent is “activated” by conversion to T_3 with the help of 5'-deiodinase.
3. Forty-five percent is converted to reverse- T_3 by 5-deiodinase.

Deiodinases: Deiodination takes place to some extent within the thyroid but mostly in the kidney and liver. It is dominated by **deiodinase** isoforms that are directed at the 5' position in the outer ring or the 5 position in the inner ring (see Figure 9–18).

Actions of Thyroid Hormones

Interactions of thyroid hormones with target cells. Thyroid hormones enter target cells by (1) diffusion (they are lipophilic), (2) association with lipoproteins, and (3) specific carrier mechanisms. T_4 is then deiodinated to form the more active T_3 , and T_3 reaches the nucleus, possibly by a transport system, and binds to a nuclear receptor. Each ligand-coupled thyroid hormone receptor forms a dimer either with another ligand-coupled thyroid hormone receptor or with one of a number of **thyroid receptor auxiliary proteins** (TRAP).*

Nuclear receptors for thyroid hormone: Thyroid receptors are encoded by two separate genes, designated $TR\alpha$ and $TR\beta$, located, respectively, on chromosomes 17 and 3, and resulting in several nuclear T_3 -binding proteins and nonbinding homologues (Table 9–6). Thyroid hormone receptors, unlike steroid receptors, bind to DNA response elements, even in the absence of ligand. Unliganded thyroid hormone receptors act as repressors of gene function, whereas liganded receptors promote transcription.

Biologic effects of thyroid hormones. Thyroid hormones exert many effects (Figure 9–19). Many are caused not simply by activation of the T_3 nuclear receptor but by subtle influences arising from (1) different receptor variants (see Table 9–6), (2) variety in the interactions between ligand-

*The thyroid-related auxiliary proteins include retinoic acid receptors and 9-cis-retinoic acid receptors.

Table 9-6

Thyroid Receptor Proteins and Homologues

Protein	Binds T_3 ?	Tissue Distribution
TR β_2	Yes	Mainly pituitary
TR β_1	Yes	Ubiquitous
TR α_1	Yes	Brain, skeletal muscle. Especially important for normal cardiac function
TR α_2	No	Most organs except liver
TR α_3	No	

receptor complexes either with other ligand-receptor complexes or with TRAPs, (3) modulation of the ligand-receptor complex by proteins like **c-erb A** and **rev erb A α_2** , (4) influence of the underlying basal thyroid state, and (5) cooperative effects of hormones, such as the catecholamines or growth hormone.

Effects of thyroid hormones on development and growth: In fetal life and the early postnatal period, thyroid hormones promote body growth and normal development of nervous tissue including (1) promotion of dendrite branching, (2) proliferation of axons, (3) formation of synapses, and (4) myelination and growth of glia, cerebellar cortex, and cerebral cortex. Absence of thyroid hormones causes **cretinism**, a disease characterized by growth disturbances and severe mental retardation.

From birth onward, thyroid hormones stimulate development, linear growth, and maturation of bone, as well as chondrocyte activity. These actions result from modulation of (1) growth hormone secretion and somatomedin synthesis and (2) somatomedin action at the epiphyseal growth plate in bone.

Effects of thyroid hormones on energy metabolism: In adults, the main physiologic role of thyroid hormones is the regulation of energy metabolism. Thyroid hormones increase metabolic rate, O_2 consumption, and heat production.

Some, but not all, of the metabolic effects are secondary to a T_3 -mediated increase in Na^+ - K^+ -ATPase activity, which drives active transport of Na^+ and K^+ , the main energy-consuming process of the body.

Thyroid hormones and carbohydrate metabolism: Carbohydrate metabolism is increased at several levels by thyroid hormones because they control key enzymes of glycolysis and oxidative metabolism. As a result, they increase (1) intestinal carbohydrate absorption and whole-body glucose

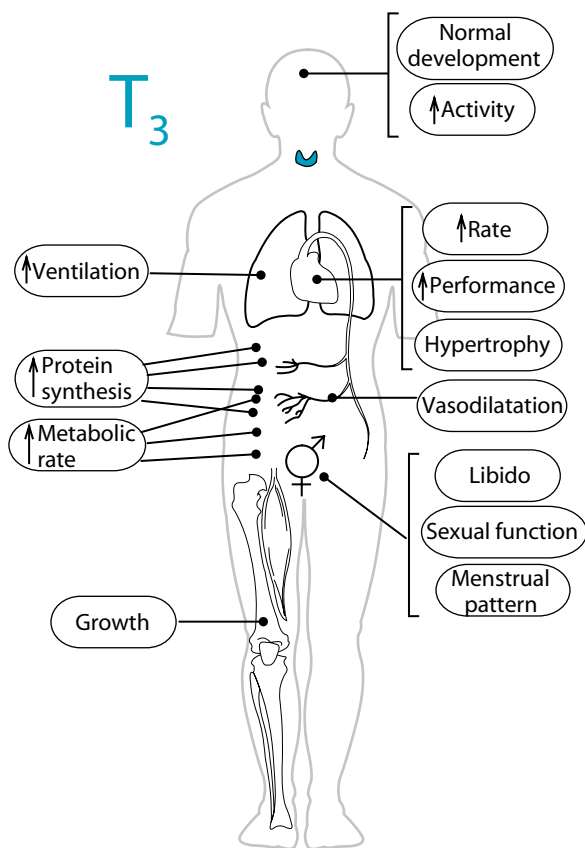


Figure 9-19 Summary of thyroid hormone effects.

turnover, (2) glucose utilization (particularly in muscle and adipose tissue), and (3) hepatic glycogenolysis.

Thyroid hormones and fat metabolism: Thyroid hormones stimulate cholesterol synthesis, its conversion to bile, bile secretion, and formation of low-density lipoprotein (LDL) receptors in the liver. The net effect is a decrease in serum LDL cholesterol. Triglyceride turnover and plasma levels are only modestly affected, but body fat stores will eventually be depleted in prolonged hyperthyroidism. Some of this is due to thyroid hormone-mediated increases in the lipolytic actions of other hormones (catecholamines, glucagons, and ACTH).

Thyroid hormones and protein metabolism: Protein degradation is stimulated in hyperthyroidism because of increased availability of proteolytic enzymes. This results in skeletal muscle wasting. Cardiac muscle, on the other hand, shows increased protein content in hyperthyroidism because thyroid hormones promote cardiac myosin synthesis.

Cardiovascular and respiratory effects of thyroid hormones: Thyroid hormones have a variety of cardiovascular and secondary respiratory effects. They

- increase the number and affinity of cardiac β -adrenoreceptors. This increases the chronotropic and inotropic effects of catecholamines and causes both increased heart rate and increased cardiac performance;
- change the balance of cardiac muscle isoforms in that they increase synthesis of α -myosin heavy chain* and inhibit synthesis of β -myosin heavy chain;
- increase expression of sarcolemmal Ca^{++} -ATPase; and
- decrease the barrier function of capillary endothelial cells and, thereby, promote extravasation of albumin and edema formation.

The functional cardiovascular effects of increased thyroid hormone levels are increased cardiac output and decreased total peripheral resistance (arising from both enhanced β -adrenergic activity and cutaneous vasodilatation, which is a reflex response to increased heat production and body temperature). Thyroid hormones also increase ventilation. This effect is probably a compensatory response to the metabolic effects that lead to increased O_2 consumption.

In the elderly, hyperthyroidism is often associated with tachyarrhythmias, such as atrial fibrillation.

Central nervous effects of thyroid hormones: The importance of thyroid hormones to normal fetal nervous development is included in the description of their role in development and growth. In addition,

- thyroid hormones are required during infancy for normal intellectual development;
- hyperthyroid young individuals show central nervous symptoms that include diffuse anxiety, emotional lability, extreme nervousness, and frequent movement†;
- hyperthyroid individuals of any age show increased perception of hunger and thirst, increased density and affinity of β -adrenoreceptors, and decreased reaction time of somatic nervous reflexes, such as the Achilles tendon reflex‡; and
- hypothyroid individuals show decreased mental performance, impaired memory, and personality changes.

* α -MHC is dominant in adult ventricles. It has more ATPase activity than does β -MHC.

†In young thyrotoxic individuals, nervous symptoms dominate the clinical picture. In older thyrotoxic individuals, cardiovascular effects and symptoms of muscle weakness dominate.

‡Ankle jerk in response to tapping of the Achilles tendon.

Endocrine effects of thyroid hormones: Thyroid hormones affect a variety of hormone systems. They

- potentiate the actions of insulin in the promotion of glycconeogenesis and glucose utilization;
- alter menstrual patterns in that lack of thyroid hormone is associated with excessive and frequent menstrual bleeding, whereas excess thyroid hormone causes reduction or cessation of menstrual bleeding; and
- alter sensitivity to catecholamines by increasing the number and affinity of β -adrenergic receptors.

Effects of thyroid hormones on skin and hair: Normal epidermal and hair follicle functions require the modulating influence of thyroid hormones on the secretion of fibronectin, collagen, and glycosaminoglycans. Hypothyroid individuals have dry hair and skin.

Effects of thyroid hormones on the GI tract: Thyroid hormones increase GI motility to the extent that hyperthyroidism is often associated with frequent bowel movements and diarrhea, whereas hypothyroidism is associated with reduced esophageal peristalsis, gastroesophageal reflux, and constipation.

Effects of thyroid hormones on the kidney: Hyperthyroid states are accompanied by (1) increased renal blood flow and glomerular filtration rate, which may be secondary to increased cardiac output, and (2) increased transport capacity of the tubular epithelium, which may arise from thyroid-mediated increases in Na^+ - K^+ -ATPase activity.

Calcitonin

Calcitonin is synthesized in thyroid C cells (see Figure 9–15). It decreases extracellular Ca^{++} by inhibiting bone resorption.

Structure of Calcitonin

Calcitonin is a 32-amino acid peptide with a small loop that is formed by a disulfide bridge at its carboxy terminal. It is transcribed from a gene that is also the basis for **calcitonin gene-related peptide** (CGRP).

Synthesis and Secretion of Calcitonin

C cells (parafollicular cells) are stimulated primarily by elevated levels of plasma $[\text{Ca}^{++}]$ but also by estrogens, dopamine, β -adrenergic agonists, gastrin, cholecystokinin, glucagon, and secretin. They are inhibited by low plasma $[\text{Ca}^{++}]$.

Actions of Calcitonin

Calcitonin lowers extracellular $[Ca^{++}]$ by inhibiting bone resorption and promoting urinary Ca^{++} excretion.

Its long-term effects on serum Ca^{++} are small in adult humans because such effects trigger compensatory changes in osteoblastic activity and **parathyroid hormone** secretion.

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide is formed in nervous tissue. Its physiologic function is not yet certain. Its localization in peripheral autonomic nerves suggests a neurotransmitter function. It is also thought to participate in cardiovascular regulation as the neurotransmitter in vasodilator peptidergic nerves and as the transmitter responsible for the “flare” that is caused by vasodilatation in the axon reflex.

THE PARATHYROID GLANDS

Anatomy of the Parathyroid Glands

The human parathyroid glands are four pill-sized structures, embedded in the upper and lower poles of the posterior aspect of the thyroid gland. They contain two distinct cell populations. The smaller cells, named **chief cells**, have the appearance of secretory cells in that they have a prominent rough endoplasmic reticulum and Golgi apparatus as well as an abundance of secretory granules. The larger cells are named **oxyphil cells** and are characterized by large numbers of mitochondria.

Parathyroid Hormone

Structure of Parathyroid Hormone

Human parathyroid hormone (PTH) is a linear polypeptide of 84 amino acids.

Synthesis and Secretion of Parathyroid Hormone

The chief cells synthesize a 115–amino acid **pre-pro-PTH** that is cleaved in the endoplasmic reticulum to form the 90 residue **pro-PTH**, which is reduced in the Golgi apparatus to PTH, the main secretory product of these cells.

Regulation of secretion. The major stimulus for PTH secretion is low plasma $[Ca^{++}]$, and it is directly inhibited by elevated levels of 1,25-dihydroxycholecalciferol, the biologically active form of vitamin D (Figure 9–20).

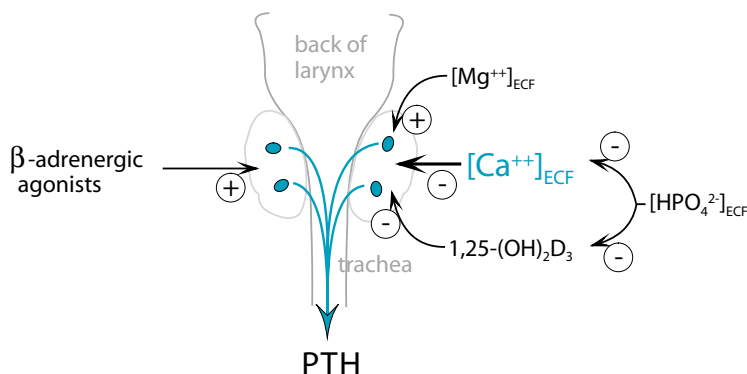


Figure 9–20 Regulation of parathyroid hormone (PTH) secretion. The parathyroid glands are located at the back of the thyroid. They are stimulated most strongly by low extracellular Ca^{++} concentration. The diagram should be interpreted to show that elevated $[Ca^{++}]$ inhibits PTH secretion. Extracellular $[Mg^{++}]$ promotes PTH while $1,25-(OH)_2D_3$ (the active form of vitamin D) inhibits PTH. Extracellular phosphate, which exists mostly in the HPO_4^{2-} form, has no direct effect on PTH secretion but does act via influences on vitamin D and extracellular $[Ca^{++}]$. ECF = extracellular fluid.

Plasma levels of Ca^{++} are sensed by a serpentine membrane receptor that is coupled to phospholipase C through a G protein. The details of the steps that lead from decreased extracellular $[Ca^{++}]$ to increased PTH secretion are not yet known. Inhibition by vitamin D ($1,25-(OH)_2D_3$) is by activation of its nuclear receptor and subsequent inhibition of mRNA for pre-pro-PTH.

Plasma phosphate has no direct effect on PTH secretion. Nevertheless, increased $[HPO_4^{--}]$ leads to increased PTH secretion by secondary mechanisms that depend partly on a fall in plasma $[Ca^{++}]$ and partly on inhibition of vitamin D activation.

Actions of Parathyroid Hormone

The major physiologic role of PTH is homeostasis of body calcium and phosphate. Although there are three types of membrane receptors for PTH, most effects are brought about by interaction with the PTH/PTH-related protein (PTHrP) receptor in bone and kidney. It binds the amino end of either PTH or PTH-related protein (PTHrP), activates both adenylate cyclase and phospholipase C, and leads to increased $[cAMP]$, $[IP_3]$, and $[DAG]$.

Parathyroid Hormone actions in bone. Parathyroid hormone acts to increase bone resorption, and this is an effective mechanism for

counteracting hypocalcemia because 99% of body calcium is located in bone. Parathyroid hormone receptors are located in the plasma membrane of **osteocytes** and **osteoblasts**. Early PTH action can be observed within 2 to 3 hours and initially takes the form of increased Ca^{++} conductivity of the osteocyte membrane and consequent Ca^{++} influx into osteocytes from the surrounding lacunal fluid. The more delayed and pronounced action of PTH on bone is by paracrine stimulation of **osteoclasts**, which have no PTH receptors themselves (see Figure 13–11). Parathyroid hormone–mediated factors, generated in osteocytes or osteoblasts, activate existing osteoclasts and promote formation of new osteoclasts. Increased osteoclast activity dissolves bone and increases serum $[\text{Ca}^{++}]$.

Parathyroid Hormone actions in the kidney. Parathyroid hormone (1) stimulates renal HPO_4^- excretion by suppressing HPO_4^- reabsorption in the proximal nephron, (2) suppresses renal Ca^{++} excretion by increasing Ca^{++} reabsorption in the distal nephron, and (3) stimulates vitamin D activation by increasing the activity of **1α -hydroxylase**, the enzyme that converts the inactive precursor, 25-(OH) D_3 to the active form, 1,25-(OH) $_2\text{D}_3$.

Parathyroid Hormone actions in the gastrointestinal tract. Parathyroid hormone has no direct effect on intestinal transport of Ca^{++} or HPO_4^- . However, PTH-mediated increases in plasma levels of 1,25-(OH) $_2\text{D}_3$ cause increased intestinal reabsorption of both minerals.

Metabolism of Parathyroid Hormone

The plasma half-life of PTH is nearly 20 minutes. It is cleaved in the liver by **Kupffer's cells** into two fragments, only one of which retains biologic activity.

Parathyroid Hormone–related Protein

Parathyroid hormone-related protein is a 140–amino acid peptide that is synthesized mostly in the breasts but also in several other tissues. It has PTH activity, even though it is larger than PTH and is encoded by a gene on a different chromosome (chromosome 12) from that which encodes PTH (chromosome 11). It binds to the PTH/PTHrP receptor,* which is found in the skin, hair follicles, breast, and developing cartilage.

The main biologic function of PTHrP is promotion of normal skeletal growth. This occurs by promotion of chondrocyte proliferation and inhibition of their mineralization. Its function in the breast is not known yet.

*The PTH/PTHrP receptor is a G protein–coupled membrane receptor whose activation increases cytosolic $[\text{cAMP}]$ as well as $[\text{IP}_3]$ and $[\text{DAG}]$.

THE ADRENAL CORTEX

Anatomy and Embryology of the Adrenal Cortex

The adrenal cortex is the outer shell of the adrenal glands, is located under the adrenal capsule, and constitutes between 80 and 90% of the adrenal glands. It is of mesenchymal origin and produces steroid hormones from each of its three zones. The zones differ histologically (Figure 9–21) and functionally in that different steroid hormones are synthesized in each.

- The **zona glomerulosa** lies under the capsule and consists of round or horseshoe-shaped cells. The dominant secretory product is mineralocorticoids, such as **aldosterone**.
- The **zona fasciculata** is the thickest layer. Its cells are polygonal and lie in long, parallel, vertical bands. They synthesize **glucocorticoids** and precursors for the **androgens**.
- The **zona reticularis** lies next to the medulla. Its cells are small and irregularly arranged. They synthesize predominantly **androgens** and some **estrogens**.

The adrenal has a rich blood supply. Capillaries originate partly from the **suprarenal arteries** and partly from **penetrating arterioles**. The cap-

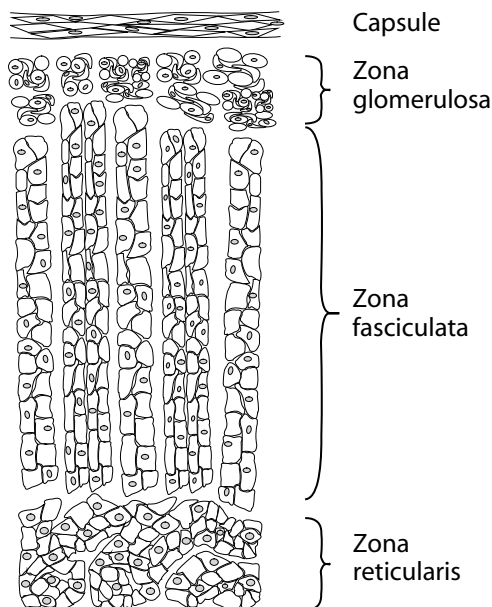


Figure 9–21 Sketch of the histology of the adrenal capsule and the underlying layers of the cortex. The adrenal medulla lies under the zona reticularis and is not shown.

illary plexus of the suprarenal arteries supplies the capsule and also enmeshes the zona glomerulosa cells. They continue on to the zona fasciculata, zona reticularis, and medulla before they drain into a central medullary vein. Because of this vascular arrangement, steroid hormones are transported toward the medulla, and their concentration increases progressively from cortex to medulla.

Penetrating arterioles are fewer in number. They penetrate directly from the capsule to the medulla and break up there into a capillary bed.

Synthesis of Steroid Hormones

Steroids are synthesized from cholesterol, which derives mostly from circulating LDL. Adrenocortical cells are especially rich in LDL receptors. The receptors take up cholesterol into the cytosol, lysosomal enzymes hydrolyze the receptor-cholesterol complex, and cholesterol is then stored as **cholesteryl esters** in lipid droplets. When free cholesterol is needed, it is extracted from the esters by **cholesterol ester hydrolase** and transported out of the droplet to mitochondria by the carrier protein **sterol carrier protein 2**. In the mitochondria, the first step is a reaction in which cholesterol is converted to **isocaproaldehyde** and **pregnenolone** with the help of **side chain cleavage cytochrome P-450** ($P-450_{sc}$) (Figure 9–22) that is embedded in the inner mitochondrial membrane. This first step is also the rate-limiting step in steroid synthesis. $P-450_{sc}$ is induced when a controlling messenger acts on the cell synthesizing the steroid hormone.

The subsequent steps in steroid synthesis occur mostly outside the mitochondria, in the smooth endoplasmic reticulum, but 11-hydroxylation, the last step in the formation of corticosterone and cortisol (see Figure 9–22), takes place only inside mitochondria.

Although the adrenals produce a large number of steroids, only five of them are secreted in physiologically significant quantities: the androgens **dehydroepiandrosterone** (DHEA) and **androstenedione**, the glucocorticoids **corticosterone** and **cortisone**, and the mineralocorticoid **aldosterone** (see Figure 9–22). The androgens and glucocorticoids are produced in both the zona fasciculata and zona reticularis. Aldosterone is produced only in the zona glomerulosa because it alone has the enzymes required for action on the carbon in the 18 position (see Figure 9–22). The zona glomerulosa lacks 17 α -hydroxylase and is, therefore, not capable of forming androgens or 17-hydroxy steroids, such as cortisol.

Mineralocorticoid Synthesis

Deoxycorticosterone and aldosterone are normally secreted in equal amounts, exist mostly in the free form rather than being bound to plasma proteins and are, therefore, quickly metabolized (in the liver). Their plasma

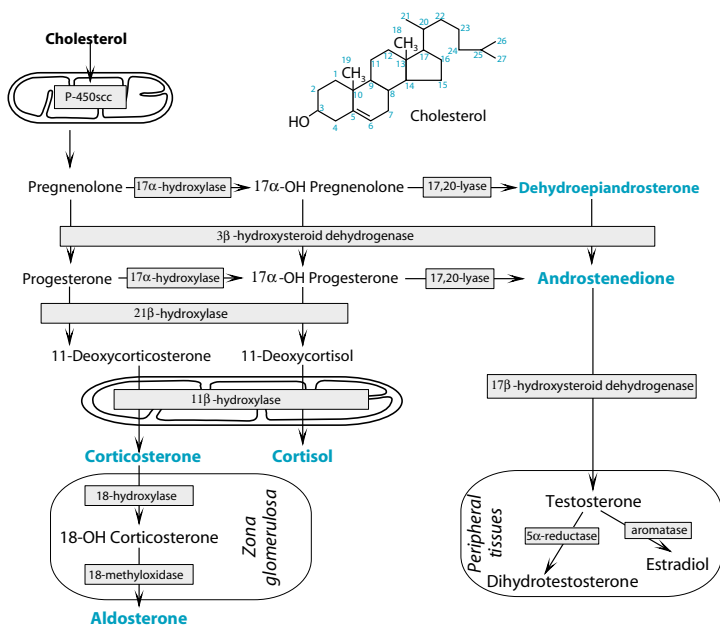


Figure 9-22 Synthesis of steroid hormones from their precursor, cholesterol, which is a 21 carbon molecule whose nucleus is the cyclopentanoperhydrophenanthrene structure. The convention for numbering the carbon atoms is shown in color. The letters α and β refer, respectively, to projections below and above the plane of the applicable steroid ring.

The first step is conversion of cholesterol to pregnenolone with the help of the inner mitochondrial membrane cytochrome P-450 side chain-cleavage enzyme, cholesterol desmolase (20, 22 desmolase). Pregnenolone then diffuses out of the mitochondria and enters the smooth endoplasmic reticulum where some of it is dehydrogenated to form progesterone while the remainder is hydroxylated to form 17α -OH pregnenolone. Some of the 17α -OH pregnenolone is converted to dehydroepiandrosterone (DHEA) and the remainder becomes 17α -OH progesterone. Progesterone and 17α -OH progesterone are hydroxylated in a reaction that is catalyzed by 21β -hydroxylase and yields 11-deoxycorticosterone and 11-deoxycortisol. Some 17α -OH progesterone is converted to androstenedione, as is some of the DHEA. The bulk of the DHEA is converted to DHEA sulfate by the enzyme adrenal sulfokinase (not shown).

Both 11-deoxycorticosterone and 11-deoxycortisol move back into the mitochondria where they are hydroxylated to form corticosterone and cortisol. Corticosterone and cortisol are end products in the zona fasciculata and zona reticularis. However, zona glomerulosa cells contain the enzymes that allow conversion of corticosterone to the end product aldosterone.

Androstenedione is a precursor of testosterone, which is produced in several peripheral tissues by the enzyme 17β -hydroxysteroid dehydrogenase. P-450_{scc} = cytochrome P-450 side chain cleavage enzyme.

half-life is only 10 to 20 minutes. Deoxycorticosterone has negligible mineralocorticoid potency, compared with aldosterone.

Glucocorticoid Synthesis

Corticosterone possesses glucocorticoid activity, but its plasma concentration in humans is generally too low for significant biologic effects. Therefore, cortisol is the dominant glucocorticoid.

Most plasma cortisol is bound to **corticosteroid-binding globulin** (also called **transcortin**), whose synthesis (by the liver) is stimulated by estrogen. Globulin-bound cortisol is biologically inactive but acts as a pool from which free cortisol can be drawn for biologic activity. Cortisol is an especially important adrenal product because it provides feedback inhibition of ACTH synthesis (Figure 9–23) and because its presence is important for activation of **phenylethanolamine-N-methyltransferase**, the adrenal medullary enzyme that promotes conversion of norepinephrine to epinephrine.

Androgen Synthesis

The principal androgens secreted by the adrenals are **dehydroepiandrosterone** and **androstenedione** (see Figure 9–22). Their major function is as precursors of testosterone, which is produced in several peripheral tissues by the enzyme **17 β -hydroxysteroid dehydrogenase** (see Figure 9–22). In adult males, the adrenals represent a minor source of androgens when their output is compared with that of the testes, which synthesize it from cholesterol in the Leydig cells. In females, the adrenal cortex is a more important source of androgens because the ovaries produce only minor amounts.

Regulation of Steroid Synthesis and Secretion

Adrenal cortical steroids are not stored but are secreted immediately after synthesis. Two responses are observed, and they can be separated on the basis of time. The acute response to a stimulus involves mostly the regulation of substrate supply in that it is mediated by quickly acting effects on the activity of **cholesteryl ester hydrolase**, the enzyme that controls liberation of cholesterol from its intracellular esterified storage form. The effects are achieved mostly by way of changes in cytosolic $[Ca^{++}]$ and phosphorylation of protein kinases A or C. Although an increase in free cholesterol would appear to increase synthesis of all steroid hormones, specificity of outcome is derived from localization of receptors to each of the three cortical layers.

All acute responses occur on a background of chronic regulation by ACTH. Adrenocorticotrophic hormone does bring about a weak level of acute changes in cholesterol supply, but its major function is the maintenance of optimal levels of **steroid hydroxylases** and related enzymes. It operates through a membrane receptor to increase cAMP and then mRNA for enzymes of the steroidogenic pathway, particularly the enzymes of the **cytochrome P-450 superfamily**. These include the mitochondrial enzymes P-450_{sc} (see Fig-

ure 9–22) and P-450_{11 β} (11 β -hydroxylase) as well as the cytosolic enzymes, P-450_{17 α} (17 α -hydroxylase), P-450_{C21} (21 β -hydroxylase), and other P-450 species.

Regulation of Mineralocorticoid Synthesis

Under normal physiologic conditions mineralocorticoid synthesis is modulated mostly at the level of cholesterol conversion to pregnenolone (see Figure 9–22). However, it does require an up-regulation of the enzymes involved in converting corticosterone to aldosterone and that up-regulation is promoted by enzymes of the P-450 superfamily.

Figure 9–23 summarizes the ways in which aldosterone synthesis is regulated by the two primary regulators, angiotensin and extracellular [K⁺]. The cellular mechanisms by which they and other modulators bring about their effects are summarized in Table 9–7.

Regulation by angiotensin II and III. Renin secretion from juxtaglomerular cells of the renal afferent arteriole is promoted most strongly by diminished stretch of the afferent arteriolar wall and weakly by decreased distal tubular delivery of NaCl to the **macula densa**.^{*} Renin produces **angiotensin I** from the freely circulating substrate **angiotensinogen**.

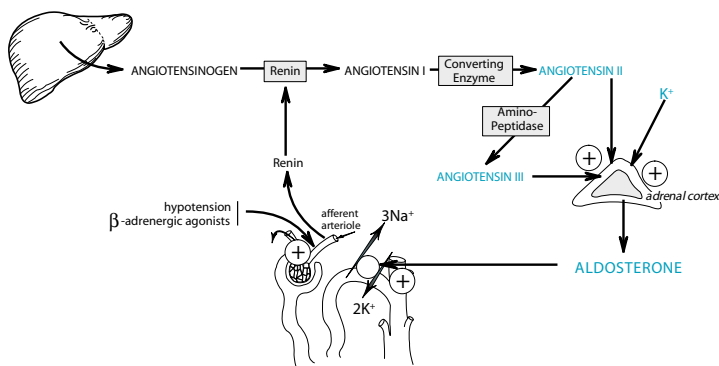


Figure 9–23 Regulation of the renin-angiotensin-aldosterone system, an important regulator of arterial blood pressure, body electrolytes, and extracellular fluid volume. A variety of renal afferent arteriolar stimuli promote the secretion of renin from juxtaglomerular cells. Renin cleaves angiotensin I from freely circulating angiotensinogen and angiotensin I is further cleaved to produce angiotensin II and III. Angiotensin II and III, both acting via the AT₁ receptor, are the most important acute stimuli for aldosterone secretion. Hyperkalemia is of less importance. The major biologic role of aldosterone is to synthesize and enhance the activity of Na⁺-K⁺-ATPase in the distal nephron.

^{*}This is opposite to former interpretations and is more fully explained under “Tubuloglomerular feedback” in Chapter 7, “Body Fluids and Electrolytes.”

Table 9–7

Cellular Mechanisms of Modulating Cholesterol Supply

Ligand	Membrane Effect	Intracellular Effect	Operative Principle
Promoters			
Ang II and Ang III	G (AT ₁ receptor)	↑ IP ₃ and ↑ DAG	↑ [Ca ⁺⁺] Activation of PKC
K ⁺	voltage	Ca ⁺⁺ channel conductivity	↑ [Ca ⁺⁺]
ACTH	G	↑ cAMP	Activation of PKA
Serotonin	G (5HT ₄ receptor)	↑ cAMP	Activation of PKA
	G (5HT ₂ receptor)	↑ IP ₃ and ↑ DAG	↑ [Ca ⁺⁺] Activation of PKC
Inhibitors			
Dopamine	G (D ₂ or D ₃ receptor)	↓ cAMP	Inactivation of PKA
ANP	receptor	↑ cGMP	↓ [Ca ⁺⁺]
Somatostatin	G (SS ₂ receptor)	↓ cAMP	Inactivation of PKA

ANP = atrial natriuretic peptide; DAG = diacylglycerol; G = G protein–coupled receptor; IP₃ = inositol trisphosphate; PKA = protein kinase A; PKC = protein kinase C.

Angiotensin I has no biologic activity. It is converted mostly in endothelial cells but also in adrenal zona glomerulosa cells by **converting enzyme** to **angiotensin II**, which is converted to **angiotensin III** by an **aminopeptidase**.

Angiotensin II and III act on zona glomerulosa cells to increase cholesterol supply and P-450 enzymes and, thereby, promote secretion of aldosterone and its precursor, 18-OH corticosterone.

Regulation by K⁺. Increased extracellular [K⁺] partially depolarizes zona glomerulosa cells. This increases Ca⁺⁺ conductivity, and the consequent increase in cytosolic [Ca⁺⁺] promotes cholesterol availability and activates 18-hydroxylase.

Other modulators of mineralocorticoid synthesis. Atrial natriuretic peptide, dopamine, and somatostatin inhibit aldosterone synthesis whereas serotonin increases it.

Regulation of Glucocorticoid Synthesis

Cortisol synthesis and secretion are regulated most importantly by ACTH (see Figure 9–24), which is secreted in bursts, most prominently early in the morning. Both short-term effects arising from increased cholesterol availability and long-term effects involving the P-450 enzymes are involved.

Adrenocorticotrophic hormone, in turn, is regulated most importantly by CRH.

One of the especially important biologic effects of cortisol is its feedback inhibition of ACTH synthesis. It occurs at both the pituitary and hypothalamic levels (see Figure 9–24) by steroid receptor–mediated inhibition of protein synthesis.

Regulation of Adrenal Androgen Synthesis

Adrenal androgen secretion generally follows the same pattern as ACTH and cortisol, but there are instances when the patterns are dissociated. As a result, it is believed that other regulatory factors exist. They have not yet been identified.

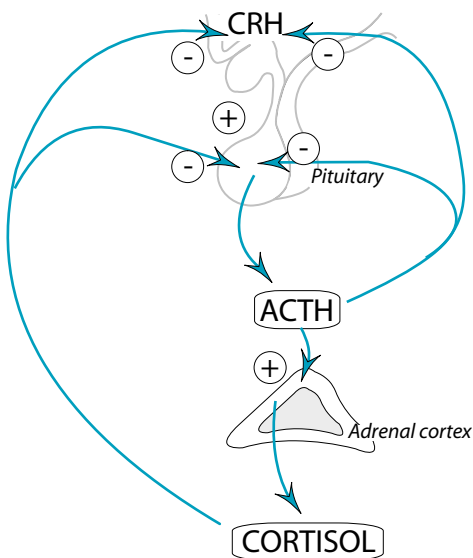


Figure 9–24 Cortisol secretion is regulated mostly by ACTH. Increases in ACTH are driven by corticotropin-releasing hormone (CRH), whose synthesis and release from neurons in the median eminence is influenced by tracts from many central nervous nuclei and a variety of blood-borne agents. Cortisol inhibits ACTH secretion at both the pituitary and hypothalamic levels. ACTH = adrenocorticotrophic hormone.

Transport and Distribution of Steroids

Steroids are transported (1) as free hormones in plasma, (2) bound to plasma proteins, and (3) associated with erythrocytes. Biologic activity derives only from free hormones and the bound fraction provides a reservoir that is in a steady state of distribution with the free moiety.

Steroid-Binding Proteins

Three plasma proteins participate in steroid transport:

1. **Albumin** is present in high concentration and, therefore, transports a great deal of steroid, even though its binding affinity is low.
2. **Transcortin**, also called **corticosteroid-binding globulin**, is a glycoprotein that binds cortisol, corticosterone, deoxycorticosterone, and progesterone with high affinity. Nevertheless, its transport capacity is low because its serum concentration is only about one-thousandth that of albumin.
3. **Testosterone-binding globulin** is also a glycoprotein. It binds testosterone and similarly configured steroids, but its serum concentration is even lower than that of transcortin.

Table 9–8 shows the relative abundance of free and variously bound forms of the major adrenocortical steroids at normal plasma concentrations. These ratios change little unless the plasma total concentration increases by an order of magnitude or two. For such increases, the ratios can change greatly.

Actions of Steroids

Molecular and Cellular Mechanisms of Steroid Actions

While most actions of steroids arise from interactions with cytosolic or nuclear receptors that lead to long-term changes in protein transcription,

Table 9–8

Forms of Steroid Transport and Their Relative Abundance

Steroid	Plasma Total [nmol/L]	Free [%]	Bound to [%]			
			ALB	TR	TeBG	RBC
Corticosterone	12	3.5	19	78	0.1	?
Cortisol	400	2	3	90	0.1	5
Aldosterone	0.35	37	42	21	0.1	?
Androstenedione	4	8	88	1	3	?

ALB = albumin; RBC = erythrocyte; TeBG = testosterone-binding globulin; TR = transcortin.

it is becoming increasingly evident that several of them also bring about immediate changes by interactions with membrane receptors.

Mechanisms of Mineralocorticoid Action

The mineralocorticoid (type I glucocorticoid) receptor. Mineralocorticoid receptors are nuclear receptors and are expressed in the brain, vascular endothelium, and transporting epithelia of the colon, salivary glands, sweat glands, and distal nephron.

The mineralocorticoid receptor is not highly specific. It will also bind glucocorticoids and then transmit an apparently mineralocorticoid signal to the nucleus. Since normal plasma cortisol levels are three orders of magnitude greater than aldosterone levels, interactions of cortisol with the mineralocorticoid receptor must be prevented. The mechanism is likely to be its colocalization with **11 β -hydroxysteroid dehydrogenase**. This enzyme reversibly inactivates cortisol by removal of a hydrogen from the OH that is bound at C11 (see Figure 9–22) but has no effect on aldosterone, which escapes enzymatic degradation because it has a different configuration at the C11 position.

Responses to mineralocorticoid receptor activation: The cellular responses to aldosterone are summarized in Figure 9–25. They include short-term effects that can be observed within 2 hours and long-term effects that become evident after several days.

Short-term effects of mineralocorticoid receptor activation: The early effects are an increase in amiloride-sensitive Na^+ entry into the cell that is most probably caused by acute activation of inactive channels and increased rate of Na^+ - K^+ -ATPase cycling.

Long-term effects of mineralocorticoid receptor activation: Long-term effects are observed at various sites: increased expression of apical, amiloride-sensitive Na^+ channels; increased expression of both α - and β -subunits of basolateral Na^+ - K^+ -ATPase; increased energy supply to the Na^+ - K^+ pump; increased Na^+ conductance through the tight junction between neighboring cells; and increased K^+ conductance through barium-sensitive apical channels.

Biologic effects of mineralocorticoids: The homeostatic role of aldosterone is to regulate the body balance of Na^+ and K^+ . This is accomplished by its stimulatory effect on Na^+ - and K^+ transport primarily in the distal nephron.

Mineralocorticoid escape: When aldosterone is chronically administered to a normal person, there is an initial period of Na^+ and water retention with

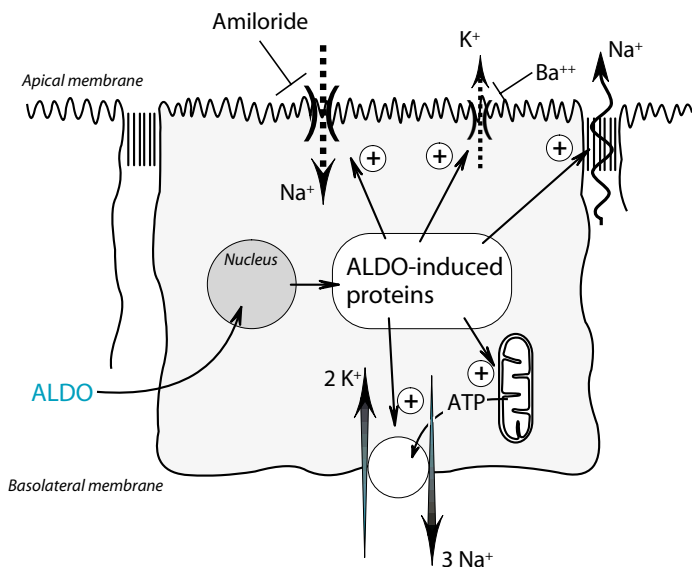


Figure 9-25 Summary of the cellular consequences of aldosterone interaction with the mineralocorticoid receptor. Most effects are due to increased transcription of aldosterone-induced proteins. They stimulate transport of Na^+ and K^+ at several sites and also up-regulate ATP formation. ALDO = aldosterone; ATP = adenosine triphosphate.

accompanying weight gain and mild hypertension. After several days, “escape” is observed, whereby distal nephron Na^+ reabsorption is no longer driven by the elevated aldosterone levels. The explanation is thought to lie in a variety of counter-regulatory mechanisms involving the control of blood volume and blood pressure.

Mechanisms of Glucocorticoid Action

The glucocorticoid receptor (type II): The glucocorticoid receptor is a cytosolic receptor. It is found in almost every tissue. Like the mineralocorticoid receptor, it lacks steroid specificity and also binds aldosterone. This is not generally a problem because the normal plasma concentration of aldosterone is one-thousandth that of the glucocorticoids.

Effects of glucocorticoids on transcription. Although some glucocorticoid effects may arise from cell surface receptors and not involve transcription, most are brought about by up-regulated transcription of glucocorticoid-induced effector proteins.

Biologic effects of glucocorticoids. Glucocorticoids are so named because their main effects are observed in the regulation of carbohydrate metabolism. In addition they adapt the organism to chronic stress and are useful, at therapeutic doses, in the treatment of inflammatory disorders.

Effects of cortisol on metabolism of carbohydrate, protein, and fat: The overall effect of cortisol is to help supply glucose to critical tissues when this is needed (Figure 9–26). It is accomplished by promoting synthetic processes in the liver while at the same time promoting catabolism in other tissues. In addition, glucose uptake in those tissues is decreased by cortisol-mediated decreases in insulin sensitivity and down-regulation of glucose carriers.

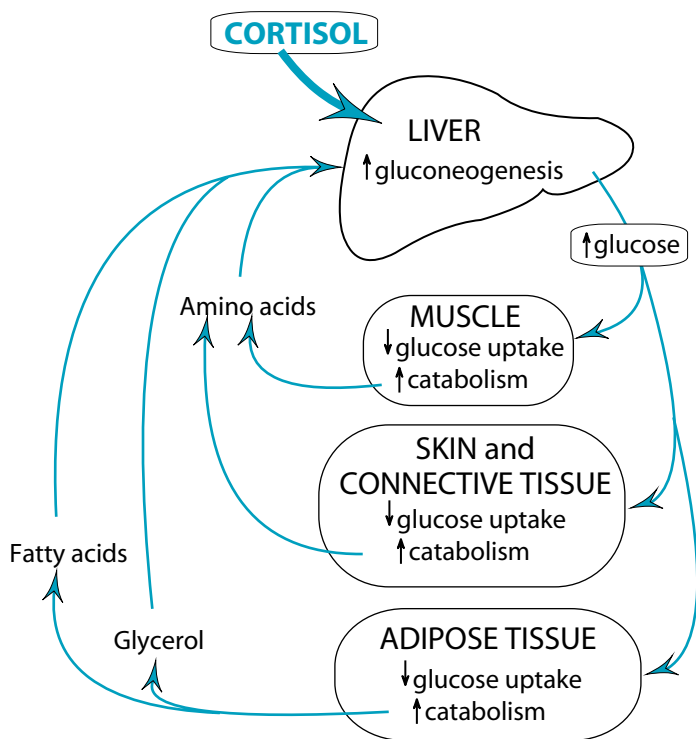


Figure 9–26 Metabolic and catabolic effects of cortisol in key tissues. Cortisol promotes gluconeogenesis by increasing both the levels of important enzymes and the availability of substrates. Increased substrates derive from catabolic actions of cortisol in muscle, skin, connective tissue, and adipose tissue. While more glucose is being made available, glucose uptake in tissues is also decreased by cortisol.

Effects of cortisol on gluconeogenesis: Cortisol increases hepatic glucose production in (a) direct ways that include increased levels and activities of key enzymes, such as **phosphoenolpyruvate carboxylase** and **glucose 6-phosphatase**, and (b) permissive ways that include up-regulation of transaminases and increased enzyme sensitivity to other gluconeogenetic stimulants such as glucagon or catecholamines.

Effects of cortisol on proteolysis: Cortisol increases catabolism of proteins so that there is an increase in glucogenic amino acid substrate for hepatic glucose production.

Effects of cortisol on lipolysis: Cortisol increases blood levels of free fatty acids, glycerol, and ketones provided that this action is not inhibited by elevated insulin levels.

Nonmetabolic physiologic effects of cortisol: Cortisol has widespread effects in many tissues. These are summarized in Table 9–9.

Cortisol as an anti-inflammatory agent: Cortisol induces regulatory proteins that inhibit (1) phospholipase A₂, (2) degranulation of mast cells, macrophages, and granulocytes, and (3) fibroblast activity.

Inhibition of phospholipase A₂: Inhibition of phospholipase A₂ reduces the levels of arachidonic acid, the precursor for the prostaglandins and leukotrienes, both of them responsible for local swelling and irritation.

Degranulation of mast cells, macrophages, and granulocytes: Mast cells are the source of histamine, while macrophages and granulocytes release **serotonin** and **lysosomal enzymes**. Cortisol stabilizes membranes and, thereby, inhibits the release of these factors in allergies or during inflammation.

Inhibition of fibroblast activity: Such inhibition prevents (1) encapsulation of foci of infection and (2) formation of keloid or adhesions around surgical wounds.

Cortisol and resistance to stress: Elevated levels of circulating glucocorticoids are necessary to withstand the physiologic impact of “stress.” Their benefits derive largely from mechanisms that are still not known but may include maintenance of vascular responsiveness to catecholamines and permitting catecholamines to boost energy supplies by liberating free fatty acids.

Table 9–9

Nonmetabolic Physiologic Effects of Cortisol

System	Effect	Mechanisms
Endocrine	↓ ACTH secretion	Steroid receptor–mediated inhibition of protein synthesis at pituitary and hypothalamus
	↑ Vasopressin synthesis	
	↑ ANP synthesis	
	↓ Secretion of growth hormone	
Cardiovascular	↑ Cardiac performance	1) ↑ Secretion of adrenal medullary catecholamines 2) ↑ Responsiveness of the heart to catecholamines and 3) ↑ Quantal release of norepinephrine from cardiac sympathetic nerve terminals
	↑ Peripheral vascular reactivity	Glucocorticoids must be present for epinephrine and norepinephrine to affect the tone of vascular smooth muscle and for capillaries to maintain normal permeability
Nervous	Lack of cortisol causes greater irritability, feeling of unease, distractedness, increased sensitivity to olfactory and gustatory stimuli	
Fluid and Electrolytes	When glucocorticoids are absent: GFR is low and hypertonic urine is excreted. Ability to excrete a water load is curtailed. “Water intoxication” may be present, complete with cell swelling and its central nervous consequences	

Continued

Table 9–9

Nonmetabolic Physiologic Effects of Cortisol—Continued

System	Effect	Mechanisms
Fluid and Electrolytes (continued)	When glucocorticoids are high: <ul style="list-style-type: none"> • Na⁺ retention, hypokalemia, and increased arterial blood pressure • ↓ Intestinal uptake and renal reabsorption of Ca⁺⁺ 	Cortisol binding to and activation of the aldosterone receptors in the distal nephron
Bone	↓ Osteoblast function (↓ bone formation) ↑ Osteoclast activity (↑ bone resorption)	
Growth and Development	Cortisol aids in maturation of the fetal surfactant system ↓ Secretion of growth hormone	
Immune	↓ Release of interleukin-1 (IL-1) from stimulated macrophages ↓ Effects of IL-1 on target cells*	

*The significance of these effects is that IL-1 promotes IL-2 release from activated T_H-cells and IL-2 induces (1) formation of *interferon* and (2) proliferation of cytotoxic T cells. Thus, cortisol inhibits the cascade of immune responses that follows exposure to an antigen.

ANP = atrial natriuretic peptide; GFR = glomerular filtration rate.

Mechanisms of Androgen Actions

Dehydroepiandrosterone and androstenedione, the principal androgens secreted by the adrenal cortex (see Figure 9–22), have little biologic potency. They become active only after peripheral tissues have converted them, chiefly to testosterone. Testosterone and other androgens have some biologic activity in most tissues at all stages of life.

Biologic actions of androgens in fetal life. Androgens determine the development of gender-linked features in the anatomy and patterns of gonadotropin release. High levels of androgens have a masculinizing effect. Thus, androgen concentration in fetal blood during the first 10 weeks

determines whether (1) female or male genitalia (internal as well as external) develop, and (2) the hypothalamus will develop a cyclic pattern of gonadotropin release after puberty (female) or a noncyclic pattern (male).

Biologic actions of androgens in adult life. Two androgen effects are observed, depending on the target organ. Androgens (1) stimulate protein synthesis (anabolic effects) and (2) influence development and growth of male sexual characteristics, such as muscle development, maturation of external genitalia, size of the larynx and vocal cords, as well as patterns of hair growth and hair loss. Effects of androgens on gender-specific behavior have been asserted, but the evidence for such effects in humans is conflicting.

Catabolism of Adrenocortical Steroids

Steroids are catabolized (1) within the target tissues, (2) in the liver, and (3) in the kidney. Such catabolism serves three general purposes: (1) to inactivate biologic activity, (2) to create incompatibility with steroid receptors, or (3) to increase water solubility in order to facilitate renal excretion.

THE ADRENAL MEDULLA

Anatomy and Embryology of the Sympatho-Adrenal System

The adrenal medulla contains neuronal cells (**chromaffin cells**) that have endocrine function in that they synthesize the **catecholamines**. These compounds belong to the **amine** family and contain the ring structure shown in Figure 9–27. Chromaffin cells are arranged in close relationship with preganglionic cholinergic fibers and with venules that drain the adrenal cortex. As a result of this anatomic arrangement, both sympathetic nervous activity and adrenocortical chemical products influence the synthesis of catecholamines.

The enzyme **phenylethanolamine-N-methyltransferase** (PNMT) is a unique feature of chromaffin cells. Its function is to convert norepinephrine to epinephrine.

The preganglionic autonomic supply of the adrenal medulla is chiefly by way of the greater splanchnic nerve.

Catecholamines

Synthesis and Storage of Catecholamines

The significant catecholamines are **dopamine**, **epinephrine**, and **norepinephrine**.*

*Epinephrine and norepinephrine are also called adrenaline and noradrenaline, respectively.

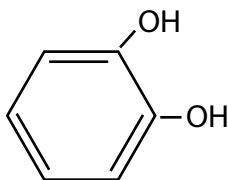


Figure 9–27 Structure of the catechol moiety.

The steps involved in epinephrine synthesis from the amino acid **tyrosine** are summarized in Figure 9–28. Some of the tyrosine is formed by hydroxylation of **phenylalanine**, but most of it derives from dietary sources, where it is found in most proteins. Epinephrine synthesis can be broken down into five important steps:

1. Conversion of tyrosine to **DOPA** is the first and also the rate-limiting reaction. It requires O_2 and is catalyzed by **tyrosine hydroxylase**, an

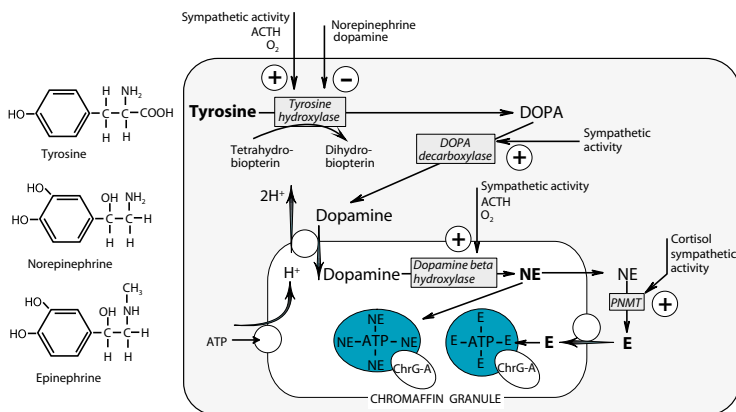


Figure 9–28 Adrenal medullary synthesis of epinephrine from the amino acid, tyrosine in chromaffin cells, and the chromaffin granules contained within them. The first step is conversion of tyrosine to DOPA by tyrosine hydroxylase. DOPA is converted to dopamine, which is transported into chromaffin granules in exchange for $2H^+$ by VMAT-1. Action of dopamine β -hydroxylase, which is located only within the granules, produces norepinephrine (NE), and it diffuses into the cytosol, where it is converted to epinephrine by PNMT, which is found only in the cytosol. In their storage forms, both epinephrine and norepinephrine are bound to ATP and associated with the protein chromagranin-A (ChrG-A). Sympathetic nervous activity, ACTH, norepinephrine, and cortisol are important regulators of epinephrine synthesis. ACTH = adrenocorticotropic hormone; ATP = adenosine triphosphate; DOPA = dihydroxyphenylalanine; Dopamine = dihydroxyphenylethylamine; E = epinephrine; PNMT = phenylethanolamine-N-methyltransferase; VMAT-1 = vesicular monoamine transporter-1.

enzyme that is maintained by ACTH and elevated above normal levels mostly by sympathetic activity. **Tetrahydrobiopterin** acts as a cofactor and is transformed into **dihydrobiopterin** in the process. Dihydrobiopterin is then changed back to tetrahydrobiopterin by the enzyme dihydrobiopterin reductase with simultaneous formation of NADP^+ from NADPH and H^+ .

2. Removal of the terminal COOH group from DOPA produces **dopamine**. The reaction is catalyzed by **DOPA decarboxylase**, which is also called **L-amino acid decarboxylase**.
3. Transport of dopamine into vesicles is required for further processing because only these vesicles contain the enzyme **dopamine β -hydroxylase**. Dopamine transport is by the vesicular monoamine transporter VMAT-1* that is located in the granule membrane of adrenal chromaffin cells, is driven by an H^+ gradient† and exchanges 2 H^+ for each monoamine molecule. Dopamine β -hydroxylase catalyzes formation of norepinephrine from dopamine in the presence of O_2 . Dopamine β -hydroxylase is also under sympathetic control, but to a lesser extent than either tyrosine hydroxylase or DOPA decarboxylase. As a result, high levels of sympathetic nervous activity, such as may occur under stress, can alter the proportion of dopamine to epinephrine or norepinephrine released from sympathetic nerves and from the adrenal medulla.
4. Norepinephrine diffuses out of the vesicles into the cytoplasm so that the cytosolic enzyme **phenylethanolamine-N-methyltransferase** (PNMT) can convert norepinephrine to epinephrine. PNMT is regulated by (1) cortisol, which drains from the adrenal cortex and is required in high concentration for activation of PNMT, and (2) sympathetic stimulation, which elevates PNMT above its resting level. In healthy adult humans, so much PNMT is present that mostly epinephrine is released into the circulation when the adrenal medulla is stimulated.
5. Finally, epinephrine is pumped actively into the originating and other vesicles for storage and later secretion on demand by sympathetic nerve stimulation. Some of norepinephrine, dopamine, and dopamine β -hydroxylase is co-released.

*VMAT-2, a closely related vesicular transporter, is found mostly in sympathetic nerves and central neurons that use biogenic amines as transmitters.

†The H^+ gradient is maintained by active transport.

Dopamine

Some cells within autonomic ganglia and the brain do not have dopamine β -hydroxylase and in them catecholamine synthesis stops at dopamine (see Figure 9–28), which is then secreted as a synaptic transmitter.

Epinephrine Secretion

Stored epinephrine is secreted into the circulation by exocytosis in response to cholinergic preganglionic nerve activity.

Receptors for Catecholamines

Dopaminergic receptors. There are five subtypes of dopaminergic receptors (D_1 to D_5), and they are located mainly and in different parts of the brain. All are G protein–coupled membrane-spanning proteins with seven transmembrane domains. Activation of D_1 and D_5 increases cytosolic cAMP, whereas D_2 , D_3 , and D_4 activation decreases cytosolic cAMP.

Adrenoreceptors. Adrenoreceptors are subdivided on the basis of their affinities for certain agonists or antagonists into the classes alpha and beta adrenoreceptors. Within each of these there are further subdivisions, most notably into α_{1A-D} , α_{2A-C} , β_1 , β_2 , and β_3 subtypes. Epinephrine has higher affinity for β -adrenoreceptors, whereas norepinephrine has greater affinity for α -adrenoreceptors.

Molecular structure of adrenoreceptors: The adrenoreceptors are serpentine receptors in the plasma membrane. They have seven transmembrane domains and, depending on the cytosolic loop between transmembrane domains 5 and 6, are linked to either a stimulatory (G_s) or inhibitory (G_i) intracellular G protein.

Signal transduction:

Alpha adrenergic receptors: The dominant intracellular signalling pathway for activated α_1 -adrenoreceptors is the phospholipase C path by way of G_q . This causes elevated IP_3 , DAG, and Ca^{++} in the cytosol.

α_2 -Adrenoreceptors operate by way of inhibiting adenylate cyclase through G_i .

Beta-adrenergic receptors: β -Adrenoreceptors all activate adenylate cyclase and, thereby, promote formation of cAMP from ATP.

Table 9–10

Physiologic Effects of Increased Adrenal Medullary Secretion

Target	Effect	Receptor
Metabolism (observed at 5 to 6 times basal plasma levels of EPI or NOREPI)	↑ Energy substrates ↑ Heat production	
Liver	↑ Glycogenolysis ↑ Gluconeogenesis ↑ ketone bodies	β_2 and α_1 β_2 and α_1
Muscle	↑ Glycogenolysis ↑ Lactate and pyruvate ↓ Uptake of glucose, ketone bodies	β_2 β_2 β_2
Adipose tissue	↑ Lipolysis	α_1 , β_1 , and β_3
Cardiovascular (observed at 2 to 3 times basal plasma levels of EPI or 5 to 6 times basal NOREPI)	↑ Cardiac output Distribution of CO to brain, heart, and skeletal muscle	β_1 β_2
Heart	↑ Heart rate ↑ Contractility ↑ Coronary blood flow	β_1 β_1 β_2
Arterioles*	Dilatation in skeletal muscle, liver, heart Constriction in skin, kidney, mucosae	β_2 α_1
Various		
GI tract	↓ GI motility ↑ GI sphincter contractions ↓ Secretions	β_2 and α_1 α_1 α_2
Pancreas	↑ Insulin and glucagon ↓ Insulin and glucagon (epinephrine >400 pg/mL)	β_2 α_2
Kidney	↑ Renin secretion ↓ Renal blood flow	β_2 α_1
Skin	↑ Sweating ↓ Cutaneous blood flow	α_1 α_1
Mouth	↓ Saliva flow	α_1
CNS	↑ Alertness, anxiety, and fear	

*The effects of epinephrine on total peripheral resistance are complicated by its α (constrictor) effects in some tissues and β (dilator) action in skeletal muscle and liver. The dilator effect usually wins out and contributes to fainting during extreme emotional responses.

CO = cardiac output; EPI = epinephrine; GI = gastrointestinal; NOREPI = norepinephrine.

Actions of Epinephrine and Norepinephrine

Normal plasma levels of epinephrine and norepinephrine in humans are, respectively, 25 and 250 pg/mL. The adrenal medulla is stimulated under conditions of stress, and increased secretion of catecholamines leads to many effects (Table 9–10). Their net purpose is twofold: (1) metabolic effects ensure an increased supply of glucose and free fatty acids, and (2) cardiovascular effects ensure both increased cardiac output and preferential distribution of cardiac output to brain, heart, and skeletal muscle.*

Actions of Dopamine

Dopamine is an important central nervous neurotransmitter. Its physiologic role as a circulating ligand is not clear and is probably overshadowed by epinephrine and norepinephrine. When dopamine is injected, it dilates the renal afferent and mesenteric arterioles but constricts all other vascular beds. It also increases cardiac performance, probably by activating β_1 -adrenoreceptors.

Catecholamine Metabolism

Metabolic and excretory pathways.

Metabolism of circulating epinephrine and norepinephrine: The liver is the main metabolic site and the major enzymes are **catecholamine O-methyltransferase** (COMT), which is located in the cytosol and **monoamine oxidase** (MAO), which is located on the outer mitochondrial membrane (Figure 9–29). The most abundant metabolite is **3-methoxy-4-hydroxy-mandelic acid**, also called **vanillylmandelic acid** (VMA). It is excreted in urine.

Metabolism of neuronal norepinephrine: Catecholamine O-methyltransferase is found in most postsynaptic tissues but not in nerve endings. However, MAO is abundantly present in norepinephrine-secreting nerve terminals. It converts norepinephrine to **3,4-dihydroxy-mandelic aldehyde**, which is either oxidized to produce **3,4-dihydroxy-mandelic acid** (DOMA) or glycosylated to produce **3,4-dihydroxy-phenylglycol** (DHPG) (Figure 9–30). Dihydroxy-mandelic acid and DHPG enter the circulation

*The fraction of cardiac output that is directed to a tissue is determined by the vascular resistance that is offered by that tissue in comparison to all other tissues. Net tissue vascular resistance, in turn, is determined by the degree of imbalance between local vasoconstrictor factors and local vasodilator factors. Tissues that have a high proportion of vascular smooth muscle β_2 -adrenoreceptors (for example, skeletal muscle) show a high potential for vasodilatation in the presence of epinephrine.

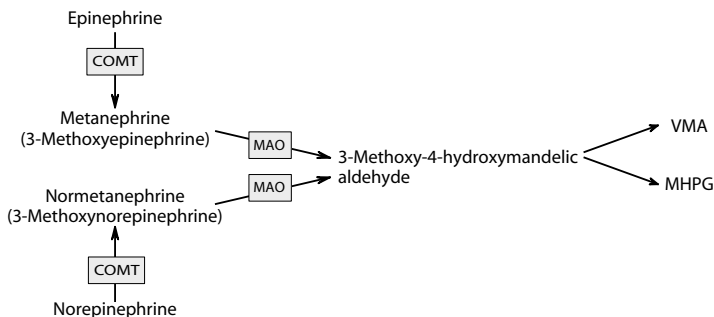


Figure 9–29 Circulating epinephrine and norepinephrine are metabolized by the enzymes COMT and MAO. COMT = catecholamine O-methyltransferase; MAO = monoamine oxidase; MHPG = 3-methoxy-4-hydroxyphenylglycol; VMA = vanillylmandelic acid (3-methoxy-4-hydroxy-mandelic acid).

and are further broken down to VMA or **3-methoxy-4-hydroxy-phenylglycol** (MHPG), respectively.

Metabolism of dopamine: Dopamine that is taken up into the secreting nerve terminals is oxidized by MAO to produce **3,4-dihydroxyphenyl acetic acid** (DOPAC) while circulating dopamine is methylated by COMT to 3-methoxytyramine (MTA). Action of COMT on DOPAC or of MAO on MTA yields the final metabolite, homovanillic acid (HVA).

Adrenomedullin

This 52-amino acid peptide and its related gene product **proadrenomedullin N-terminal 20 peptide** (PAMP) were first isolated from cells of adrenal medullary tumors (pheochromocytomas). They are now known to be synthesized in many tissues, the most abundant transcription

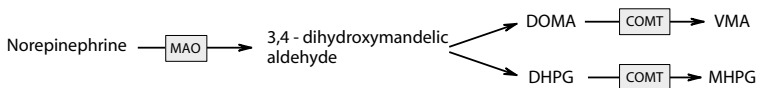


Figure 9–30 Sympathetic nerve terminals contain MAO but no COMT. Therefore, norepinephrine taken back into the terminals is metabolized to 3,4-dihydroxymandelic aldehyde. The aldehyde is converted to DOMA or DHPG, which diffuse into the circulation where COMT can metabolize them further. COMT = catecholamine O-methyltransferase; DHPG = 3,4-dihydroxy-phenylglycol; DOMA = 3,4-dihydroxy-mandelic acid; MAO = monoamine oxidase; MHPG = 3-methoxy-4-hydroxyphenylglycol; VMA = vanillylmandelic acid (3-methoxy-4-hydroxy-mandelic acid).

being observed in endothelial cells. Potent inducers of transcription are (1) cytokines like **interleukin-1** and **lipopolysaccharide** and (2) growth factors (GF), such as fibroblast, platelet-derived, or epidermal-derived GF.

Adrenomedullin is a potent vasodilator. It acts by way of an endothelial membrane receptor to activate adenylate cyclase and phospholipase C through G protein mechanisms. The consequent elevation of endothelial cytosolic $[Ca^{++}]$ promotes formation of nitric oxide. PAMP is also a vasodilator but acts presynaptically to inhibit norepinephrine release from sympathetic noradrenergic nerves. The action is receptor mediated and relies on four effects: (1) inhibition of voltage-gated Ca^{++} channels, (2) activation of inwardly rectifying K^{+} channels, (3) inhibition of Na^{+} channels, and (4) inhibition of tyrosine hydroxylase.

In addition to their vasoactive effects, adrenomedullin and PAMP cause increased natriuresis and diuresis and, by central nervous action, inhibit water and salt intake. These actions, as well as positive inotropic effects on cardiac function, have led to the view that adrenomedullin and PAMP may play a significant part in cardio-renal regulation.

ENDOCRINE PANCREAS

Anatomy of the Islets of Langerhans

The endocrine pancreas comprises only 1 to 2% of the organ and consists of one to two million histologically distinct, highly vascularized islands, called the **islets of Langerhans**. They are distributed throughout the pancreas and contain four distinct cell types, each being responsible for the synthesis, storage, and release of one of the hormones insulin (B cells), glucagon (A cells), somatostatin (D cells), and pancreatic polypeptide (F cells).

Each islet measures between 75 and 250 μm , and its core consists mostly of B cells (up to 80% of the islet). A, D, and F cells form surrounding layers. Each cell is in close apposition to a fenestrated capillary and secretes its endocrine product into such capillaries by exocytosis. There are numerous gap junctions between neighboring sibling cells so as to unite them in a functional syncytium and also between cells of different types.

Islets are located near the pancreatic arteries and have, therefore, a direct arterial supply. They are perfused first, and the blood then perfuses the exocrine pancreas and, from there, enters the portal vein. Within an islet, B cells are perfused first, then A cells, and then D cells and F cells. This sequence explains some of the mechanisms by which the secretory products of the different cell types influence one another.

Islets are innervated by sympathetic adrenergic, parasympathetic cholinergic (right vagus), and peptidergic nerves and contain adrenergic (mainly α_2) and muscarinic receptors (mainly M_4).

Insulin

Insulin is a small peptide and is secreted only by pancreatic B cells. It consists of an A chain (21 amino acids) and a B chain (30 amino acids). They are linked by two disulfide bridges. Before it is secreted and while still undergoing processing within the secretory granules, a connecting peptide (C peptide) links the A and B chains (Figure 9–31).

Insulin from different species differs from human insulin by no more than four residues.*

Synthesis and Storage of Insulin

The insulin gene is located on the short arm of human chromosome 11 and its product is synthesized in the rough endoplasmic reticulum of pancreatic B cells. It begins as **pre-proinsulin**, a 104–amino acid peptide whose first 23 residues are a signal peptide. Removal of the signal peptide and folding and insertion of disulfide bridges create **proinsulin** (see Figure 9–31). Proinsulin is transported in microvesicles to the Golgi apparatus, and its conversion to insulin begins in clathrin-coated vesicles that bud off specialized regions in the trans-Golgi apparatus. This conversion involves removal of the 30–amino acid C peptide with the help of several enzymes. Simultaneously, the coating is stripped from the vesicles, and they become secretory vesicles. Insulin is stored within them as six molecules bound to two central Zn^{++} ions. Upon

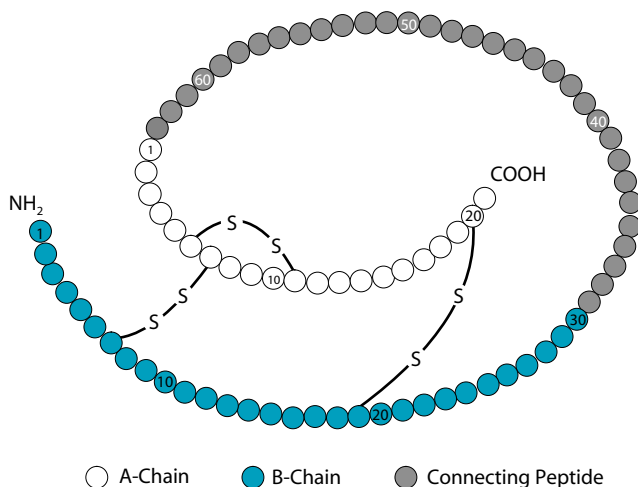


Figure 9–31 Proinsulin is a folded peptide of three connected chains.

*Such differences do not markedly affect biologic activity, but they can elicit immunologic responses.

stimulation, the vesicles are transported along cytoskeletal elements to the secreting plasma membrane. C-peptide is released with insulin, but its circulating form has no known biologic function.

Secretion of Insulin

Exocytosis of insulin-containing vesicles is initiated and maintained by elevation of cytosolic $[Ca^{++}]$ in B cells above the normal resting value of 60 to 100 nmol/L. The exact relationship between cytosolic Ca^{++} and the steps of exocytosis is not yet known but is likely to be similar to the relationship between Ca^{++} and transmitter release in nerve terminals (see Figure 4–8).

Regulation of insulin secretion. The most important regulator is glucose. There is a measurable increase in insulin secretion when plasma glucose concentration rises above its normal level of 100 mg/dL (5 mmol/L). The linkage between glucose and insulin secretion rate is summarized in Figure 9–32. Table 9–11 summarizes the influence of other agents. Those causing increased intracellular $[Ca^{++}]$ will promote insulin secretion and those causing decreased intracellular $[Ca^{++}]$ will inhibit insulin secretion.

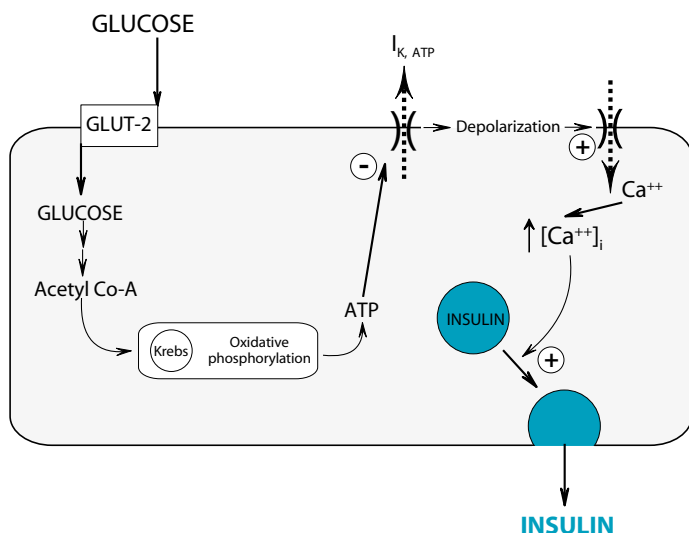


Figure 9–32 Relationship between plasma glucose concentration and insulin secretion. Glucose enters pancreatic islet B cells via the GLUT-2 transporter, which does not require insulin for activation. Intracellular metabolism of glucose produces ATP, which inhibits $I_{K, ATP}$, the ATP-sensitive K^+ channel. Such inhibition restricts K^+ outflow, depolarizes the cell, and causes voltage-gated, L-type Ca^{++} channels to open. $I_{Ca,L}$ and possibly additional sources of Ca^{++} raise intracellular $[Ca^{++}]$, cause activation of Ca^{++} -dependent kinases, and lead to exocytosis of insulin-containing vesicles.

Table 9–11

Regulation of Insulin Secretion by Influences on B-Cells

	Agent	Mechanism
Promoters of secretion	Glucose	↑ B-cell [ATP] _i
	Digestive products of proteins and fats	↑ B-cell [ATP] _i
	Incretins*	↑ B-cell [Ca ⁺⁺] _i
	Cortisol	↑ Plasma [glucose]
	Growth hormone	↑ Plasma [glucose]
	Thyroxine	↑ Plasma [glucose]
	Progesterone	↑ Plasma [glucose]
	Estrogen	↑ Plasma [glucose]
	Testosterone	↑ Plasma [glucose]
	Glucagon	↑ B-cell [cAMP] [†]
	β ₂ -Agonists	↑ Glucagon
	M ₄ -agonists	↑ B-cell [Ca ⁺⁺] _i
	↑ Plasma [K ⁺]	B-cell depolarization
Inhibitors of secretion	Epinephrine, norepinephrine, α ₂ -agonists	↓ B-cell [cAMP]
	Somatostatin	↓ B-cell [cAMP] [†]
	Insulin	↓ Plasma [glucose]
	Galanin [‡]	Activation of K _{ATP}
	↓ Plasma [K ⁺]	B-cell hyperpolarization

*The insulin response to oral glucose is much greater than that to an equivalent intravenous load. This is called the incretin effect, and it is attributed to the release of several GI hormones following oral food intake. The most important incretins are glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), cholecystokinin, gastrin, and secretin.

[†]There is a direct correlation between [cAMP]_i and conductance of L-type Ca⁺⁺ channels.

[‡]Galanin is a polypeptide that is co-released with norepinephrine from pancreatic sympathetic nerves.

Insulin release from individual B cells is normally oscillatory. The reason is that Ca⁺⁺ influx, once it has been initiated, will further depolarize the cell and eventually cause voltage-gated K⁺ channels to open when their threshold potential is reached. The cell will then be repolarized by K⁺ efflux, [Ca⁺⁺]_i will return toward resting values, and exocytosis stops. If plasma glucose continues to be high, the process repeats.

B-cell exhaustion atrophy. Pancreatic B cells show an unusual atrophic response to stimulation that is either strong or prolonged. Like other cells

they respond initially with hypertrophy and increased secretory output. However, they soon stop secreting, atrophy, die, and disappear.

Insulin Receptor

Insulin receptor activation triggers several biologic effects as well as endocytotic internalization of the ligand-receptor complex. Within the endosomes, insulin then dissociates from the receptor and is degraded by lysosomal enzymes. The receptor, on the other hand, is recycled to the plasma membrane.

Molecular structure. The insulin receptor exists as a tetramer and is composed of two α -subunits and two β -subunits. The α -subunits are extracellular, and one of them contains the insulin binding site, whereas the β -subunits span the plasma membrane and contain tyrosine kinase activity within the intracellular domains.

Signal transduction. There are two pathways of signal transduction; one depends on the participation of **Ras**,* the other does not. After ligand binding, the first steps of signal transduction in either pathway are (1) autophosphorylation of the cytosolic tyrosine kinase domain, (2) binding of **insulin receptor substrate 1** (IRS1) to a phosphorylated tyrosine residue of one of the β -subunits of the insulin-receptor complex, and (3) phosphorylation of IRS1 by the activated tyrosine kinase. The two pathways differ in their subsequent steps.

Ras-independent insulin receptor signaling: As summarized in Figure 9–33, receptor-bound, phosphorylated IRS1 binds to phosphoinositide-3 kinase (PI-3) and eventually causes activation of **protein kinase B**. Most short-term metabolic effects of insulin arise from activated protein kinase B.

Ras-dependent insulin receptor signaling: The kinase cascade that is involved in most long-term effects of insulin on metabolic enzymes and protein synthesis is summarized in Figure 9–34. The cascade includes the enzymes **Raf**, **MEK**,† and **MAP** kinase. Activated MAP kinase phosphorylates a variety of proteins and can translocate to the nucleus and, thereby, cause many biologic effects.

*Ras is a switchable protein that resembles G proteins in function. When Ras is inactive, it binds GDP. When it is active, it binds GTP.

†MEK is a kinase that can phosphorylate both tyrosine and serine residues within proteins. MAP = mitogen-activated protein.

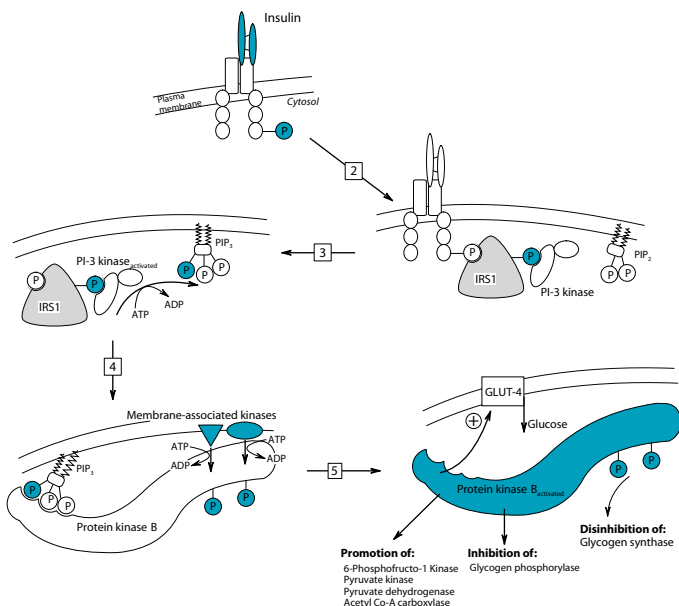


Figure 9-33 Many short-term effects of insulin are caused by a cascade that culminates in phosphorylation of protein kinase B and its subsequent dissociation from the plasma membrane of target cells. The first steps are binding of insulin to one of the α -subunits of the insulin receptor, autophosphorylation of the β -subunit, and activation of the receptor kinase domain. Step 2: Phosphorylated IRS1 binds to one subunit of phosphoinositide-3 kinase (PI-3 kinase) and activates the enzyme. Step 3: The other subunit of activated PI-3 kinase catalyzes phosphorylation of membrane-associated PIP_2 to form PIP_3 . Step 4: PIP_3 binds protein kinase B and draws it toward the plasma membrane where two different kinases phosphorylate and activate protein kinase B. Activated protein kinase B is released from the membrane and its different portions modulate different aspects of target cell intermediary metabolism or promote insertion of GLUT-4 glucose transporters into the plasma membrane. IRS1 = insulin receptor substrate 1; PI-3 kinase = phosphoinositide-3 kinase; PIP_2 = phosphatidylinositol bisphosphate; PIP_3 = phosphatidylinositol trisphosphate.

Actions of Insulin

The insulin receptor is found predominantly in the liver, muscle, and adipose tissue. Its activation elicits immediate and long-term effects in these target organs by promoting both $Na^+-K^+-ATPase$ and intracellular storage of the substrates for intermediate metabolism. The latter effects are known best.

Insulin effects on intermediate metabolism. The details of the metabolism of carbohydrate, protein, and fat are described in Chapter 10.

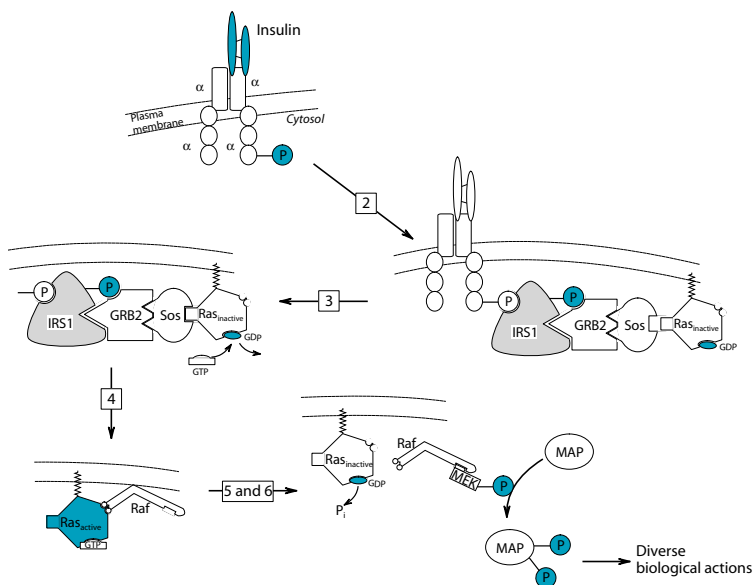


Figure 9-34 Long-term effects of insulin arise from the kinase cascade that is initiated by activated Ras. The first steps are ligand binding, autophosphorylation of the β -subunit, and activation of the receptor kinase domain. Step 2: Phosphorylated IRS1 binds to GRB2 and then to Sos. Step 3: The GRB2-Sos unit binds Ras and activates the Ras-GDP unit by allowing GTP to replace GDP. Step 4: Activated Ras binds to the kinase, Raf. Steps 5 and 6: Binding of Raf to the Ras-GTP complex hydrolyzes GTP to form GDP and then causes Raf to be activated and dissociated from the Ras-GDP unit. Raf_{activated} binds and phosphorylates MEK. Phosphorylated MEK then activates MAP kinase (MAP). Activated MAP kinase phosphorylates a variety of proteins and thereby causes many biologic effects. It is also translocated to the nucleus and there affects protein transcription.

Aspects that are particularly relevant to insulin and glucagon are summarized in Figure 9-35.

Insulin effects on glycogen: Although muscle and liver are equally important as glycogen stores, muscle glycogen stores cannot be used to buffer hypoglycemia because muscle cells lack **glucose 6-phosphatase**, the enzyme that converts glucose 6-phosphate to glucose (see Figure 9-35).

Insulin disinhibits **glycogen synthase** and inhibits **glycogen phosphorylase**. As a result, formation of glycogen is promoted and glycogenolysis is inhibited.

Insulin effects in the liver: One importance of the liver in body metabolism is that it acts as a buffer for blood glucose changes. This is possible because only hepatocytes contain **glucokinase**, which is an isoenzyme of

Table 9–12

Effect of Insulin on Liver Metabolic Activity

Effect	Mechanisms
↑ Glucose utilization	Promotion of glucokinase
↑ Glycogen formation and storage	Promotion of glycogen synthase and inhibition of glycogen phosphorylase
↑ Glycolysis	Activation of phosphofructokinase , pyruvate kinase , and pyruvate dehydrogenase
Synthesis of fatty acids is promoted more than is synthesis of cholesterol	Stimulation of acetyl CoA carboxylase , but not cytosolic HMG CoA synthase . [*] Acetyl CoA carboxylase forms malonyl CoA , an intermediary in the synthesis of fatty acids as well as an inhibitor of the enzyme carnitine palmitoyl transferase-1 (CPT-1) .
↓ Breakdown of fatty acids	Carnitine palmitoyl transferase-1 (CPT-1), which is required to shuttle free fatty acids across the outer mitochondrial membrane, is inhibited
↑ Ketone body formation	1. Acetyl CoA levels are increased by glycolysis [†] 2. Mitochondrial HMG CoA synthase is promoted

^{*}Hepatocytes contain two isoforms of the enzyme HMG CoA synthase. One is found in mitochondria and is involved in formation of ketone bodies; the other is found in the cytosol and is involved in cholesterol synthesis.

[†]Ketone bodies (β -hydroxybutyric acid and acetone) are formed in mitochondria when the intramitochondrial level of acetyl CoA is high. Under such conditions, **HMG CoA** is formed within the mitochondria and is broken down by **HMG CoA lyase** to acetyl CoA and acetoacetic acid. HMG CoA lyase is present in high concentration in liver mitochondria but not elsewhere. As a result, the liver is the primary producer of ketones.

transport in the liver because the liver has few, if any, insulin-sensitive glucose transporters.

Insulin effects in striated muscle: Insulin promotes glucose uptake by increasing GLUT-4^{*} activity, and the glucose is mainly converted to and stored as glycogen. In addition, uptake of amino acids is increased, and this, plus long-term up-regulation of anabolic enzymes, increases protein synthesis.

Insulin effects in adipose tissue: Glucose uptake is increased (GLUT-4 effect) and is converted to fatty acids. Up-regulation of endothelial lipoprotein lipase increases the availability of fatty acids, and they are used to

^{*}In tissues that contain the GLUT-4 transporter, the molecules exist in a cytoplasmic pool. Insulin causes them to move toward and insert in the plasma membrane.

increase intracellular synthesis of triglycerides. Simultaneously, down-regulation of hormone-sensitive lipase[†] within adipocytes reduces triglyceride breakdown.

Insulin effects on ion transport. Insulin activates the $\text{Na}^+\text{-H}^+$ transporter and the $\text{Na}^+\text{-K}^+$ pump that is found in most cells as well as the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ transporter in the thick ascending limb of the loop of Henle. As a result, insulin stimulates entry of K^+ , Na^+ , and Cl^- into cells. Subsequent net changes in membrane potential depend mostly on the final $[\text{K}^+]$ gradient and determine whether PO_4^{3-} or Mg^{++} is drawn into the cell. The osmotic effects draw water and increase cell volume.

The magnitude of the insulin effect on K^+ is such that insulin is considered to be a significant regulator of serum K^+ levels.

Diabetes Mellitus

Fasting blood glucose levels above 6.7 mmol/L (135 mg/dL) constitute **diabetes**, a disease that affects about 5% of the population. Two types are distinguished and are named in one of three ways, according to different criteria.[‡] The metabolic consequences of insulin lack or target organ insensitivity to insulin are readily apparent. The symptoms of glucosuria and osmotically driven polyuria and compensatory polydipsia are also readily derived. The secondary pathologic changes that accompany prolonged hyperglycemia are less readily understood. They affect mostly the basement membrane, eyes, cardiovascular system, and peripheral nerves.

Effects of hyperglycemia on basement membrane. Glucose attaches to amino groups in proteins, and over the course of several weeks, these attachments form **advanced glycosylation end (AGE) products** that remain irreversibly attached to proteins, even if the plasma glucose level should be returned to normal levels. The presence of AGE products in matrix proteins, such as collagen, causes abnormal cross-linking and also activates macrophages. The outcomes are (1) basement membrane thickening, (2) increased filtration resistance, and (3) decreased affinity for proteoglycans whose cloud of negative charges normally forms part of the capillary filtration barrier and prevents anions from leaving the capillary.

[†]Endothelial lipoprotein lipase lyses circulating lipoproteins and, thereby, provides fatty acids for cellular uptake and metabolism. Intracellular, hormone-sensitive lipase breaks down intracellular triglycerides.

[‡] (1) **Juvenile-onset diabetes** or **maturity-onset diabetes**, if the criterion is the age of onset.
(2) **Insulin-dependent diabetes** (IDDM) or **non-insulin-dependent diabetes** (NIDDM), if the criterion is therapeutic responsiveness.
(3) **Type I diabetes** or **type II diabetes**, if the criterion is antibody occurrence.

Effects of hyperglycemia on the eyes. The lens of the eye is one of the tissues that contain **aldose reductase**, an enzyme that is used to convert glucose to sorbitol when osmolytes are required for cell volume regulation. Excess glucose will, therefore, cause the lens to accumulate excess sorbitol, to swell, and to become prone to cataract formation.

Effects of hyperglycemia on the cardiovascular system. Persistent hyperglycemia affects both blood vessel structure and function.

Effects on blood vessel structure: The presence of AGE products in matrix proteins and their stimulation of macrophages affect blood vessels in that there will be (1) thickening of the vessel walls, (2) narrowing of the vessel lumen, (3) reduced vessel compliance, and (4) increased permeability of the vascular wall.

Effects on blood vessel function: Glucose resembles **myoinositol**, an important substrate for the synthesis of **phosphatidylinositol**, and competitively inhibits its entry into cells. As a result, chronic hyperglycemia compromises the formation of second messengers in the phospholipase C pathway, which is used by many vasoconstrictor and inotropic agents.

Effects of hyperglycemia on peripheral nerve function. The deficiency in phosphatidylinositol that arises from competitive inhibition of myoinositol entry by glucose is associated with diminished protein kinase C activity because the levels of diacylglycerol (DAG) are reduced. Protein kinase C stimulates $\text{Na}^+\text{-K}^+\text{-ATPase}$, and its lack will reduce active $\text{Na}^+\text{-K}^+$ transport. Lack of insulin will also reduce active $\text{Na}^+\text{-K}^+$ transport because insulin stimulates $\text{Na}^+\text{-K}^+\text{-ATPase}$. The resultant accumulation of extracellular Na^+ and depletion of intracellular K^+ will alter membrane potentials, action potential amplitudes, and nerve conductivity. In myelinated nerves, where $\text{Na}^+\text{-K}^+\text{-ATPase}$ is concentrated at the nodes of Ranvier, the electrolyte disturbances will also be localized and, therefore, magnified and may lead to structural disruption of the myelin sheath.

Effects of Insulin Excess

Insulin excess causes hypoglycemia. Because glucose is the major fuel used by the brain,* its shortage causes symptoms that arise from compromised central nervous function. These include (1) increased autonomic discharge leading to palpitations, sweating, and apprehension; (2) mental confusion; and (3) lethargy, convulsions, and coma.

*It is only after prolonged starvation that the brain is able to use ketone bodies as fuel.

Glucagon and Related Peptides

Glucagon is a linear, 29–amino acid peptide. Its major source is the A cells of the pancreatic islets; A cells in the upper GI tract are a relatively minor source in humans.

Synthesis of Glucagon

Glucagon is cleaved from preproglucagon, a 179–amino acid polypeptide that is produced from a single mRNA and is processed differently in tissues that contain it (Table 9–13).

Of all the post-translational products, glucagon has the most clearly established physiologic role.

Regulation of glucagon secretion. The most important metabolic stimulus for the secretion of glucagon is a decrease in plasma glucose levels. However, a number of other agents can promote or inhibit glucagon secretion (Table 9–14).

The cellular mechanisms by which glucagon secretion is effected are poorly understood. They may include removal of insulin-mediated inhibition and electrophysiologic changes in either A cells or adjacent B cells whose ultimate effect is a change in the availability of extracellular Ca^{++} . A role for γ -aminobutyric acid (GABA) in B cells has been postulated but not proven.

Glucagon Receptor

Molecular structure of the glucagon receptor. The glucagon receptor is a membrane-bound, serpentine receptor protein that is coupled to a stimulatory G protein.

Signal transduction and molecular basis of glucagon action. The liver is the major target organ for glucagon. Two signal transduction pathways are used in liver cells.

Table 9–13

Tissues Differ in Their Processing of Preproglucagon

Tissue	Products of Preproglucagon
A cells of pancreatic islets and upper GI tract	Glucagon, major proglucagon fragment (MPGF), some oxyntomodulin and glycentin-related polypeptide (GRPP)
L cells of the distal GI tract and brain	Glycentin, glucagon-like polypeptides 1 and 2 (GLP-1 and GLP-2), some oxyntomodulin and glycentin-related polypeptide (GRPP). GLP-1 is further processed to yield GLP-1 (7-36) amide.

Table 9–14

Regulation of Glucagon Secretion

Promoters of glucagon secretion	\downarrow Plasma [glucose] β_2 Agonists like epinephrine* Cortisol
Inhibitors of secretion	α_2 Agonists Somatostatin (a strong inhibitor) Insulin (a weak inhibitor)

*The stimulatory effect of β_2 agonism normally dominates over a simultaneous, α_2 -mediated inhibition.

1. Receptor activation elevates cytosolic [cAMP] and promotes phosphorylation of protein kinase A. This enhances glycogen breakdown by promoting glycogen phosphorylase (see Figure 9–35) and inhibits glycolysis by inhibiting phosphofructokinase and pyruvate kinase (see Figure 9–35). It also increases formation of glucose from available amino acids.
2. Activation of a different receptor activates phospholipase C and the IP_3 pathway. The resultant rise in cytosolic $[Ca^{++}]$ also stimulates glycogen breakdown.

Actions of Glucagon

The net effect of glucagon is enhanced glucose output from the liver. In addition, its inhibition of glycolysis will reduce malonyl CoA (see Figure 9–35) and, thereby, allow incoming free fatty acids to be directed toward increased ketone body formation (see Figure 9–35).

Somatostatin

Somatostatin, the hypothalamic inhibitor of growth hormone release, is also secreted by pancreatic D cells and it occurs throughout the GI tract. The D cells contain both SS-14 and SS-28, SS-28 being the more potent inhibitor of insulin.

Somatostatin Synthesis and Secretion of Somatostatin

Somatostatin is cleaved from a 116–amino acid precursor, named prepro-somatostatin. The first 24 residues of this molecule are a signal peptide. The last 28 residues form SS-28 and the terminal 14 residues form SS-14.

- Glucose, some amino acids (arginine, leucine), β -adrenergic agonists, cholecystokinin, and secretin all promote somatostatin synthesis.
- α -Adrenergic agonists and the parasympathetic neurotransmitter acetylcholine inhibit somatostatin synthesis and secretion.

Somatostatin Receptors

Five different somatostatin receptors have been identified (SSTR1 to 5). They each activate an inhibitory G protein and, therefore, decrease cytosolic [cAMP]. SSTR5 is relevant to somatostatin-mediated inhibition of insulin secretion.

Actions of Somatostatin

Somatostatin concentration is highest within the pancreatic islets. As a result, its major effect is the local, paracrine inhibition of insulin and glucagon secretion. This action is most probably brought about by decreasing the transmembrane Ca^{++} current (see Figure 9–32). The roles of somatostatin in the regulation of digestive functions or hypothalamic secretions are described elsewhere.

Pancreatic Polypeptide

Pancreatic polypeptide (PP) is a 36–amino acid product of F cells in the pancreatic islets. Its major role is in the regulation of intestinal absorption.

Synthesis and Secretion of Pancreatic Polypeptide

Pancreatic polypeptide secretion is increased by protein-containing foods, hypoglycemia, and cholinergic nervous activity. Its secretion is decreased by somatostatin and hyperglycemia.

Actions of Pancreatic Polypeptide

Pancreatic polypeptide slows mucosal absorption of digestion products. Its function may be to smooth fluctuations in absorption of nutrients.

Amylin

Amylin is a 37–amino acid peptide that is cosecreted with insulin from pancreatic B cells in response to nutrient stimuli. Its major role appears to be to delay the appearance of meal-derived glucose in the circulation. The mechanisms of this action are not yet clear. It also suppresses secretion of insulin and glucagon and slows gastric emptying. It has also been reported to reduce food intake in rodents and has, therefore, been described as a **satiety agent**.

Fuel Metabolism and Nutrition

Living cells require energy to maintain their functions. The common link between energy production and utilization in mammalian cells is adenosine 5'-triphosphate (ATP) (Figure 10–1). Energy production involves the formation of the terminal phosphate group of the ATP molecule,* whereas energy utilization involves its hydrolysis. Some ATP can be formed in the cytosol without requirement for oxygen, but only from the degradation of carbohydrates. Most ATP is formed in mitochondria by aerobic oxidative metabolism of glucose, fatty acids, or amino acids.

Different cells have evolved so as to use some substrates in preference to others: (1) Brain cells use only glucose and ketone bodies as substrates and always require glucose. (2) Cells that have no mitochondria (erythrocytes) or, like renal medullary tubular cells, operate in a low-oxygen environment, cannot produce energy by oxidative mechanisms and, therefore, require glucose. (3) Adult cardiac muscle cells prefer fatty acids as a substrate.

Some organs are capable of storing energy for their own use (for example, glycogen storage in resting skeletal muscle) and others store energy for global use (for example, glycogen storage in the liver or triglyceride storage in adipose tissue). There is no specific protein reservoir, although portions of skeletal muscle and liver can be used to provide amino acids in settings such as in starvation.

*A variety of enzymes catalyze the transfer of the terminal, energy-rich phosphate bond from ATP to other nucleotides that are involved in transferring energy during cellular processes. Such other nucleotides include (1) **guanosine triphosphate** (GTP), which is the energy source used in gluconeogenesis and protein synthesis, (2) **uridine triphosphate** (UTP), which is used in glycogen synthesis, and (3) **cytidine triphosphate** (CTP), which is used in lipid synthesis.

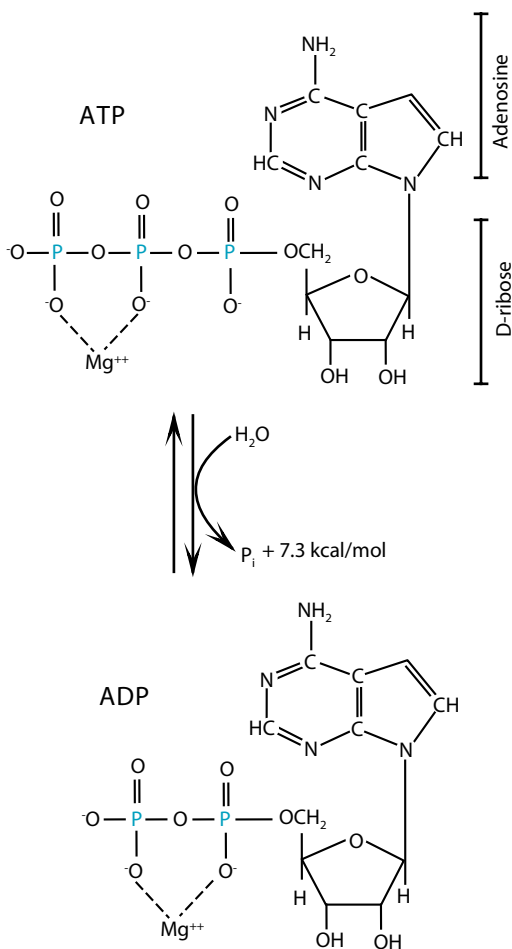


Figure 10–1 Chemical structure of ATP and ADP. The physiologic form of ATP is chelated with a divalent metal ion such as Mg^{++} . The 2 terminal phosphate groups in ATP are attached by high-energy bonds, each yielding 7.3 kcal/mol upon hydration.

ENERGY BALANCE

Daily energy requirements vary with gender, ambient temperature, and physical activity. For example, a mostly sedentary North American adult requires an average daily energy turnover of 10,000 kJ (2,500 kcal). The

energy is derived from food intake and metabolism of energy stores* in liver, muscle, and adipose tissue.

Energy Sources

In the fed state, most energy derives from dietary sources of glucose and fatty acids, and the liver makes additional contributions of glucose and ketone bodies.

Glucose

Most of the daily consumption of glucose (2,700 kJ; 660 kcal) derives from dietary carbohydrates. Hepatic glycogenolysis or gluconeogenesis normally makes a small contribution, but this can be increased when necessary. Anaerobic consumption of glucose in relevant tissues produces lactate, which is readily converted to glucose in the liver

Free Fatty Acids

Metabolism of dietary fats provides the bulk of the daily resting energy need of 10,000 kJ (2,500 kcal). Their poor water solubility requires that they be transported in special packages, the **lipoproteins** (chilomicra and lipoproteins of very low, low, intermediate, or high density). They are taken up into cells as free fatty acids (FFAs) and can also be synthesized in cells in that form. Free fatty acids are transported in plasma in association with albumin and, therefore, cannot easily escape through the capillary endothelium and reach tissues. The liver can convert FFAs to **ketones**, which are water soluble and can be utilized as a source of energy.

Amino Acids

Amino acids enter cells through a variety of specific Na^+ -coupled transporters and are used mostly for protein synthesis. They can be used as a substrate for ATP only in organs that can eliminate the ammonia (NH_3) that is produced during the metabolism of nitrogen-containing compounds. As a result, the liver and intestine are the major sites for amino acid degradation. The liver can detoxify NH_3 by the formation of urea, and NH_3 that is formed in the intestine is transported to the liver by way of portal venous blood.

*As a result of intermittent food intake, the human body requires energy stores so that biologic energy can be produced when it is needed, even between meals.

$$RQ = \frac{\text{Rate of CO}_2 \text{ Production}}{\text{Rate of O}_2 \text{ Utilization}}$$

Example 1: Oxidation of Glucose



$$RQ = \frac{6}{6} = 1.0$$

Example 2: Oxidation of Palmitic Acid



$$RQ = \frac{16}{23} = 0.7$$

Figure 10–2 The respiratory quotient is the ratio of CO₂ produced to O₂ consumed in the complete oxidation of foodstuffs.

Caloric Values of Foods

If carbohydrate, fat, or protein were completely catabolized to CO₂ and H₂O, they would provide an energy yield of 17.2 kJ/g (4.1 kcal/g) of carbohydrate or protein and 38.9 kJ/g (9.3 kcal/g) of fat.

Respiratory Quotient

The total body respiratory quotient (RQ) can be measured under appropriate conditions as respiratory CO₂ excretion rate divided by O₂ consumption rate (Figure 10–2). Respiratory quotient is used to estimate the contributions of carbohydrate, protein, or fat to body metabolism. The basis of the determination is that RQ is 1 when carbohydrate is the only substrate being utilized, 0.7 when only fatty acids are oxidized, and 0.8 when only protein is metabolized. The amount of protein catabolized can be estimated from urinary nitrogen excretion, and in that way, a nonprotein RQ can be calculated. It will be between 0.7 (pure fat) and 1 (pure carbohydrate), and the contribution of each can be apportioned.

Energy Sinks

Three physiologic functions are the major consumers of energy: (1) basal metabolism (4,800 kJ; 1,200 kcal), (2) voluntary muscle activity (4,400 kJ; 1,100 kcal), and (3) diet-induced thermogenesis (processes of food absorption).

ENERGY METABOLISM

The term energy metabolism encompasses conversion of chemical energy into biologic work. This conversion is not 100% efficient because cells dissipate energy in the form of heat.

Metabolism of Carbohydrates, Fats, and Proteins

Societies differ with respect to the fractions of carbohydrate, fat, animal protein, and plant protein in their normal diets. In western societies, the approximate fractional contributions of the three substrates to daily energy intake are carbohydrate (mostly glucose) 25%, fat 60%, and protein 15%.

After a meal and following digestion in the gastrointestinal (GI) tract, glucose and amino acids are absorbed into the circulation and reach the liver by way of the portal vein. In contrast, fatty acids and glycerol are packaged in lipoprotein particles and are absorbed in the first instance into intestinal lymph. Figure 10–3 summarizes the disposition of carbohydrates, fats, and proteins in the production of ATP for a liver cell.

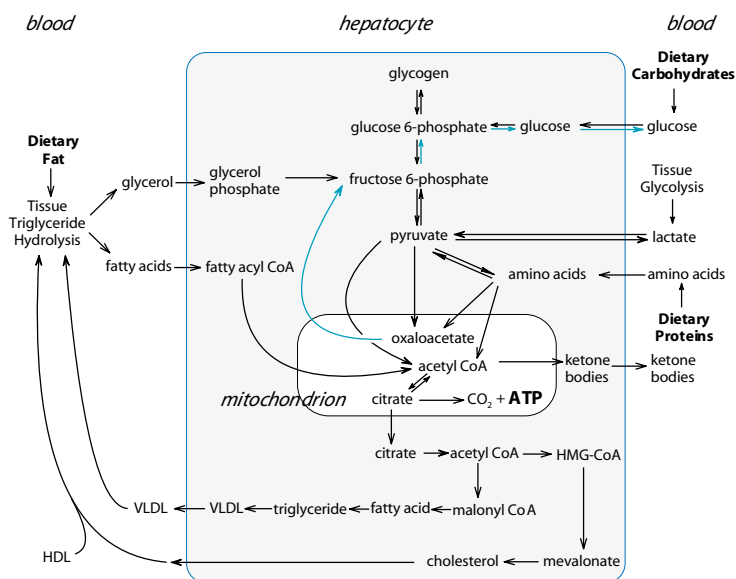


Figure 10–3 Summary of the pathways of metabolism in liver cells and their mitochondria. Three stages can be identified: (1) large dietary molecules are broken down into simple sugars (glucose), amino acids, glycerol, and fatty acids; (2) most of the molecules produced in stage 1 are converted into the acetyl unit of acetyl CoA; (3) acetyl CoA brings acetyl units into the Krebs cycle, where they are completely oxidized to CO₂, while ATP is generated by oxidative phosphorylation. The colored arrows are an outline of gluconeogenesis, which is shown in greater detail in Figure 10–4. 1 = glycogen phosphorylase; 2 = glucose 1-phosphate uridylyltransferase; 3 = phosphoglucomutase; 4 = hexokinase; 5 = glucose 6-phosphatase; 6 = phosphoglucosomerase; 7 = lactate dehydrogenase.

Carbohydrate Metabolism

Dietary carbohydrates are broken down to and absorbed as monosaccharides, glucose being the dominant monosaccharide. Maintenance of its plasma level is essential in order to maintain within the tissues an easily metabolizable energy source.

Sources of plasma glucose.

Dietary sources. Dietary carbohydrates, such as starch and glycogen, are broken down by pancreatic and brush border enzymes, such as α -amylase, maltase, and isomaltase, to yield the monosaccharides glucose, fructose, and galactose. These are absorbed in that form in the early portions of the small intestine.

Hepatic sources. When dietary intake is insufficient for body needs, the liver becomes a significant supplier of glucose. About 75% of this supply comes from breakdown of **glycogen**. The remainder derives from **gluconeogenesis**, half from lactate, which is produced in muscle, erythrocytes, and leukocytes, and half from amino acids, which originate from proteolysis.

Glycogenolysis: Glycogen is a large, branched polymer of glucose units. It is stored in granules, mainly in the liver and in skeletal muscle. Its degradation requires (1) **debranching enzyme** and (2) **glycogen phosphorylase**. Once the debranching enzyme has removed the branches, glycogen phosphorylase removes one glucose unit at a time, producing glucose 1-phosphate in the process (see Figure 10-3). Glucose 1-phosphate is then converted to glucose 6-phosphate (see Figure 10-3). The liver contains the enzyme **glucose 6-phosphatase**, which converts glucose 6-phosphate to glucose (see Figure 10-3).

A high level of glucose in the liver deactivates glycogen phosphorylase and thereby decreases the rate of glycogen breakdown.* Glycogenolysis is increased most significantly by **glucagon** and, to some extent, by **epinephrine**.

Gluconeogenesis: Gluconeogenesis is the process by which glucose is synthesized from noncarbohydrate precursors, such as lactate, pyruvate, amino acids, or glycerol. It is important during (1) starvation, when the preferred substrates are amino acids from protein breakdown and glycerol from fat breakdown, and (2) vigorous, prolonged exercise, when lactate that is produced in muscle is the preferred substrate. Gluconeogenesis occurs mostly

*In muscle, glycogenolysis is increased by increased cytosolic concentration of adenosine monophosphate (AMP).

in the liver, and its major raw materials are lactate and alanine, which is produced in active skeletal muscle by transamination of pyruvate.*

Both lactate and alanine are first converted to pyruvate (see Figure 10–3). Pyruvate is converted to oxaloacetate by means of the mitochondrial matrix enzyme **pyruvate carboxylase** (Figure 10–4), assisted by **biotin** as a CO₂ carrier. The inner mitochondrial membrane is impermeable to oxaloacetate. In order to transport this compound out of the mitochondria, it is first converted to **malate**, using **mitochondrial malate dehydrogenase**. Malate is transported across the mitochondrial membrane by a special carrier and is then converted again to oxaloacetate by **cytoplasmic malate dehydrogenase**. Cytosolic oxaloacetate is converted to glucose in a series of steps involving the intermediate products, phosphoenolpyruvate, glyceraldehyde 3-phosphate, fructose 1,6 bisphosphate, fructose 6-phosphate, and glucose 6-phosphate (see Figure 10–4).

Regulation of hepatic glucose synthesis and release: Liver cells can break glucose down to pyruvate (= glycolysis) or form new glucose (= gluconeogenesis). If both glycolysis and gluconeogenesis occurred simultaneously, the outcome would be a **futile cycle** because glycolysis generates two ATP per glucose molecule whereas gluconeogenesis consumes four ATP plus two GTP per glucose molecule. Futility is prevented by coordinated regulation of the two processes. Figure 10–4 shows the enzymes involved and the factors controlling them.

Lipid Metabolism

The biologically significant lipids are (1) free fatty acids, (2) sterols, such as cholesterol, (3) triglycerides, and (4) phospholipids.

Adipose tissue. Adipose tissue accounts for 20 to 50% of body weight in humans. It is widely distributed throughout the body with special deposits concentrated under the skin, around the kidneys and heart, and in the mesentery, buttocks, hips, and breasts. Its distribution is influenced by gonadal steroids and, therefore, varies between women and men.

Structure. Most of the adipose tissue in humans is **white fat**. In this tissue, mature adipocytes consist of a large lipid droplet, surrounded by a thin rim of cytoplasm that bulges locally to accommodate the nucleus. About 90% of the mass of adipocytes is stored triglycerides, and the cell has an almost unlimited ability to take up and store triglycerides. There are few

*Active muscle uses a great deal of glucose and, therefore, produces pyruvate.

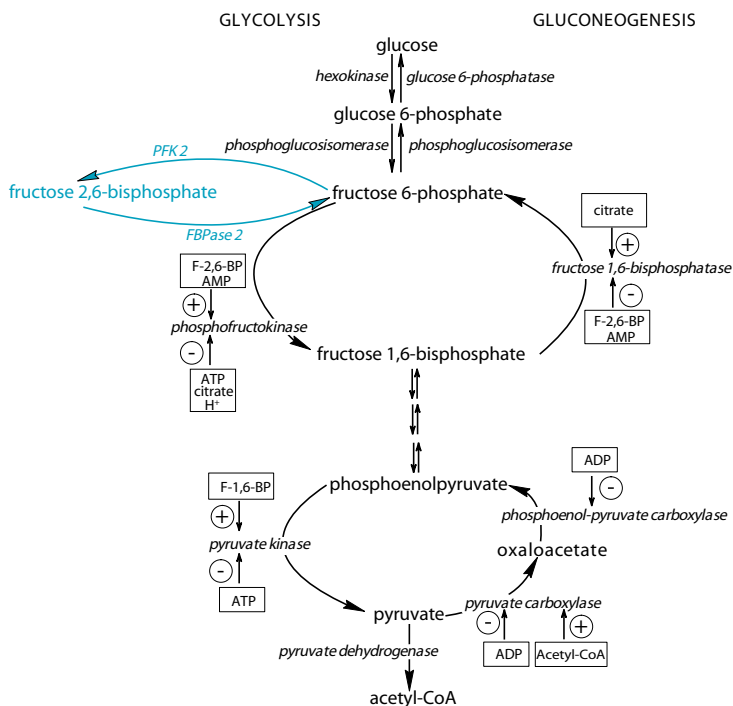


Figure 10-4 The steps in glycolysis and gluconeogenesis. Control points are provided by enzymes that are not common to the two processes. The pathway shown in color shows synthesis and degradation of fructose 2,6-bisphosphate, a molecule that has important functions in switching the liver from glucose breakdown to glucose production. It is synthesized from fructose 6-phosphate by phosphofructokinase 2 (PFK-2). F-2,6-BP is hydrolyzed back to fructose 6-phosphate by fructose bisphosphatase 2 (FBPase 2). The activities of PFK 2 and FBPase 2 are resident in one and the same polypeptide. ADP, AMP, ATP = adenosine di-, mono-, and triphosphate, respectively; F-1,6-BP = fructose 1,6-bisphosphate; F-2,6-BP = fructose 2,6-bisphosphate; PFK 2 = phosphofructokinase 2.

mitochondria, and the cells are not innervated. However, they do have α , β_1 , and β_3 membrane adrenoreceptors.

A small amount of adipose tissue in adult humans is **brown fat**, so named because of its reddish brown color that derives from pigments in their mitochondria. Mature brown fat adipocytes are small cells, containing many mitochondria and many small fat droplets around a central nucleus. They are richly innervated by the sympathetic nervous system.

Function. White adipose tissue has three major functions: (1) mechanical cushioning of the viscera, (2) insulation against heat loss, and (3) continuous energy storage and release. Brown adipose tissue functions mainly to be metabolically active and thereby produce heat.

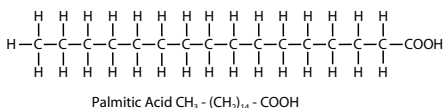
Structure and function of lipids.

Fatty acids. Fatty acids are unbranched hydrocarbon chains containing an even number of up to 18 carbon atoms and terminated by a carboxylic acid group (COO^-) (Figure 10–5A).

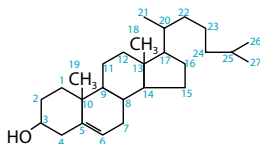
Cholesterol. Cholesterol is a steroid, which means that it contains the four hydrocarbon rings that are typical of steroids. Most of the molecule is hydrophobic, but the OH group at position 3 is a hydrophilic region (Figure 10–5B).

Complex lipids. Triglycerides consist of three fatty acid chains esterified to a glycerol backbone (Figure 10–5C). Phospholipids consist of two long-chain fatty acids (tails), linked to a hydrophilic group (head) (Figure

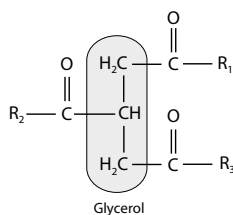
A) Fatty Acids



B) Cholesterol



C) Triglyceride (Triacylglycerol)



D) Phospholipid

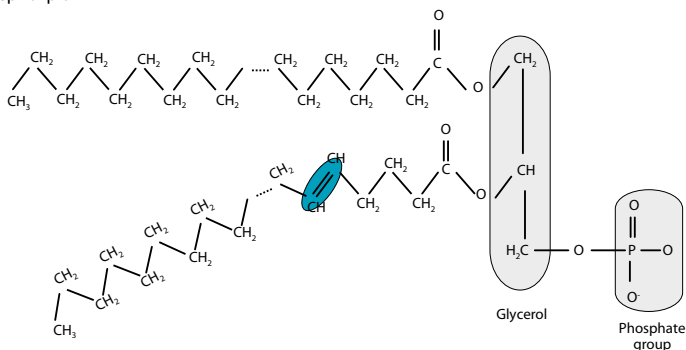


Figure 10–5 Chemical structure of the four major lipids that circulate in the human body. The convention for numbering carbon atoms in cholesterol is shown in color.

10–5D). They are the major components of cell membranes and are described more fully in Chapter 1, “General Physiologic Processes.”

Biosynthesis and metabolism of lipids.

Cholesterol biosynthesis. Cholesterol is a component of cell membranes and a precursor of bile salts and steroid hormones. It can be obtained from the diet (see Chapter 8, “Gastrointestinal Physiology”) or synthesized *de novo* from acetyl coenzyme A (CoA), mainly in the liver (see Figure 10–3). The first biosynthetic steps are important because they represent an important point of control: (1) acetyl CoA combines with acetoacetyl-CoA to form **3-hydroxy-3-methylglutaryl CoA** (HMG-CoA) in the cytosol, and (2) HMG-CoA is then reduced to **mevalonate** by the action of **HMG-CoA reductase** (see Figure 10–3). The second step is the committed step in cholesterol biosynthesis and is a key control point because HMG-CoA reductase is feedback-inhibited by cholesterol and is also inhibited by drugs that are commonly used in the treatment of **hypercholesterolemia**.

Metabolism of dietary lipids. Triglycerides are the major dietary lipids and also the major energy store in humans. Their conversion to fatty acids, transport in blood, and metabolism in tissues are summarized in Figure 10–6.

Metabolism of triglycerides and free fatty acids: The first step in the breakdown of stored or dietary fat is the hydrolysis of triglycerides by **lipases**. Pancreatic lipases dominate in the breakdown of dietary fat (see Chapter 8, “Gastrointestinal Physiology” for details). The lipases release fatty acid chains from the glycerol group and also produce 2-monoglyceride. The fatty acids are then broken down in **β -oxidation** to generate energy by way of the Krebs cycle. The glycerol group is transformed into dihydroxyacetone phosphate, an intermediary in glycolysis.

Ketones: The metabolism of FFAs requires that they first be broken down to form acetyl CoA by the process of β -oxidation in the mitochondria. Acetyl CoA then enters the Krebs cycle, provided that there is enough oxaloacetate available. When gluconeogenesis depletes the supply of oxaloacetate, then the level of acetyl CoA in liver cells exceeds that which can be accommodated by the Krebs cycle, and acetyl CoA is converted to acetoacetate and β -hydroxybutyrate in the liver mitochondria in the process of **ketogenesis**. Beta-hydroxybutyrate, acetoacetate, and its breakdown product, acetone, are collectively known as **ketone bodies**. Ketones readily leave the mitochondria, enter the cytosol and the circulation, and are used as an energy source in tissues, such as the heart, muscle, and kidney cortex. Under circumstances of food deprivation, the brain also is able to adjust its preference for metabolic substrate from glucose to ketones.

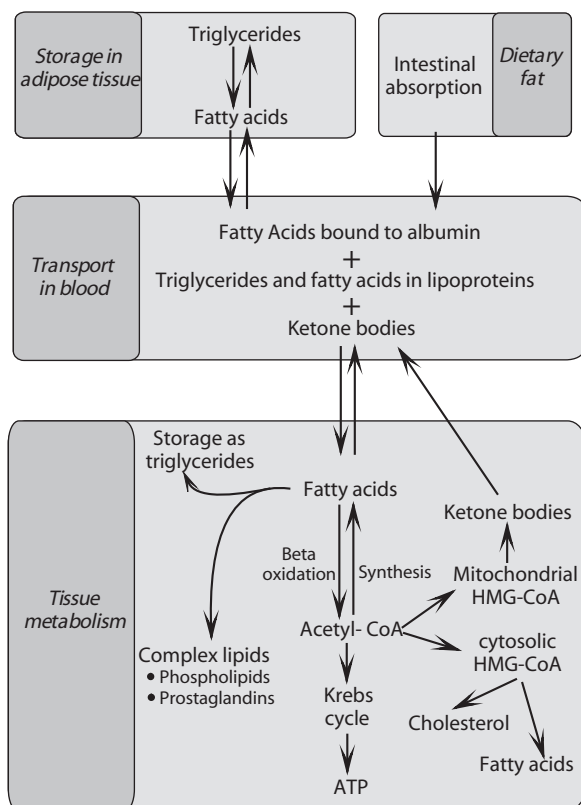


Figure 10–6 Stored and dietary fats are broken down by lipases into fatty acids and mono-glycerides. They are transported in the blood as lipoprotein particles and eventually enter cells as fatty acids. Depending on requirements and cell type, they then follow one of three paths: storage as triglycerides, formation of complex lipids, or beta oxidation to acetyl CoA. Acetyl CoA is used to produce ATP, ketone bodies, cholesterol, or fatty acids.

Lipoprotein metabolism. The lipoproteins form a system for the transport of lipids and cholesterol throughout the body. They aggregate as lipid–protein emulsion droplets and are classified into six groups on the basis of size, mobility, density, lipid species, and associated proteins, as follows: chylomicron, chylomicron remnant, VLDL, IDL, LDL, and HDL.* Their compositional details and functions are described in Chapter 8, “Gastrointestinal System.”

*HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

Amino Acid Metabolism

Proteins are being turned over continuously, and dietary proteins are degraded to amino acids. Since there is no store for excess amino acids, they must be degraded constantly. The α -amino group (NH_3) is removed first in the process of **transamination**, and the resulting carbon skeleton is either converted to metabolic intermediates that can be converted to glucose or oxidized in the Krebs cycle and used to support the energy needs of the body.

The carbon skeletons of the 20 standard amino acids are funneled into only seven molecules: acetyl CoA, acetoacetyl CoA, α -ketoglutarate, succinyl CoA, fumarate, oxaloacetate, and pyruvate. Amino acids that are degraded to one of the Krebs cycle intermediates (α -ketoglutarate, succinyl CoA, fumarate, oxaloacetate) or to pyruvate are called **glucogenic** because they can be converted to phosphoenolpyruvate and then be used for the net synthesis of glucose (see Figure 10–4). Amino acids that are degraded to acetyl CoA or acetoacetyl CoA are called **ketogenic** because they give rise to **ketone bodies**.

Regulation of Energy Metabolism

Long-term control of metabolism is significantly influenced by the glucocorticoid **cortisol** and the **thyroid hormones**. Cortisol modulates genes so as to permit hormones, such as insulin or glucagon, to activate metabolic genes. The thyroid hormones T3 and T4 regulate the level of important metabolic enzymes, thereby increasing the capacity for (1) O_2 uptake in the liver, muscle, and adipose tissue; (2) gluconeogenesis and glycolysis in the liver; (3) lipolysis in adipose tissue; and (4) protein breakdown in muscle.

In the short and intermediate time frames, metabolism is regulated (1) at the cellular level by mechanisms that control the plasma concentration and cell membrane transport of energy substrates and (2) at the whole body level by mechanisms that control body weight.

Regulation at the Cellular Level

Cellular mechanisms of regulation are driven by plasma glucose concentration and the ratio of plasma insulin to glucagon. Their normal ranges in plasma levels (basal to peak after a normal meal) are as follows: glucose 4 to 8 mmol/L; insulin 100 to 600 pmol/L; glucagon 40 to 30 pmol/L.

When plasma glucose levels are high, regulatory mechanisms allocate the use of energy substrates between production of ATP and synthesis of energy stores. **Insulin** and **parasympathetic nervous activity** are of primary importance in this setting. When plasma glucose levels are low or

when energy usage is high, regulatory mechanisms operate to control release of energy substrates from stores. **Glucagon** and **catecholamines** are of primary importance in these settings.

When glucose supply exceeds immediate needs. A carbohydrate-enriched meal will increase plasma insulin concentration to about 800 pmol/L. At the same time, the glucagon concentration is decreased to about 25 pmol/L. Thus, a carbohydrate-rich meal will change the insulin/glucagon ratio from 2.5 to about 30, and plasma glucose is directed toward glycogen synthesis (Figure 10–7).

Hormonal factors. Elevated catecholamines and growth hormone have small inhibitory effects on glucose uptake by cells. The main chemical regulator of glucose uptake from plasma is **insulin**. Insulin acts both on glucose transporters to regulate substrate uptake into target cells and on metabolic enzymes to control their rates and activities. Its major actions are to (1) increase glucose uptake into skeletal muscle, cardiac muscle, and adipose tissue, but not into the liver; (2) stimulate hepatic synthesis of glycogen, fatty acids, and ketone bodies; and (3) stimulate glycogen synthesis in skeletal muscle (see Figure 10–7).

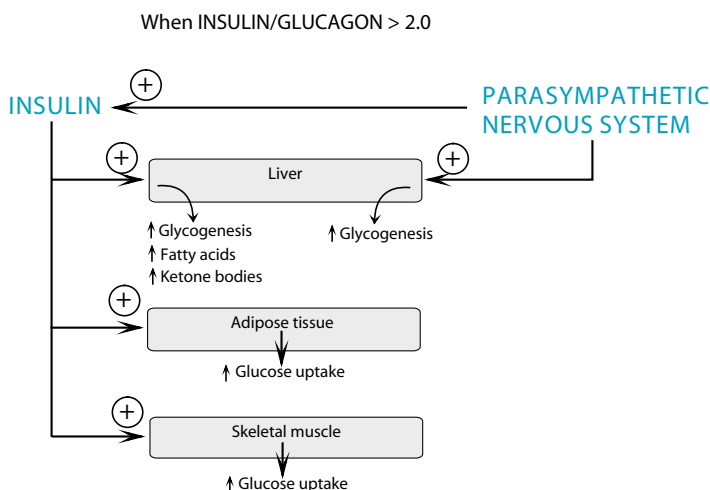


Figure 10–7 Regulation of energy metabolism in the well-fed state. The dominant hormonal influence is insulin. It promotes glucose uptake in tissues that have insulin-sensitive glucose transporters (fat and muscle). In the liver, insulin promotes glucose utilization to form glycogen and fatty acids. Some ketone bodies are formed as well. Nervous influences derive from the parasympathetic nervous system.

The details of these actions are described in Chapter 9, “Endocrine System.”

Neural factors. Parasympathetic nerves exert the most significant effect by (1) stimulating insulin release from the pancreas and (2) stimulating glycogen synthesis in the liver.

When glucose demand exceeds immediate supply. Settings in which there is a decrease in the insulin/glucagon ratio below its basal level of 2 include (1) a meal that is low in carbohydrates, but rich in protein, (2) increase in physical activity, and (3) starvation. The relative increase in the levels of glucagon over insulin shifts the energy metabolism so that breakdown of energy stores will dominate over storage (Figure 10–8).

Hormonal factors. Glucagon and the catecholamines are the dominant humoral factors in settings where energy needs exceed the supply that is immediately available in the form of plasma glucose. Hypoglycemia (plasma glucose levels of 3.5 mmol/L or less) also triggers increased secretion of cortisol and growth hormone, but they alone do not offer an effective counter-regulatory mechanism.

Glucagon stimulates all processes that supply energy substrates from body stores. It stimulates glycogen breakdown in the liver (but not in muscle), stimulates lipolysis in adipose tissue, and increases protein degradation

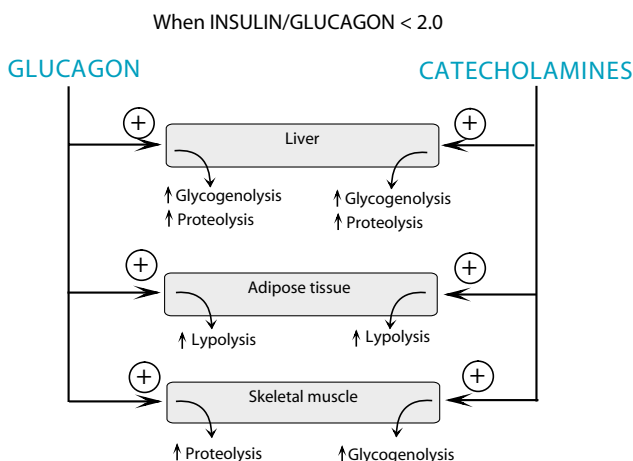


Figure 10–8 Regulation of energy metabolism when glucose demand exceeds readily available supply. Hypoglycemia stimulates release of glucagon and catecholamines. Both operate on tissues to break down available energy stores so that substrates become available for the formation of new glucose.

in muscle and liver. The cellular mechanisms of these actions are described in Chapter 9, "Endocrine System."

In humans, epinephrine (adrenaline) is secreted mostly from the adrenal medulla and norepinephrine (noradrenaline) derives from stimulated sympathetic nerve endings. The levels of both are increased in hypoglycemia or exercise. Hypoglycemia is a strong stimulus for the adrenal secretion of epinephrine. The afferent mechanisms are thought to be glucose-sensitive hypothalamic neurons (**central glucostat**) and glucose-sensitive peripheral cells (in the portal vein and other areas) with central projections. Exercise not only causes hypoglycemia (by increased substrate utilization) but is also a strong stimulus for sympathetic nervous activity.

The catecholamines (epinephrine and norepinephrine) exert short-term effects. They increase hepatic glucose production from glycogen breakdown and promote lipolysis in adipose tissue. Their role in hepatic glycogenolysis is mediated by α_1 -adrenoreceptor activation.* Such activation causes an increase in cytosolic $[Ca^{++}]$ and a subsequent activation of glycogen phosphorylase kinase by Ca^{++} -calmodulin. The final step is activation of the target enzyme **glycogen phosphorylase**.

Adipose tissue contains α_1 , β_1 , and β_3 adrenoreceptors. Therefore, catecholaminergic effects on lipolysis are exerted by elevated cytosolic $[Ca^{++}]$ and cAMP. **Hormone-sensitive triglyceride lipase** is a key target enzyme.

Neural factors. Nerves promote the breakdown of energy stores in two ways: (1) The sympathetic nervous system operates by elevating plasma levels of catecholamines. Their actions are described above; and (2) the somatic nervous system is active in contracting muscle. Its neurotransmitter is acetylcholine. Activation of muscarinic receptors depolarizes the plasma membrane and causes elevation of cytosolic $[Ca^{++}]$. The Ca^{++} -dependent stimulation of **glycogen phosphorylase** is of greater importance in muscle than is the cAMP-dependent mechanism that is activated by way of β -adrenergic receptors.

Control of Body Weight

Although obesity[†] is a significant health problem in western societies, most individuals between the ages of 20 and 50 years maintain a nearly constant

*In muscle, catecholamines slightly stimulate glycogenolysis by way of β -adrenoreceptor-mediated elevation of cytosolic cAMP. Elevated cAMP promotes activation of glycogen phosphorylase by a protein kinase A-dependent mechanism. This path differs from the α -adrenergic mechanism that is observed in the liver.

[†]Two definitions of obesity are used. It is said to exist (1) when the fraction of body weight that is due to fat (normally 12 to 18% in men and 18 to 24% in women) exceeds 20% in men or 25% in women; (2) when the body mass index (body weight in kilograms divided by the square of the height in meters) exceeds 30 kg/m². Its normal value is 20 to 25. In women, it may increase gradually to reach normal values of 24 to 29 by age 65 years.

or only slowly increasing body weight by balancing daily food intake with daily energy expenditure. When there is an imbalance, excess caloric intake is accumulated in body energy stores. These amount to approximately 10,500 kJ (2,600 kcal) per kilogram body weight and are mainly composed of fat (76%), protein (23%), and glycogen (1%).

The mechanisms that maintain body weight through the regulation of appetite are critically dependent on the hypothalamic areas that respond to a variety of stimuli, such as plasma glucose level, glucose consumption rate, rate of heat production, and concentration of hormones, such as cholecystokinin (CCK) and leptin.

Feeding and satiety. Food intake is regulated by hypothalamic neurons (Figure 10–9). When neurons in the ventromedial hypothalamus are stimulated, eating is evoked, and when the same neurons are destroyed by lesioning, anorexia follows. These neurons form a nucleus called the **feeding center**. They are stimulated by α_2 -adrenergic agonists. The feeding center neurons are continuously inhibited by neurons that are located in the lateral hypothalamus, constituting the **satiety center**. The satiety center neurons are activated by β -adrenergic agonists.

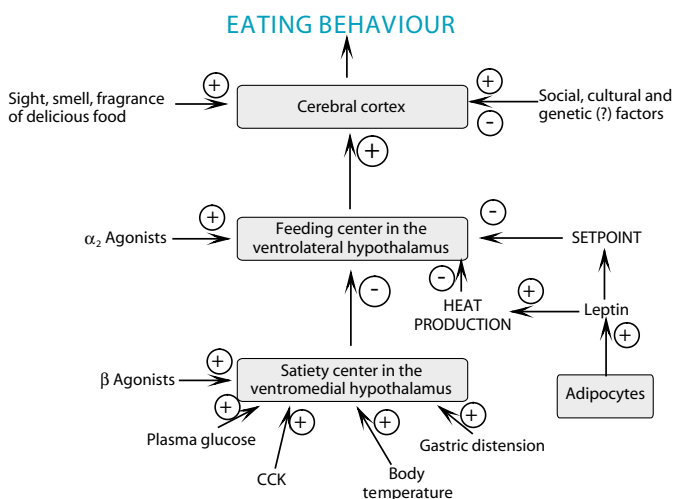


Figure 10–9 Eating behavior is a dominant influence on the control of body weight. Relevant hypothalamic neurons appear to be grouped into two populations, named the satiety center and the feeding center. The satiety center tonically inhibits the feeding center and the feeding center provides visceral drive toward eating behavior. Adipocytes produce the hormone leptin, and the plasma levels of leptin are directly proportional to total body fat mass. Leptin promotes heat production in body tissues and inhibit appetite, possibly by downward adjustment of the appetite setpoint.

Afferent information for the hypothalamic neurons derives from (1) their own glucose utilization; (2) CCK-B receptors in the brain; (3) peripheral CCK-A receptors; (4) thermoregulatory centers; (5) gastrointestinal stretch- or gluco sensors; (6) cultural, environmental, and experiential factors related to sight, smell, and taste; and (7) activation of hypothalamic leptin receptors.

When the hypothalamic or peripheral sensors indicate that glucose levels are low, nervous activity in the satiety center is suppressed, the feeding center is disinhibited, and there is a perceived need for food. Activation of CCK receptors decreases food intake, and antagonists of both A-type (located in the periphery) and B-type (located in the central nervous system) CCK receptors inhibit satiety. Appetite is depressed in a hot environment. Distension of the gastrointestinal tract inhibits food intake and contraction of an empty stomach stimulates appetite. Appetite is stimulated by the sight, smell, or taste of food that is perceived to be delicious.

The protein leptin is liberated mostly by adipocytes but is also synthesized in such tissues as the placenta, skeletal muscle, and mammary epithelium. Its expression is increased when total body fat is increased or when adipocyte size is increased. It is not increased in response to individual meals and, therefore, does not function as a meal-related satiety signal. One isoform of the leptin receptor lacks transmembrane and cytosolic domains and circulates as a soluble receptor. The other isoforms are transmembrane proteins, and only one of them, called the **long receptor**, contains cytosolic motifs that are required for signal transduction. The long receptor is coexpressed with neuropeptide Y, pro-opiomelanocortin (POMC), and agouti-related peptide (AgRP). Leptin-sensitive neurons are located in the arcuate nucleus* of the hypothalamus and project to the paraventricular nucleus. Thus, leptin also participates in neuroendocrine regulation.

Leptin enters the brain either through circumventricular organs that lack a blood-brain barrier or through a transport mechanism across the blood-brain barrier. It is cleared mainly by the kidney.

A rise in leptin decreases appetite and increases thermogenesis. Its physiologic role is thought to be to regulate the set point of the hypothalamic satiety center. Exogenous leptin induces weight loss that is restricted to adipose tissue and does not affect lean body mass. Its mechanism of action is to induce the expression of the key enzymes of lipolysis. The ability of leptin to decrease body weight and fat content has led to the view that leptin is an antiobesity hormone. However, **leptin resistance** is a common finding in the obese.

*The arcuate nucleus is normally associated in humans with regulation of prolactin and growth hormone, but it has projections to various hypothalamic and forebrain sites.

Overeating. Overeating is the usual cause of overweight and obesity. If overeating involves a diet that is rich in carbohydrates or proteins, there is an increase in the plasma level of thyroid hormones, and weight gain is attenuated by an increase in the basal metabolic rate (BMR). However, a fat-rich diet initiates no such compensatory mechanism, and the body fat stores are expanded as dietary triglycerides are deposited by the chylomicron lipoprotein lipase pathway (Figure 10–10). As a rule of thumb, an excess energy intake of 10 kcal results in deposition of 1 g of adipose tissue.

Endurance exercise is an effective way of counteracting fat accumulation. Such exercise decreases plasma insulin levels and increases plasma catecholamines. Decreased insulin lowers the activity of lipoprotein lipase and, thereby, suppresses lipogenesis. Increased catecholamines raise the activity of hormone-sensitive lipase and, thereby, promote lipolysis.

Undernutrition and starvation. A body mass index of less than 18.5 defines underweight. In societies of abundance, it is caused by one of three conditions: (1) maldigestion or malabsorption arising from gastrointestinal ailments; (2) insufficient protein intake to meet the amino acid requirements imposed by the continuous turnover of body proteins; and (3) psychogenic eating disorders, such as **anorexia nervosa** or **bulimia**. Undernutrition and starvation trigger metabolic adaptations whose aim is to maintain the supply of energy substrates for use by the brain, to protect lean body mass, and to promote survival.

The energy reserves of an average adult human are about 20 g of free glucose (enough to meet normal needs for 1 hour), 400 g of glycogen (enough for about 8 hours), 10 kg of fat (enough for about 40 days), and negligible free protein. As a result, when there is no dietary intake, plasma glucose tends to fall, glucagon becomes the dominant hormonal influence on metabolism, and the liver becomes the only source of energy (Figure 10–11).

The liver as an energy source. Glucose breakdown and gluconeogenesis are made responsive to starvation by the level of the regulatory molecule **fructose-2,6-bisphosphate (F-2,6-BP)**, which acts to promote glucose breakdown and to inhibit gluconeogenesis (see Figure 10–4). Hepatic glucose production can be increased by glucagon, epinephrine, and sympathetic nerve stimulation. Although glucagon and the catecholamines operate by different intracellular messengers in the liver,* they both achieve the

*Glucagon elevates cAMP, while the catecholamines operate via α_1 -adrenoreceptors to elevate cytosolic $[Ca^{++}]$.

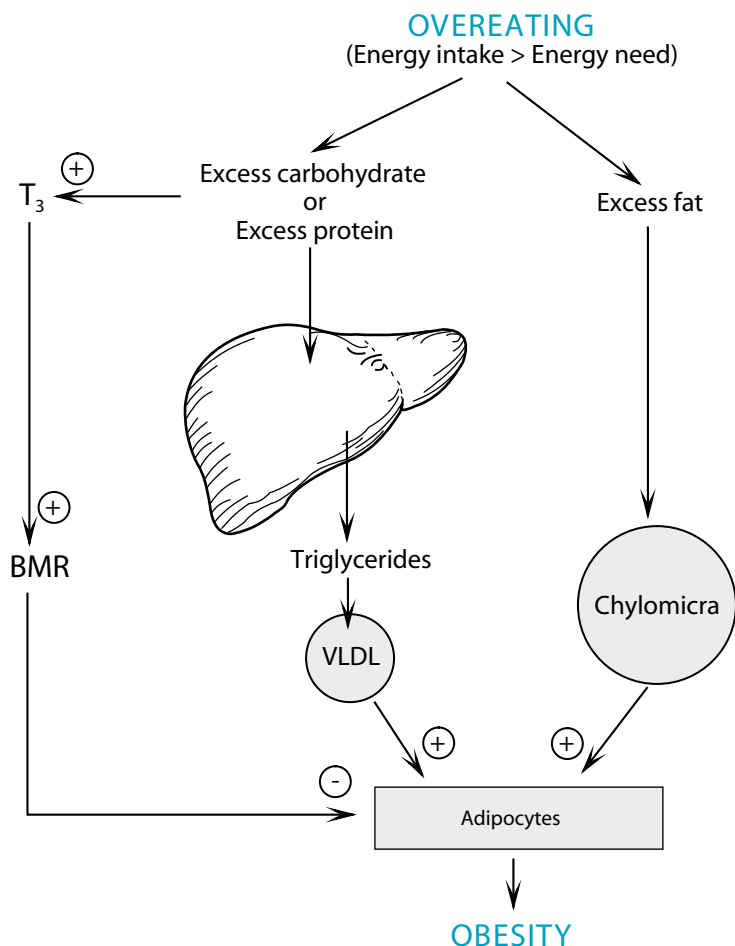


Figure 10–10 Food intake in excess of energy needs is defined as overeating and results in obesity as the excess is stored as fat in adipocytes. Excess intake in the form of carbohydrates or protein stimulates thyroid hormone release, which will increase basal metabolic rate (BMR) and thereby consume some of the excess intake. No such partial protection is present when excess fat is consumed. T₃ = tri-iodothyronine.

same major end result, namely, activation of glycogen phosphorylase, which promotes glycogen breakdown.

Glucagon has several complementary effects, all promoted by cAMP, to inhibit glycogen formation, decrease glycolysis, and increase gluconeogenesis. These effects include the following:

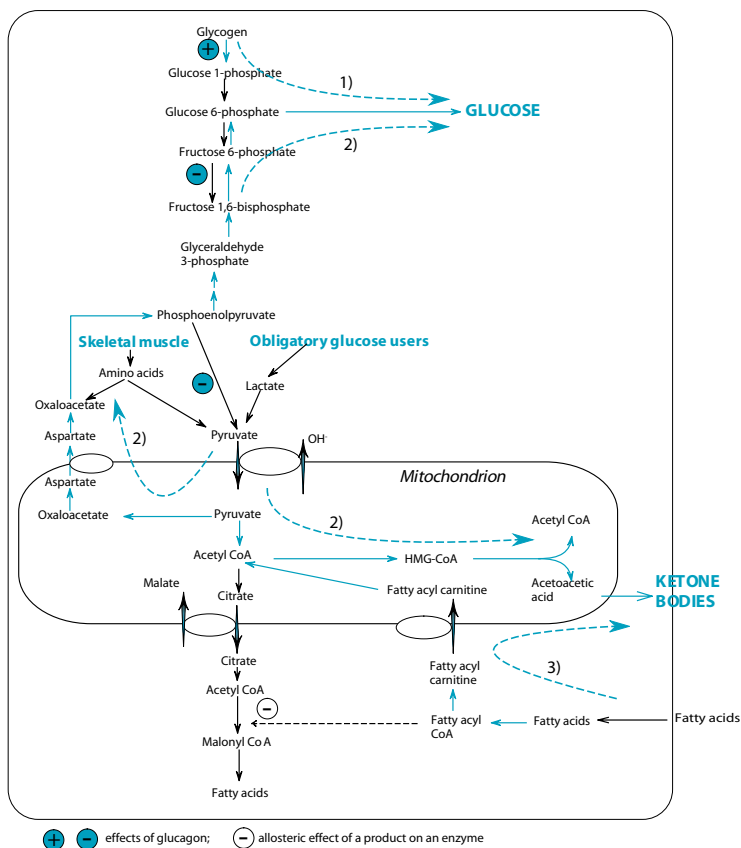


Figure 10-11 The liver as an energy source during starvation. Glucagon and allosteric effects combine to drive metabolic processes such that (1) glycogen is broken down to form glucose, (2) pyruvate is used to produce glucose or ketone bodies, and (3) fatty acids are used to produce ketone bodies. Allosteric inhibition of fatty acyl CoA on the formation of malonyl CoA also removes the inhibition that is normally exerted by malonyl CoA on the fatty acyl carnitine transporter. As a result, mitochondrial fatty acyl carnitine rises, as does mitochondrial acetyl CoA, and this drives formation of ketone bodies. (See Figure 9-35 for enzymes involved in the various steps.)

1. Inactivation of glycogen synthase and consequent inhibition of glycogen formation.
2. Phosphorylation of the PFK 2/FBPase 2 polypeptide. This activates its FBPase 2 activity (formation of fructose 6-phosphate from fructose 2,6-bisphosphate) while inhibiting its PFK 2 activity (formation of fructose

2,6-bisphosphate from fructose 6-phosphate). The net result is a decreased level of fructose 2,6-bisphosphate (see Figure 10–4) and, consequently, decreased glycolysis and increased gluconeogenesis.

3. Inhibition of pyruvate kinase, thereby further inhibiting glucose breakdown (see Figure 10–4).

The first days of starvation: Early increases in hepatic glucose production are derived from glycogenolysis. However, the total glycogen stored in the body is merely 400 g (6,400 kJ; 1,600 kcal) so that it can provide a fuel reservoir for only a few hours. Thereafter, gluconeogenesis assumes greater prominence. Glycerol and the carbon skeletons of amino acids can be used as substrates.

Glycerol is first converted to dihydroxyacetone phosphate (see Figure 10–3), which is then converted to fructose 1,6-bisphosphate by the enzyme aldolase. Subsequent steps in gluconeogenesis are shown in Figure 10–4. The carbon skeletons of amino acids are converted to oxaloacetate either directly or by way of the Krebs cycle. Figure 10–4 summarizes the gluconeogenic paths from oxaloacetate.

The first weeks of starvation: During the first week or two of fasting, hepatic gluconeogenesis provides glucose, which continues to be required as a substrate by tissues like nervous tissue, erythrocytes, and leukocytes. Adipose tissue provides free fatty acids and ketone bodies for use by other tissues.

Prolonged starvation: When starvation is prolonged, glucose requirements decline gradually because metabolic adaptations in the brain allow it to use ketone bodies as a fuel. As ketone utilization becomes more effective, the need for amino acids as a substrate for gluconeogenesis declines, muscle proteolysis diminishes, and fat reserves are used to a greater extent, until they approach depletion after about 6 weeks of starvation. At that time, body proteins are the only remaining energy substrate, and the rate of proteolysis increases again because there are virtually no free proteins stored in the body. As a result, mobilization of protein for energy produces deficits in physiologic function. Death occurs when metabolic requirements have depleted body proteins to a level where protein-dependent cellular functions can no longer be maintained. In an adult, this occurs after about 8 weeks of starvation.

VITAMINS

Vitamins are organic, vital components of the diet. Their function is different from supplying energy. However, most vitamins function in the steps of metabolism, either globally or in specific organs.

Vitamin A

Vitamin A can be derived from (1) plant sources (yellow vegetables or fruit), where it is present as the precursor **carotene**, or (2) animal sources, where it is present as the fatty acid esters of retinol. Carotene is the dominant source. It is a constituent of visual pigments and is necessary for cell development throughout life. Its absence is associated with night blindness and dry, scaly skin.

Thiamine (B₁)

Vitamin B₁ is found in unrefined cereal grains. It is a precursor for thiamine pyrophosphate and is a cofactor in decarboxylation reactions. Its lack causes **beriberi**.

Riboflavin (B₂)

Vitamin B₂ is found in dairy products and is a constituent of flavoproteins. B₂ deficiency causes inflammation of the tongue as well as scaling and fissuring of the lips.

Pyridoxine (B₆)

Yeast, wheat, and corn contain vitamin B₆, and it forms a central group in certain decarboxylases and transaminases. Its deficiency causes central nervous system symptoms, such as convulsions.

Niacin (Nicotinic Acid)

Niacin is found in yeast and lean meat. It is a constituent of the coenzymes nicotinamide adenine dinucleotide (NAD⁺) and nicotinamide adenine dinucleotide phosphate (NADP⁺), which function as electron carriers in oxidation-reduction reactions. Lack of niacin causes **pellagra**, a disease characterized by diarrhea, dermatitis, and dementia.

Pantothenic Acid

This vitamin is a precursor of coenzyme A. It derives from eggs and yeast, and its deficiency causes hair loss, dermatitis, and adrenal insufficiency.

Biotin

Biotin is a common component of enzymes that catalyze CO₂ binding. It is found in egg yolk and tomatoes. Deficiency is associated with dermatitis and inflammation of the small intestine.

Folates

Folic acid and its derivatives are coenzymes that are involved in methylating reactions. They are found in leafy green vegetables. Their lack causes anemia and **sprue**, a disorder that is characterized by intestinal malabsorption and fatty stool.

Cyanocobalamin (B_{12})

Vitamin B_{12} is contained in meat, milk, and eggs. It is a coenzyme in amino acid metabolism and is required for erythrocyte maturation. Its deficiency causes anemias that are characterized by the presence of a large number of immature red blood cells. One such anemia, named **pernicious anemia**, is caused by atrophy of the gastric mucosa and the associated deficiency in **intrinsic factor**, which is obligatory for B_{12} absorption in the small intestine.

Vitamin C (Ascorbic Acid)

Citrus fruits and leafy green vegetables are rich in vitamin C. The vitamin is required for normal collagen synthesis and its deficiency causes a variety of connective tissue disorders, including **scurvy**.

Vitamin D

Vitamin D is derived from one of two precursors. Dietary previtamin D_2 (**ergocalciferol**) is found mostly in fish liver. On the other hand, previtamin D_3 results from the exposure of 7-dehydrocholesterol in the skin to ultraviolet radiation. Both previtamins are delivered to the liver, and there they undergo hydroxylation to form the inactive precursor 25-(OH) D_3 (**cholecalciferol**) that is used as a substrate by mitochondria in renal tubular cells to produce the active form of vitamin D, namely, 1,25-(OH) $_2D_3$. This vitamin stimulates intestinal absorption of Ca^{++} and PO_4^{3-} . Its deficiency causes **rickets**.

Vitamin E (Tocopherol)

Vitamin E is contained in meat, eggs, dairy products, and leafy vegetables. It is an antioxidant and prevents the formation of **oxygen free radicals**. Deficiency causes **muscular dystrophy**.

Vitamin K

Vitamin K_1 is present in leafy green vegetables, whereas K_2 is formed by the action of bacteria in the colon. Both catalyze the carboxylation of glutamic

acid in various blood-clotting proteins. Vitamin K deficiency is associated with clotting disorders.

TRACE ELEMENTS

Trace elements are derived from the diet and are present in tissues in minute amounts. Nevertheless, they are essential for health and life, and their absence causes definite deficiency syndromes. On the other hand, if they are present in excess, they are toxic.

Chromium

Chromium is required for the proper functioning of insulin, and chromium deficiency causes insulin resistance. Chromium toxicity is associated with renal failure, skin disorders, and lung cancer.

Cobalt

Cobalt is part of the vitamin B₁₂ molecule. B₁₂ is required for the maturation of erythrocytes. Cobalt excess leads to cardiomyopathy.

Copper

Lack of copper causes anemia, changes the ossification process, and causes mental retardation. Copper excess is toxic to the liver and the kidneys.

Fluorine

Fluorine deficiency increases the incidence of dental caries, whereas fluoride excess causes (1) mottling of dental enamel; (2) abdominal malfunction, including cramps, vomiting, and diarrhea; and (3) cardiovascular collapse.

Iodine

Iodine is required for the formation of thyroid hormones.

Iron

Iron is a crucial part of the heme molecule. Its lack causes **anemia**. Excess iron causes liver failure, atrophy of the testes, cardiomyopathy, and arthritis.

Manganese

Manganese is used in oxidative phosphorylation and the metabolism of lipids and mucopolysaccharides. Manganese deficiency increases prothrombin time and, therefore, leads to bleeding (clotting) disorders. Manganese toxicity is associated with central nervous system malfunctions that resemble parkinsonianism or encephalitis.

Selenium

Selenium is an antioxidant. When it is deficient, striated muscle, including cardiac muscle, degenerates. Excess selenium is associated with hair loss, abnormal nail growth, and lassitude.

Molybdenum

Molybdenum functions in xanthine metabolism. The xanthines are inhibitors of phosphodiesterases.

Zinc

Zinc deficiency in adults depresses the immune response and causes skin ulceration as well as gonadal atrophy. Lack of zinc during development causes dwarfism. Excess zinc causes gastric ulcers, pancreatitis, nausea, vomiting, and respiratory distress.

Reproduction and Sexual Function

Sexual and reproductive functions are governed by neuroendocrine mechanisms that involve central nervous, pituitary, and gonadal endocrine aspects. Early postnatal plasma concentration of androgens determines whether female or male sexual function and behavior will be the life pattern; thereafter, the hypothalamus determines the onset of puberty, regulates pituitary-gonadal reproductive cycles, initiates lactation, and controls parenting behavior.

THE TESTIS

The human testes reside inside the scrotum, which hangs outside the body proper so as to aid in maintaining a local temperature that is one or two degrees Celsius below body temperature. The testis has both hormonal and reproductive functions. These occur in different cells: androgen synthesis occurs in **Leydig's cells**, and sperm formation takes place in **seminiferous tubules**.

Anatomy of the Testis

Spermatozoa are formed within the walls of the seminiferous tubules (Figure 11-1), drain into the **rete testis**, and are conveyed from there through the **epididymis** to the **vas deferens**. Higher up, the vas deferens loops over the top of the bladder and terminates in the **ampulla**. The ampulla is a dilated, tortuous pouch that narrows again at the distal end, joins the **seminal vesicle**, and forms the **ejaculatory duct**.

Seminiferous Tubules and Sertoli's Cells

The walls of the seminiferous tubules are formed by Sertoli's cells. They divide mitotically during testicular development but no longer divide in

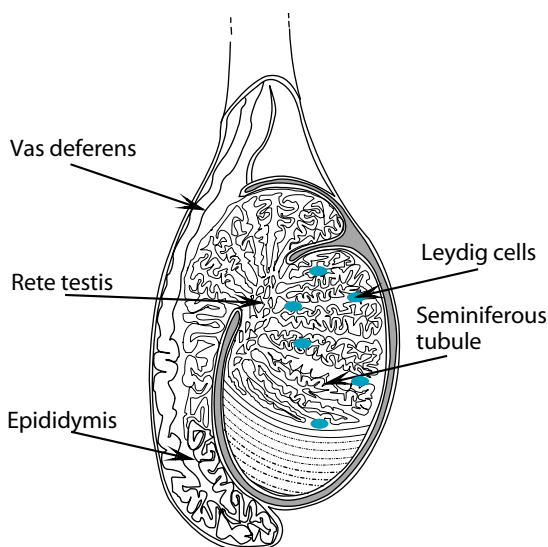


Figure 11–1 The bulk of each testis consists of loops of convoluted seminiferous tubules that originate from and drain into the rete testis at the head of the epididymis. The epididymis is a convoluted tube that conveys spermatozoa to the vas deferens.

adulthood. They are long cells that span the thickness of the tubule wall (Figure 11–2), and their junctions control the flow of molecules between the interstitial space and the tubular lumen (the **blood-testis barrier**). Their lateral walls maintain constant physical contact with spermatids throughout their formation from spermatogonia.

Leydig's Cells (Interstitial Cells)

These cells are few in number and are located in the connective tissue that lies between the seminiferous tubules.

Epididymis and Vas Deferens

The epididymis is a single, convoluted tube, about 5 m in length. Its three major functions are transport, maturation, and storage of spermatozoa.

Transport of spermatozoa along the epididymis. The epithelial lining of the epididymis is covered with kinocilia, which sweep the tube contents in the direction away from the testes. Neural factors are the main modulator of transport.

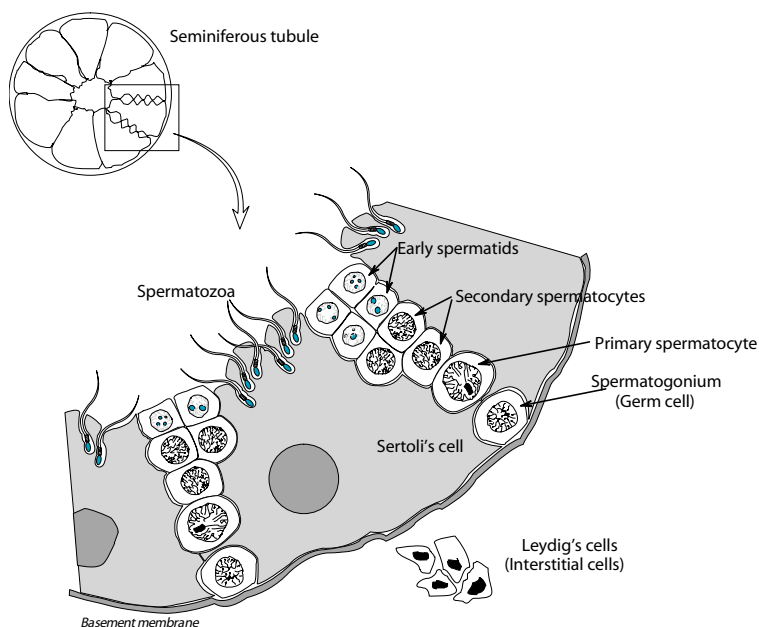


Figure 11–2 The walls of the seminiferous tubules are composed of Sertoli's cells. Their lateral boundaries nurture germ cells as they move toward the tubule lumen and become spermatozoa in the process. Leydig's cells are in the interstitium and on that side of the basement membrane that is opposite Sertoli's cells.

Maturation of spermatozoa along the epididymis. Sperm from the proximal regions of the epididymis are fully capable of fertilizing ova, but they lack motility. Spermatozoa become motile during their passage along the epididymis, which ranges from 1 to 20 days. This is probably regulated at the level of the sperm plasma membrane.

Storage of spermatozoa in the epididymis. The total content of the human epididymis is estimated to be near 600 million spermatozoa. The daily transport is near 200 million.

Seminal Vesicles and Prostate

These structures secrete a variety of products (Table 11–1) that contribute to an environment in which sperm motility and fertility can express themselves fully.

Blood Supply and Local Thermoregulation

The major supply to the testicular circulation is by way of the internal spermatic artery. It follows a convoluted course around the vas deferens and is surrounded by the **pampiniform plexus** of the testicular venous system. This anatomic arrangement functions as a heat exchanger and helps to maintain the temperature of the testes below body temperature.

Endocrine Functions of the Testis

Testosterone is the major androgen of the testes. It is carried in blood by a specific testosterone-binding globulin as well as by albumin and other plasma proteins.

Testosterone

Testosterone synthesis in Leydig's cells. Testosterone is synthesized in Leydig's cells from cholesterol by processes that are described in more detail in Chapter 9. The dominant pathway in humans leads via pregnenolone and dehydroepiandrosterone. Some testosterone is produced by the testicular enzyme **17 β -hydroxysteroid dehydrogenase** from the adrenal steroid **androstenedione** (see Figure 9–22), which reaches the testes by the circulation.

Hormonal regulation of testosterone synthesis: Leydig's cells are under the control of luteinizing hormone (LH) (Figure 11–3). The LH receptor is a serpentine membrane receptor, and its second messenger is cyclic adenosine

Table 11–1

Secretions from the Seminal Vesicles and Prostate

Source	Secretory Product	Main Function
Seminal vesicles	Fructose	Energy source for motility
	Seminogelin	Prevents semen coagulation
	Prostaglandins	Membrane surface effects; smooth muscle contraction or relaxation
Prostate	Citric acid	—
	Acid phosphatase	—
	Prostate-specific antigen	Liquefaction of ejaculate

monophosphate (cAMP). Its effects are (1) to increase release of cholesterol from the esterified storage form and (2) up-regulation of enzymes controlling testosterone synthesis, particularly those of the P-450 superfamily.

Testosterone is synthesized in the fetus, when human chorionic gonadotropin (hCG) is present, and after puberty, when LH levels are sufficient, but it is not synthesized in childhood (Table 11–2).

Transport and metabolism of testosterone. Only 2% of testosterone circulates in the free form. The remainder is bound to **gonadal steroid-binding globulin** (65%) or albumin (33%).

Biologic actions of testosterone.

During development.

Gender differentiation: Testosterone and other androgens determine the development of gender-linked features in anatomy and patterns of gonadotropin release. High levels of fetal testosterone have a masculinizing effect. Thus, androgen concentration in fetal blood during the first 10 weeks determines whether (1) female or male genitalia (internal as well as external) develop, and (2) the hypothalamus will develop a cyclic pattern of gonadotropin release after puberty (female) or a noncyclic pattern (male). Testosterone is responsible for the formation of male internal genitalia, and

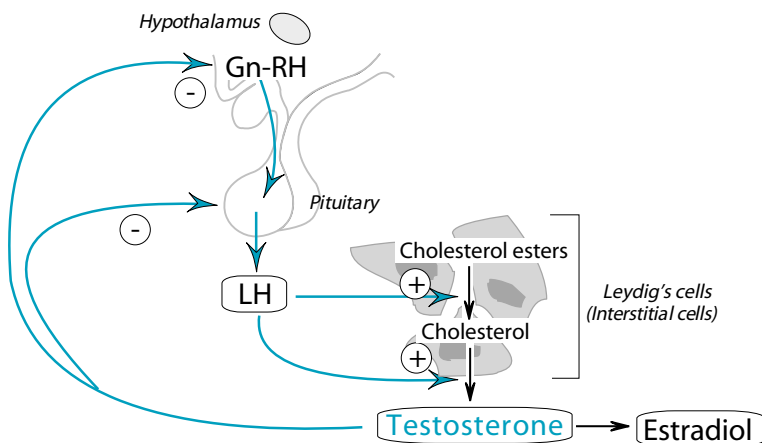


Figure 11–3 Leydig's cells synthesize mostly testosterone and use cholesterol as a substrate. The pituitary gonadotropin, LH, is the major controlling factor of synthesis. Testosterone is used in part to form estradiol in the testes. It also inhibits LH release directly by inhibiting pituitary gonadotropes and indirectly by inhibiting hypothalamic release of gonadotropin-releasing hormone (Gn-RH). LH = luteinizing hormone.

Table 11–2
Normal Plasma Total (Free + Bound) Testosterone Levels (nmol/L)

	Adulthood	Prepuberty
Men	10–35	0.2–0.7
Women	1–2.5	0.2–0.7

dihydrotestosterone (DHT), which is formed from testosterone in tissues that contain 5 α -reductase, is needed to form external male genitalia.

Primary and secondary gender characteristics: Testosterone or DHT induces the formation of the scrotum, penis, and accessory organs (Table 11–3). When they are absent, an oviduct, uterus, and vagina develop. Activation of the testes at puberty leads to adult size and function of the male organs of sexual function, secondary gender characteristics, such as hair distribution, timbre of voice, as well as bulk and distribution of skeletal muscle.

In adult life.

Regulation of sperm production: Testosterone affects sperm production by its feedback inhibition of LH (see Figure 11–3), the primary controller of spermatogenesis in Leydig’s cells.

Table 11–3
Testosterone and Dihydrotestosterone in the Control of Male Characteristics

Hormone	Controls These Characteristics
Testosterone	<ul style="list-style-type: none">• Formation of internal genitalia (transformation of the wolffian duct into the vas deferens and epididymis; prevention of the formation of the müllerian duct)• Increase in muscle mass• Development of male sex drive
Dihydrotestosterone	<ul style="list-style-type: none">• Formation of external genitalia• Prostate enlargement• Penis enlargement at puberty• Facial hair• Acne• Receding hair line

Anabolic effects; muscle building: Androgens promote hypertrophy of muscle by activating nuclear receptors that lead to changes in the transcription of growth factors increasing synthesis and decreasing breakdown of proteins. This results in formation of myofibrils.

Sexual behavior: Testosterone is thought to be responsible for male libido and has been proposed as the cause for behavior patterns that are typically male.

Modulation of bone formation: Androgens are believed by some to cause ossification and closure of the epiphyseal growth plates of the long bones. Others have stated that epiphyseal closure is caused by estrogens.

Inhibins

Inhibins A and B are synthesized in Sertoli's cells in men and ovarian granulosa cells in women. They are formed by disulfide linkages from three precursor proteins, designated α , β_A , and β_B (Figure 11–4). Both inhibin A and B are capable of inhibiting follicle-stimulating hormone (FSH) synthesis by action on pituitary gonadotropes, but it is inhibin B that is the primary physiologic regulator. Inhibins are found in a number of tissues including the brain, where they function as neurotransmitters.

Activins

Activins are formed from the same β -subunits that contribute to inhibin formation. There are three activins (Figure 11–5). They act on pituitary gonadotropes to stimulate FSH synthesis. The activins are found in tissues other than the gonads and serve a variety of functions, including neurotransmission and tumor suppression.

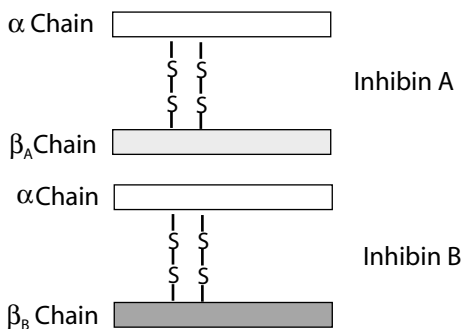


Figure 11–4 Inhibin A and B are formed by disulfide linkages from three different precursor proteins, named α , β_A , and β_B .

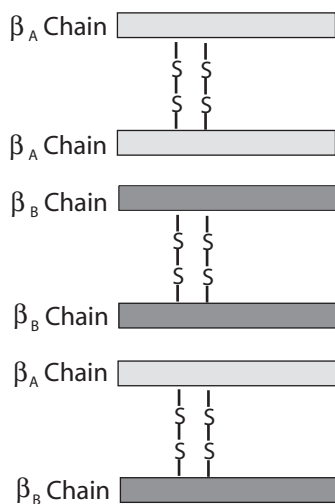


Figure 11–5 Three activins are formed by disulfide linkages from the precursors, β_A and β_B .

Spermatogenic Functions of the Testis

Sperm Production

Spermatogenesis takes place in the seminiferous tubules, within the highly regulated environment of the intercellular spaces between neighboring Sertoli's cells. Undifferentiated germ cells (spermatogonia), which are located between the base of Sertoli's cells and the basement membrane, undergo, over a period of 60 to 80 days, a series of mitotic and meiotic divisions that culminate each day in the formation of 200 to 300 million highly differentiated spermatozoa (Figure 11–6). Spermatozoa are independently mobile and carry in their heads 23 unpaired chromosomes plus the enzymes required for penetration of the ovum.

The process of spermatogenesis begins near the basement membrane (see Figure 11–2) where spermatogonia periodically emerge from a pool of stem cells and undergo a fixed number of mitotic* divisions to form diploid daughter cells. Some of these daughter cells mature and form **primary spermatocytes** and enter into meiosis. The first of two meiotic divisions yields two daughter **secondary spermatocytes** from each primary spermatocyte.

*In a mitotic division, each daughter cell receives a full set of chromosomes (diploid number). In humans, meiotic division happens only in the gametes. It is a two-stage division in which one diploid stem cell produces four daughter cells, each with only half the chromosomes (haploid number).

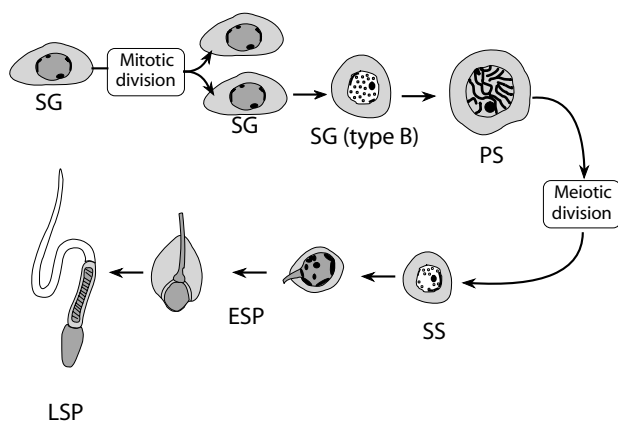


Figure 11-6 Formation of spermatozoa from a spermatogonium (germ cell). ESP = early spermatid; LSP = late spermatid; PS = primary spermatocyte; SG = spermatogonium; SS = secondary spermatocyte.

Each daughter still contains a diploid number of chromosomes. The second meiotic division yields **early spermatids**. Early spermatids have the haploid number of 23 chromosomes, and they mature into spermatozoa. As maturation of each cell type proceeds, the cells move closer and closer to the lumen of the seminiferous tubule (see Figure 11-2). The last stage, maturation of the early spermatids into mature sperms (spermatozoa), occurs in deep infoldings of the luminal surface of Sertoli's cells.

The role of the epididymis in sperm maturation. The end product of Sertoli cell nurture is nonmotile spermatozoa. They are functionally infertile in that they would have to be delivered directly to an ovum in order to fertilize it. They are released into the lumen of the seminiferous tubule in a process that is called **spermiation** and are then transported through the rete testis to the epididymis. There they undergo extensive structural and functional changes that will make them motile and fully fertile. The ability of the epididymis to provide the appropriate environment for these changes depends on the presence of androgens.

Regulation of Sperm Production

It is likely that normal spermatogenesis requires synergistic actions of LH, androgens, and FSH to nurture Sertoli's cells, which are also the source of peptides, enzymes, growth factors, and cytokines that create the environment in which spermatogenesis can occur.

Luteinizing hormone and androgens in the control of spermatogenesis.

Receptors for LH are found in no testicular cells other than Leydig's cells. Therefore, LH probably exerts all of its spermatogenic effects by way of testosterone.

Testosterone is released from Leydig's cells, travels through the interstitial spaces, and enters Sertoli's cells by still undefined processes. Some of it binds to nuclear receptors, whereas much of it is converted to DHT by the enzyme 5α -reductase that resides in Sertoli's cells. Testosterone or DHT is required for induction of spermatogenesis, but a simultaneous requirement for FSH has not been ruled out. Once spermatogenesis has been initiated, testosterone alone can maintain it for a long period of time.

In addition to its role in spermatogenesis, testosterone is required for shaping the cytoskeleton of Sertoli's cells into an adult conformation.

Follicle-stimulating hormone in the control of spermatogenesis. Follicle-stimulating hormone receptors are primarily located in the plasma membrane of Sertoli's cells. Follicle-stimulating hormone acts directly on the seminiferous tubule and is indispensable for the maintenance of spermatogenesis. Its precise role in spermatogenesis has not yet been delineated. It alone stimulates secretion of inhibin, but many of its actions may result from synergism with testosterone.

THE OVARY

Anatomy of the Ovary

Each ovary consists of (1) the cortex, which contains the germinal cells, follicles in their various stages, theca cells, granulosa cells, and corpus lutea in their various stages, and (2) the medulla, which contains theca cells, connective tissue, blood vessels, and nerves.

Ovarian Cortex

The ovarian cortex contains the physical and biochemical prerequisites for (1) storing, nurturing, and expelling oocytes and (2) maintaining and dissolving the corpus luteum that remains after each ovulation. The various phases of oocyte, follicle, and corpus are sketched in Figure 11–7.

Follicles. In women, the mitotic proliferation of ovarian stem cells stops before birth, and all oogonia enter their first meiotic division, enter a state of arrest in prophase, and become primary oocytes. They surround themselves with ovarian mesenchymal cells and become **primordial follicles** (see Figure 11–7). The flat epithelium that characterizes primordial follicles

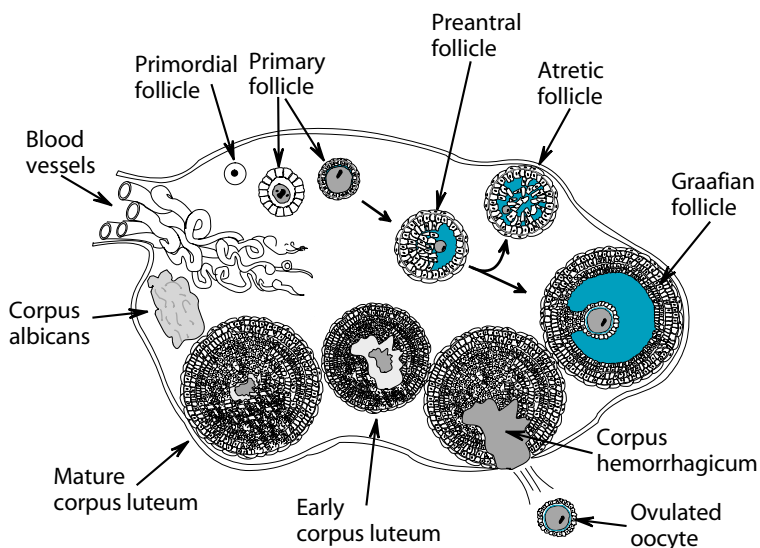


Figure 11-7 The ovarian cortex is the home of follicles in various stages of growth or atresia. It also contains the corpus luteum, the structure that develops from what remains of the graafian follicle after the oocyte has been expelled. The corpus albicans is scar tissue that remains when the corpus luteum dies.

changes to a more columnar shape, and this forms the **primary follicle**. Many degenerate, but those that survive into adulthood remain as primary follicles with their oocytes arrested in prophase of the first meiotic division. At puberty, primary follicles begin to be recruited for growth.

Primary follicles: Almost all follicles are primary follicles. They are protective spherical structures, about 20 μm in diameter, in which an oocyte is surrounded by a layer of granulosa cells, a basement membrane, and a layer of theca cells (Figure 11-8). All of these follicles were present at birth, and those remaining at maturity* will have attained only double or triple their original size. They have a centrally placed oocyte (see Figure 11-8) with a large nucleus, named the **germinal vesicle**. The most advanced among these follicles show an oocyte in a small pool of **antral fluid** that separates the oocyte from a layer of granulosa cells.

Preantral, antral, and graafian follicles: Each month during a woman's lifetime before menopause, 6 to 12 primary follicles develop further. Within the month, these follicles grow to a final diameter of several hundred micrometers. During this time, the oocyte itself grows to about 10 times its starting size

*Most of the two million oocytes that were present at birth are lost to attrition over the next 50 years.

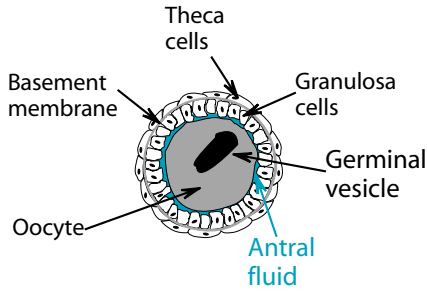


Figure 11–8 Structure of a primary follicle. The oocyte with its nucleus, the germinal vesicle, is surrounded by a thin coating of antral fluid, a layer of granulosa cells, a basement membrane, and a less organized layer of theca cells.

and synthesizes a glycoprotein coat, the **zona pellucida**, which surrounds the oocyte and separates it from the layer of granulosa cells. The granulosa and theca cells divide mitotically and form the multilayered, columnar epithelium that characterizes **secondary follicles**. The epithelium grows so rapidly that the interior structure of the follicle becomes asymmetric. Follicles that reach this stage of growth are called **preantral follicles**.

Preantral follicles: The preantral phase lasts 8 to 12 days, during which time the follicle produces increased amounts of gonadal steroids, principally from the cells of the theca interna. Many preantral follicles undergo atresia and disappear. The remainder are converted, under the influence of circulating gonadotropins, to **antral follicles** and finally a **graafian follicle**.

Antral follicles and the graafian follicle: A surge of LH causes surviving preantral follicles to accumulate further antral fluid rapidly and become antral follicles. Then, one of them, the dominant (graafian) follicle (Figure 11–9), attains a diameter of about 25 mm, bursts, and expels the oocyte into the region outside the oviduct (fallopian tube) at about the 14th day of the maturation cycle. The first meiotic division of the oocyte is completed just before ovulation. One of the resulting daughter cells receives most of the cytoplasm and is called the **secondary oocyte**. It immediately progresses to metaphase of the second meiotic division, where it halts. The other daughter cell is named the **first polar body**; it disintegrates. The secondary oocyte completes the second division only if it is fertilized. One of the daughter cells from that division then progresses to form an embryo, while the other forms the second polar body and is discarded.

The ruptured follicle: The ruptured follicle quickly fills with blood (the **corpus hemorrhagicum**) (see Figure 11–7), the theca and granulosa cells multiply, and the blood is resorbed and soon replaced with luteinized granulosa and theca cells.

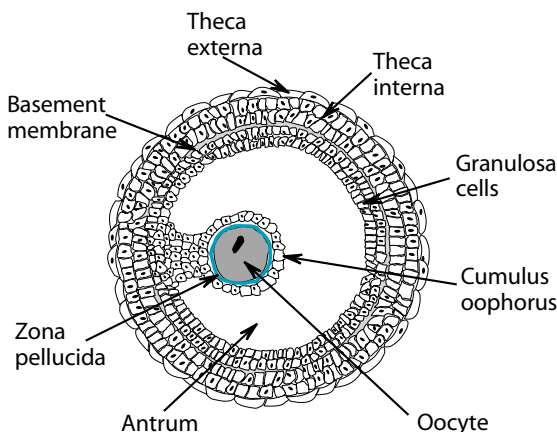


Figure 11–9 Structure of a graafian follicle. The oocyte is surrounded by the zona pellucida and a single layer of granulosa cells, termed the cumulus oophorus.

Atretic follicles: The ovarian cortex also contains preantral follicles that are clearly undergoing atresia, a process of deterioration that steadily reduces the number of oocytes during a woman's lifetime.

Corpus luteum. The corpus luteum is the final stage of the follicle from which the oocyte was expelled during that month's ovulation. It is richly vascularized and supplied with LH receptors. Their stimulation increases synthesis of progesterone, the major steroid product of the corpus luteum. If pregnancy occurs, the corpus luteum persists and maintains high levels of estrogens and progesterone for the purpose of suppressing further ovulation and optimizing the endometrium for implantation. In the absence of pregnancy, the corpus luteum regresses and degenerates during the last 4 days of the menstrual cycle. It leaves the **corpus albicans**, a region of scar tissue.

Endocrine Functions of the Ovary

The major endocrine functions of the ovary arise from theca and granulosa cells in the follicles and are controlled by LH and FSH when cells have receptors for these steroids. The dominant ovarian hormones are progesterone and the estrogens **estradiol** and **estrone**. All derive from cholesterol (Figure 11–10) and are produced by cooperation between the theca and granulosa cells (Figure 11–11). The main source of cholesterol is blood-borne LDL, although theca cells have the capacity to synthesize it *de novo* from acetate. Rates of steroid production vary greatly during different stages of the menstrual cycle (Table 11–4).

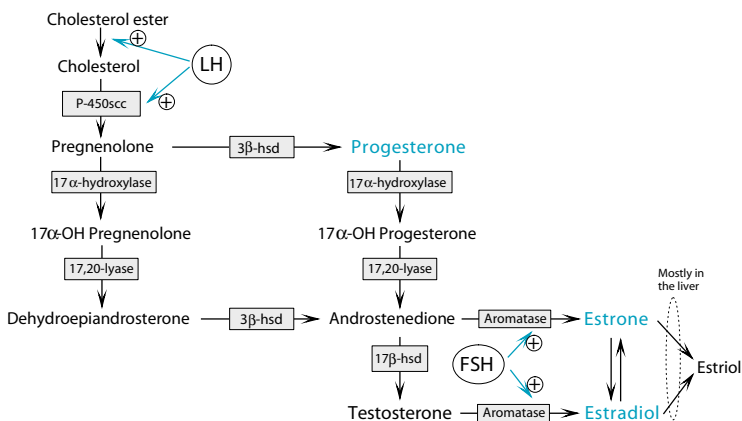


Figure 11–10 Pathways by which progesterone, androgens, and estrogens are synthesized in follicles. The sites where LH and FSH exert their influences are also shown. Estriol has weak steroid action. It is produced mostly in the liver from the other two estrogens estrone and estradiol. 3 β -hsd = 3 β -hydroxysteroid dehydrogenase.

Steroidogenic Functions of the Follicles

Primary follicles.

The role of FSH in primary follicles: The estrogens are important mitogens for granulosa cells, promote their proliferation, and, thereby, stimulate follicular growth. As a result, follicles remain in the primary state until they synthesize enough estrogen to promote growth. The trigger for increased estrogen synthesis is FSH. Only granulosa cells contain sufficient **aromatase** to form estrogens from androgen precursors (see Figures 11–10 and 11–11), and only granulosa cells contain FSH receptors. Follicle-stimulating hormone stimulates aromatase. This makes FSH of great importance during the early follicular phase.

The role of LH in primary follicles: Luteinizing hormone plays a supportive role by driving androgen synthesis in theca cells. Only theca cells have LH receptors during the early follicular phase and only they have 17 α -hydroxylase and 17,20-lyase, two requisite enzymes for the formation of androgens from pregnenolone (see Figure 11–10). Granulosa cells cannot form estrogen unless they receive androgens from theca cells (see Figure 11–11).

Preovulatory follicles. Aromatase is maximally active in the dominant, preovulatory follicle. In addition, granulosa cells begin to express LH receptors, and they induce progesterone synthesis from cholesterol in granulosa cells. Some of the progesterone diffuses into theca cells and further increases substrate for estrogen synthesis (see Figure 11–11).

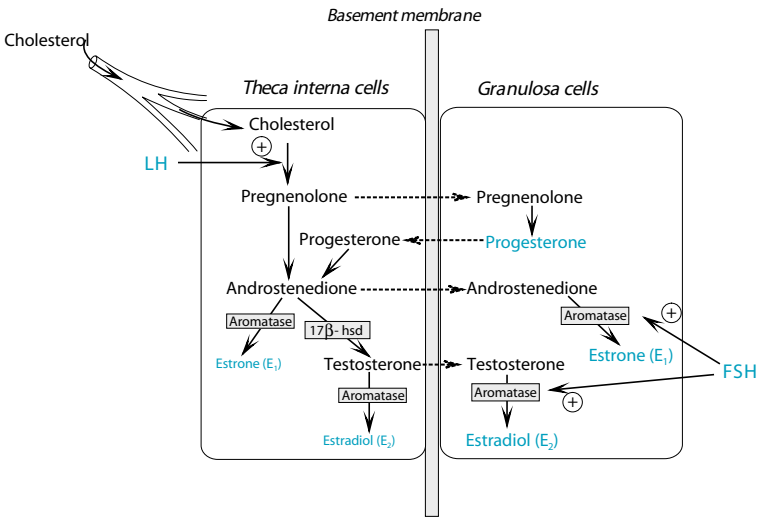


Figure 11–11 Production of androgen substrates in theca cells and their use as estrogen precursors in granulosa cells. When LH receptors are activated, intracellular cAMP increases and leads to two consequences: (1) increased release of cholesterol from its esterified storage form and (2) up-regulation of controlling enzymes, particularly those of the P-450 superfamily. The net effect is increased formation of pregnenolone from cholesterol. Some pregnenolone diffuses across the basement membrane into granulosa cells and some of it is converted to androstenedione. The portion of androstenedione that diffuses into granulosa cells is converted to estrone, whereas the portion that remains within theca cells is mostly converted to testosterone because the absence of FSH receptors in theca cells gives them very low aromatase activity.

Atretic follicles. Follicles that lag behind the maturation of the dominant follicle undergo atresia, which is a process that appears to be driven by progesterone, estrogens, and androgens. Of particular relevance may be the appearance in early atretic follicles of **5α-reductase**, the enzyme that converts testosterone to DHT.

Table 11–4

Daily Production Rates of Ovarian Steroids (mg/24 h)

Steroid	Follicular Phase (early to late)	Midluteal Phase
Progesterone	1–4	25
Dehydroepiandrosterone	7–7	7
Androstenedione	2.5–5	3.5
Testosterone	0.14–0.17	0.13
Estrone	0.05–0.35	0.25
Estradiol	0.04–0.4	0.25

Table 11–5

Normal Plasma Total (Free + Bound) Gonadal Steroid Levels (pmol/L)

Steroid	Women			Men
	Adult, Premopausal		Prepubertal, Postmeno- pausal	
	Follicular Phase	Midluteal Phase		
Progesterone	3,000	60,000	< 6,000	1,000
Estradiol	200–900	400	0.2–0.7	< 180
Testosterone	1,000–2,500		200–700	10,000–35,000

Steroid Hormones**Progesterone**

Synthesis and secretion of progesterone: The major sources of progesterone are the corpus luteum and placenta. Follicles are relatively minor contributors, but the extent of their contribution can be deduced from the observation that the plasma concentration of progesterone in women during the follicular phase is threefold that found in men (Table 11–5). It is carried in blood mostly in bound form (albumin 80%; corticosterone-binding globulin 15%), and only 2% is free.

Biologic actions of progesterone: The major target organs and local effects of progesterone are summarized in Table 11–6.

Metabolism of progesterone: The half-life of progesterone is short. It is metabolized mostly in the liver, where it is converted to **pregnanediol**, conjugated to **glucuronic acid**, and excreted in bile and urine.

Estrogens

Synthesis and secretion of the estrogens: Estrogens are secreted primarily by the granulosa cells of the follicles, the corpus luteum, and the placenta. Theca cells do not have FSH receptors, are therefore not able to have a sufficiently high level of aromatase activity, and can make only a small estrogen contribution. However, granulosa cells express neither 17 α -hydroxylase nor 17,20-lyase (see Figure 9–22) and are therefore dependent on theca cells to provide the androgen substrates from which the estrogens are synthesized (see Figure 11–11).

Table 11-6
Biologic Actions of Progesterone and Estrogens

Target Organ	Effects of Progesterone	Effects of Estrogens
Uterus	<ul style="list-style-type: none">• Increasing vascularization of the endometrium during the luteal phase• Makes cervical mucus more viscous*	<ul style="list-style-type: none">• Endometrial thickening• Make cervical mucus thinner and more alkaline
Vagina	<ul style="list-style-type: none">• Induces thick mucus secretions from the vaginal epithelium• Causes epithelium to thicken and become infiltrated with leukocytes	<ul style="list-style-type: none">• More cornified vaginal epithelium• Induce synthesis of pheromones† in vaginal secretions
Breast	<ul style="list-style-type: none">• Increases growth of breast lobules and alveoli• Induces differentiation of ductal tissue	<ul style="list-style-type: none">• Promote growth and proliferation of mammary ducts• Enlarge breasts at puberty• Antagonize milk-producing effect of prolactin
Central Nervous System	<ul style="list-style-type: none">• Inhibits secretion of LH• Causes a rise in body temperature and is probably responsible for the slight increase in body temperature at the time of ovulation• Stimulates ventilation and thereby lowers alveolar pCO₂ in both the luteal phase of the monthly cycle and in pregnancy	<ul style="list-style-type: none">• Inhibit FSH secretion• Brief exposure of the pituitary to estrogens decreases its sensitivity to Gn-RH• Prolonged exposure of the pituitary to estrogens increases its sensitivity to Gn-RH• Increase libido possibly by direct effect on hypothalamic neurons• Induce “heat” (estrus) in nonmenstruating mammalian species• Induce dendrite proliferation in neurons

Continued

Table 11-6

Biologic Actions of Progesterone and Estrogens—Continued

Target Organ	Effects of Progesterone	Effects of Estrogens
Protein Metabolism	—	<ul style="list-style-type: none">• Exert protein anabolic effect by increasing androgen output from the adrenals
Bone and Cartilage	—	<ul style="list-style-type: none">• Cause epiphyseal closure
Other	—	<ul style="list-style-type: none">• Partly responsible for female secondary sex characteristics• Renal retention of salt and water• Inhibit acne by counteracting effects of testosterone on sebaceous glands• Inhibit atherogenesis by lowering plasma cholesterol, inhibiting vascular smooth muscle proliferation, and increasing NO synthesis• Can promote thrombosis at high levels

*The viscosity of cervical mucus varies greatly over the menstrual cycle. It influences the patterns made when mucus is dried on a glass slide.

[†]Pheromones are fatty acids that act over a distance to induce behavior or physiologic changes in another member of the same species.

Biologic actions of the estrogens: Like progesterone, only 2% of circulating estrogens are free. Most are bound to albumin (60%) and to gonadal steroid-binding globulin (38%). The estrogens have many target organs, and their actions are summarized in Table 11–6.

Metabolism of estrogens: The liver converts estradiol, estrone, and estriol to glucuronide and sulfate compounds that are excreted in bile and urine.

Nonsteroid Hormones and Growth Factors

A variety of factors influence the functions of the ovary. These include cytokines and growth factors (Table 11–7).

Relaxin. Relaxin is a peptide hormone. In women, it is synthesized in the corpus luteum, uterus, placenta, and mammary glands. In men, the dominant source is the prostate. Its function in nonpregnant women is not known yet. In pregnancy, it regulates the birth process by inhibiting uterine contractions

Table 11–7
Influence of Cytokines and Growth and Other Factors on Ovary Function

Factor	Effect on Theca Cells	Effect on Granulosa Cells	Other Effects
Activin	Inhibitory	Augments trophic activity of LH and FSH	
Epidermal growth factor			Prevents follicle atresia
Fibroblast growth factor	Inhibitory	Inhibits aromatase	Prevents follicle atresia Promotes angiogenesis in corpus luteum
Follistatin	Binds and counteracts activin	Binds and counteracts activin	Promotes follicle atresia and supports corpus luteum
IGF-1	Stimulatory	Stimulates aromatase	
Inhibin	Stimulatory	Inhibits trophic activity of LH and FSH	
TGF- α		Inhibits aromatase	Promotes degeneration of corpus luteum
TGF- β	Inhibitory	Stimulates aromatase	Promotes degeneration of corpus luteum

and functions to ease delivery by relaxing, softening, and dilating the pelvic joints.

Follistatins. The follistatins are a group of four tissue glycoproteins that bind and, thereby, inactivate activins.

Women's Monthly Rhythm

The sexual and reproductive system of nonpregnant women shows a regular, approximately 28-day cycle of physical and chemical changes that is called the **menstrual cycle**. Its most overt physical sign is the vaginal bleeding (**menstruation**) that accompanies the shedding of the disintegrating superficial portion of the endometrium. The first day of bleeding is taken to be day 1 of the cycle and the subsequent days are divided into three phases: the **follicular phase** (9 to 23 days; average 15 days) spans the maturation of the selected follicle. The **ovulatory phase** (1 to 3 days) denotes the event of ovulation. The **luteal phase** (13 to 14 days) spans the maturation of the corpus luteum. These phases and accompanying hormonal, ovarian, and endometrial changes are summarized in Figure 11–12.

The Ovarian Cycle

The menstrual cycle exists for two purposes: (1) to create at some point during each cycle the best possible conditions for reproduction and nurture and (2) to ensure that normally only a single oocyte is fertilized at one time. The cycle is driven by gonadotropin-releasing hormone (Gn-RH), released in periodic bursts from the hypothalamic cells. The amplitude and frequency of these bursts are vital features in generating the other hormonal changes responsible for the monthly cycle.

Late luteal to early follicular phase. At about day 25 of each cycle, FSH output from the pituitary begins to rise (see Figure 11–12). This rise in FSH has two consequences:

1. Estradiol synthesis is stimulated in granulosa cells (see Figure 11–11). Not enough estradiol is produced to increase its plasma levels at this time or to bring about systemic effects, such as inhibition of FSH secretion, but its local concentration rises enough to induce more FSH receptors in granulosa cells.* This promotes even more estradiol production and causes a gradual increase in systemic estradiol toward day 10 of the next cycle (see Figure 11–12). The rising plasma estrogen level is an inhibitory influence on FSH and LH secretion.

*It has been proposed that the dominant follicle is the one that is able to raise its ambient estrogen concentration to the highest level by about days 5 to 7.

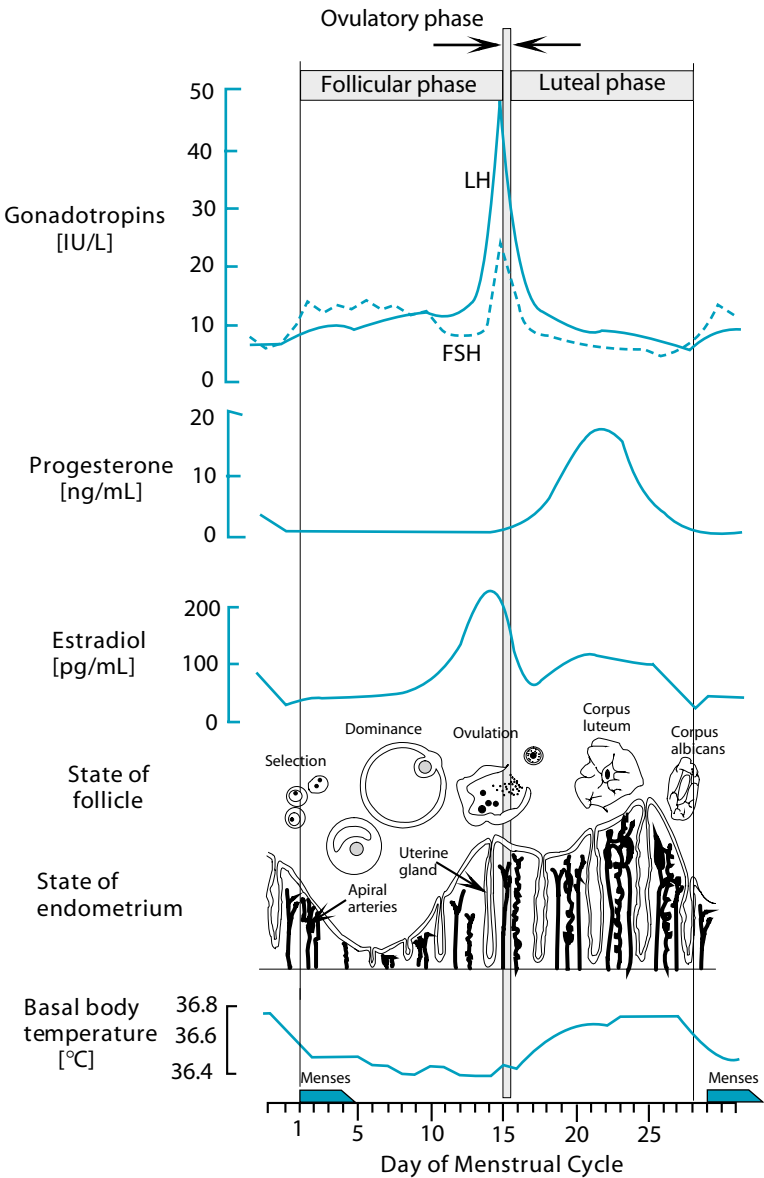


Figure 11–12 Significant hormonal, follicular, endometrial, and body temperature events in each of the three phases of the human menstrual cycle. The beginning of menstrual bleeding is taken as day 1 of the cycle.

2. Growth is induced by FSH-induced estrogen in granulosa cells of 3 to 6 primary follicles in each ovary. They will reach a peak size of about 5 mm diameter near day 10 of the next cycle and a single dominant follicle will be selected from among them.

Midfollicular phase to ovulation. At days 10 to 12 of the cycle, there is a steep rise in plasma estradiol concentration (see Figure 11–12). This rise has several consequences:

1. At 36 to 48 hours before ovulation, the increased estradiol briefly exerts positive feedback on pituitary LH release and triggers an LH surge. Endogenous opioids are thought to be an additional factor contributing to the LH surge.
2. The LH surge triggers a rise in FSH* and stimulates progesterone synthesis in granulosa cells, which have developed LH receptors at this point in the cycle. Progesterone and LH-mediated cAMP activates local proteolytic factors that weaken the follicular wall. The follicular content of prostaglandins has been shown to be elevated at this time, and they are believed to induce contractions of muscle elements and trigger ovulation from the dominant follicle. This event normally occurs 36 to 38 hours after the start of the LH surge.
3. The FSH surge induces growth in a further group of follicles. The function of this latter groups is to contribute to estradiol and inhibin synthesis in the luteal phase of the cycle (days 12 to 28).
4. Following ovulation, there is a rapid down-regulation of FSH receptors in luteinizing granulosa cells, whereas LH receptors increase. Withdrawal of FSH diminishes estrogen synthesis. Luteinizing hormone drives progesterone synthesis and secretion from the corpus luteum in the luteal phase.

Luteal phase. The corpus luteum is initially driven by LH, and its major secretory product is progesterone. Progesterone inhibits the hypothalamus and the anterior pituitary, and in this way, luteal secretion of progesterone gradually and progressively inhibits secretion of LH and FSH.

Rising levels of inhibin, synthesized in granulosa cells, also inhibit FSH secretion.

Progressive decrease in LH and FSH levels leads to regression in the corpus luteum (provided that fertilization has not occurred)[†] and diminishes plasma levels of estradiol, progesterone, and inhibin.

*The ability to increase gonadotropins at the middle of the ovarian cycle is characteristic of all female mammals. It can be prevented if the newborn is exposed to androgens during the first 5 days after birth.

[†]If fertilization has occurred, then the corpus luteum is maintained in the later luteal phase by human chorionic gonadotropin (hCG), an LH equivalent of placental origin.

By the 26th day of the cycle, the levels of estradiol, progesterone, and inhibin will be so low that (1) the pituitary can begin the FSH rise that starts the next cycle, and (2) the endometrium is without adequate steroid support and disintegrates to be sloughed in the menstrual flow.

The Uterine Cycle

Menstrual bleeding occurs for 3 to 5 days and normally amounts to no more than a total of 80 mL of fluid, of which about 30 mL is blood. It carries with it the disintegrated upper layers of the endometrium. At the end of the menstrual period, all but the deep layers of the endometrium have been sloughed.

As estrogen levels rise in the follicular phase, the endometrium proliferates and increases in thickness (see Figure 11–12). Its secretory glands are lengthened, and the coiled **spiral arteries** uncoil to provide vascularization for the thickening endometrium.

After ovulation, the combined actions of estrogens and progesterone increase the vascularization of the endometrium and promote secretion from the glands. The secretions include high levels of prostaglandins.

As the corpus luteum regresses, the levels of steroids decline (see Figure 11–12) and the endometrium becomes thinner. At the same time, the prostaglandins induce vasospasms and, thereby, reduce blood flow to the outer endometrium. Focal necrosis soon appears, and lysosomal enzymes from the necrotic areas speed the deterioration of the surrounding tissue. As the walls of the spiral arteries deteriorate, menstrual bleeding begins.

Cervix, Vagina, and Breasts

Each of these areas undergoes cyclic changes that are controlled chiefly by estradiol and progesterone. These changes are summarized in Table 11–6.

THE HUMAN SEXUAL RESPONSE

Sexual contact is a highly complex human interaction. It lies at the end of a cascade of cultural, emotional, and physiologic processes. It is dominated by psychological influences, physiologic stimuli, and unrealistic expectations that derive from cultural mythology.

Psychological influences determine the level of personal comfort. They include (1) our reactions to the partner's standard of personal hygiene, (2) our belief of what constitute savory or unsavory practices, (3) our perception of the partner's attentiveness, (4) our level of trust in the partner, (5) our attitude toward the possibility that a pregnancy might result, and (6) the extent to which we reconcile our body configuration with culturally fostered stereotypes.

Physiologic factors that can aid or hinder the sexual response include visual, tactile, olfactory, and auditory stimuli. Furthermore, initiation of sexual activity can also be influenced by hormones. Thus, men, in keeping with their noncycling gonadotropin pattern, show no cyclic variation in sexual activity. Women, on the other hand, can show increased interest when estrogen levels are high around the time of ovulation.

Unrealistic expectations arise most often from the acceptance of stereotypical assertions that (1) the greatest sexual satisfaction will be had from either young, tall, well-muscled, handsome men without skin blemishes or young, medium-tall, long-legged, large-breasted, thin-waisted women*[‡]; (2) a large penis is more satisfying to a sexual partner[†]; and (3) only vaginal penetration can lead to a full orgasm in the female sexual partner.[‡]

The Sexual Response Cycle

Humans are in a nonsexual state most of the time: attentive to many matters but, nevertheless, receptive to sexual stimuli. When the attention is drawn to a sexual stimulus and a full sexual response is permitted to develop, then at least four phases can be recognized: excitement, plateau, orgasm, resolution. These involve physiologic changes as well as changes in the intensity of feelings (Figure 11–13).

Excitement

Excitement begins with **arousal**. It is a state in which attention becomes gradually and increasingly focused on erotic feelings and sexual matters. It can be brought about by a variety of stimuli: visual stimuli, such as erotic pictures; touch and sight of a responsive partner; tactile stimulation of genitals; or simply the right kind of imagination. Its continuation and development depend on reinforcement and are marked by a progressive increase in autonomic nervous activity whose consequences include regionally specific changes in blood flow (Table 11–8).

*False. There is no correlation. However, the psychological effects of a perceived mismatch can be debilitating.

†Not necessarily true. A penis is too small if, in its fully erect state, it does not put enough pressure in the places where the partner likes to feel pressure. A penis is too large if it causes pain.

‡Sensory nerve endings are highly concentrated in the clitoris, making stimulation of the clitoris a significant aspect of sexual pleasure in most women. In addition, there may be particularly responsive areas along the vaginal walls (such as the Grafenberg [G] spot), the labia minora, and the perineal region. As a result, a woman experiences different kinds of orgasm, varying in intensity of feeling and depending on the degree of stimulation of each of her centers of sexual sensory perception.

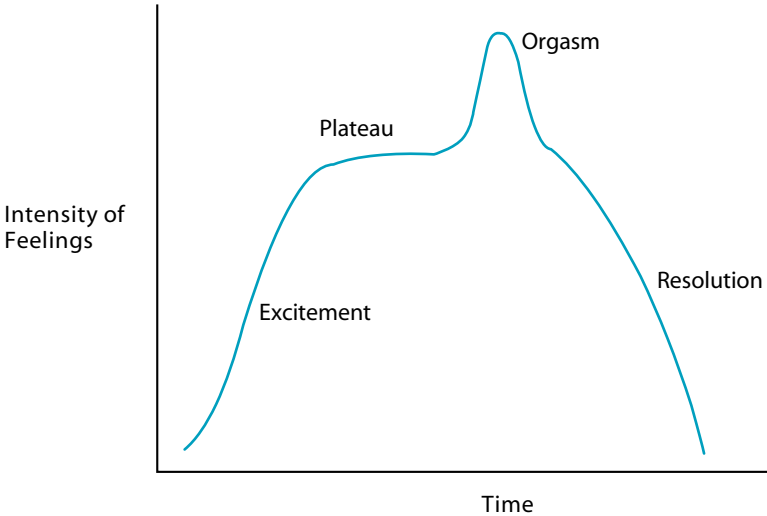


Figure 11–13 The intensity of feeling and other physiologic parameters during the phases of the human sexual response cycle.

Plateau

The plateau stage is an advanced state of arousal. Its duration varies with the effectiveness of erotic stimuli, the effectiveness of situational reinforcement, as well as with the desire, training, and age of the individu-

Table 11–8
Physical Signs of Sexual Excitement

Women	Men
Onset of generalized vasocongestion: <ul style="list-style-type: none">• Vaginal lubrication• Skin mottling (“sex flush”) in about 75% of women• Breasts swell; nipples erect• Enlargement of clitoris• Labia enlarge and separate	Onset of generalized vasocongestion: <ul style="list-style-type: none">• Erection• Skin mottling (“sex flush”) in 50–60% of men• Nipples become more erect in 50–60% of men
Uterus begins to rise	Testes begin to rise
Vagina enlarges	Scrotum thickens
Increase in respiratory rate, heart rate, and arterial blood pressure	
Increased voluntary and involuntary muscle tension	

als involved. It may culminate in orgasm. Table 11–9 summarizes its physical features.

Orgasm

Orgasm is an intense, brief, and uncontrollable response of the entire body, marked by rapid release of vasocongestion and involuntary muscular tension. Its major features are summarized in Table 11–10.

Resolution

During resolution the body returns to the resting state. Its features and approximate time scale are summarized in Table 11–11.

Table 11–9
Physical Features of the Plateau Stage of the Sexual Response Cycle

Women	Men
Labia minora are more engorged and change color from pink to bright red	Penis is at maximum size; darkens in color
Clitoris retracts to be covered by the clitoral hood <ul style="list-style-type: none">• can now be stimulated directly only through hood, but• can be stimulated indirectly by tension on labia minora, such as might accompany vaginal penetration	Testes are engorged (about 50% larger than at rest) and are raised to the perineum
“Orgasmic platform” is created in the outer third of the vagina by <ul style="list-style-type: none">• engorgement of blood vessels• local reduction of vaginal diameter	Mucoid discharge from Cowper’s gland
Uterus lifts and tilts, forming the “seminal receptacle”	A few drops of semen may be discharged
“Sex flush,” if present, spreads and increases its intensity	
Further increase in respiratory rate (up to 40/min), heart rate (up to 180/min), diastolic (increased by 20–40 mm Hg) and systolic (increased by 30–100 mm Hg) arterial pressure	
Increased tension of voluntary and involuntary muscles	

Table 11–10

Physical Features of Orgasm

Women	Men
Irregular, involuntary contractions of skeletal muscle and momentary widespread loss of voluntary control over skeletal muscle	
Irregular, but high, rates of breathing and pulse. High, but fluctuating arterial blood pressure	
Exclusion of all other sensory perceptions	
Rhythmic contractions of <ul style="list-style-type: none">• orgasmic platform• uterus• perineal muscles	Feeling of ejaculatory inevitability
	Rhythmic contractions of <ul style="list-style-type: none">• urethra• perineal muscles
	Emission of semen <ul style="list-style-type: none">• Contraction of internal structures, such as vas deferens, prostate, seminal vesicles, and internal urethra, causes emission of semen
	Expulsion of semen <ul style="list-style-type: none">• Contraction of bulbar and other muscles causes ejection of semen and seminal fluid

Variations in the Sexual Response Cycle

Both the intensity and duration of the phases of the sexual response cycle show a great deal of variation among individuals of the same gender and age, within the same individual at different ages, and between genders.

Variations among individuals. A brief excitement phase, intense orgasm, and quick resolution tends to be the pattern in young, inexperienced boys who have not yet learned to pace themselves or in an experienced lover who has been celibate for some time.

A plateau with fluctuations in intensity, not necessarily culminating in an orgasm, tends to be seen in inexperienced women or in experienced men or women who have learned to pace themselves and can control their orgasms.

Older women have an increasing ability to reach orgasm more quickly if they wish and to have multiple orgasms. Older men can show a pattern of repeated pseudo-orgasms that show almost all the feelings and intensi-

Table 11–11

Physical Features of Resolution in the Sexual Response Cycle

Women	Men
Some women and many men experience an intense desire to sleep	
Because of strong sympathetic drive to organs that include the bladder, some women and men feel a strong urge to urinate	
Heart rate, blood pressure, and respiration return to resting levels within about 5 min	
The clitoris leaves its retracted position (5 to 10 s)	The testes descend and return to resting size
The labia minora lose engorgement and color (10 to 15 s)	About 50% of the penis size is lost rapidly; the penis becomes flaccid within 5 to 30 minutes (faster with age)
The orgasmic platform and inner vaginal enlargement recede (10 to 15 min)	
The uterus descends (20 to 30 min)	
The labia majora return to resting conditions within about 1 h	
The resolution phase may last up to 2 hours	

ties of a regular orgasm but no emission or ejaculation, and might then have a full orgasm, complete with ejaculation, before resolution.

Variations with age. The cycle as a whole tends to lengthen with age (or experience). Its duration is near 5 minutes in those aged 16 to 18 years, whereas excitement and plateau can lengthen to an hour or more in a 45 year old. It has not been resolved which one of interest, comfort, confidence, experience, or pacing is likely to be the dominant factor in the age-dependent lengthening of the early parts of the cycle.

Gender differences. When men have an orgasm, there follows a refractory period during which they will not be able to respond physically to further sexual stimuli. The refractory period is 15 to 30 minutes in an 18 year old and a day or more in an 80 year old.

Women may not wish to be further aroused after orgasm but do not have a refractory period during which they cannot be aroused.

As women age, they can have an increasing ability to reach orgasm and an increasingly intense pleasure from sex. Having had a child often intensifies the ability for sexual pleasure. It has been postulated that the explanation for this is local changes in blood supply that resulted from the birth process.

As men age, their ability appears to increase to the mid-twenties and then decline, reaching a low at about the mid-forties. Thereafter, their ability to give and derive pleasure often increases again. However, their orgasms tend to be less violent, and with the gradually decreasing amount of ejaculate, they may perceive a decline in pleasure.

Neurogenic Control of Sex Organs

Both sensory and motor nerves are involved in the control of physical aspects of sexual function.

Sensory Nerves

The main pathway for sensory information is the **pudendal nerve** (Figure 11–14), particularly its branches, the **dorsal nerve** (of the clitoris or penis), and the **perineal nerve**, which innervates the labia in women and the scrotum in men. The perineal nerve also innervates the perineal region and the rectal area. As a result of this distribution, sensations received from the clitoris, penis, labia, scrotum, or anus may be perceived as similarly pleasurable. The pudendal nerve projects to the sacral segments of the spinal cord. Sensory information also travels by visceral afferents that enter the spinal cord in the region of the T₁₂ to L₂ segments.

Motor Nerves

Efferent information is transmitted by way of autonomic and somatic nerves. Parasympathetic nerves are mostly involved in controlling vasodilatation and secretion, while sympathetic efferents, traveling through the inferior mesenteric ganglion, drive the smooth muscle contractions, whose biologic purpose is most likely the transport of sperm in both men and women.

Somatic motor neurons from sacral areas of the spinal cord project by way of the pudendal nerve mostly to the bulbospongiosus muscle, which forms the labia majora in women and the scrotal wall in men.

The importance of different nerves and the requirement for brain involvement varies during different phases of the sexual response cycle and is, therefore, of relevance in those who have injured their spinal cord.

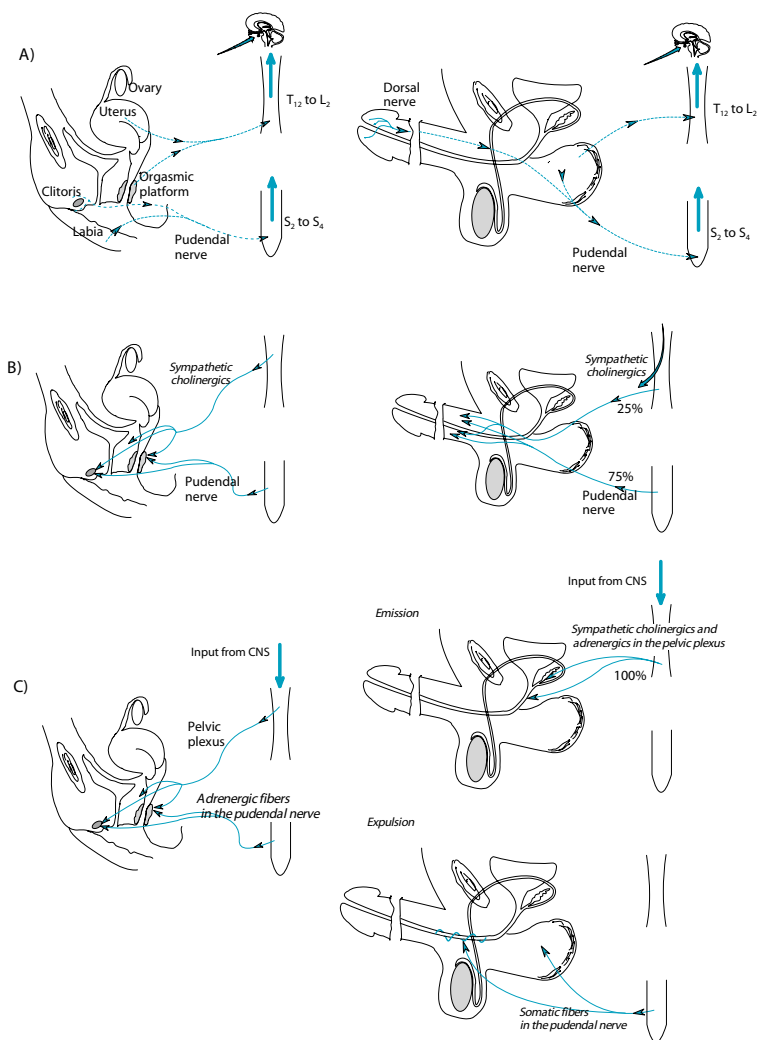


Figure 11-14 The role of nerves in the sexual response cycle. **A, Arousal:** Tactile input travels mostly in the dorsal nerve (of the clitoris or penis) and visceral sensory afferents. Input from higher centers in the central nervous system is contributed by interpretations associated with touch and sight of a responsive partner or visual stimuli such as erotic images. **B, Vasocongestion:** This phase of the response cycle is partly a local reflex from the clitoris or glans to the sacral region of the spinal cord and from there to dilator nerves. It is partly psychogenic, originating with impulses in the limbic brain. If the cord is destroyed above S_2 in men, then erection is almost always possible via a local, spinal reflex provided that there is appropriate tactile stimulation. If segments S_2 and lower are destroyed, then erection is possible in about 25% of patients. **C, Orgasm:** Sympathetic cholinergic, adrenergic, and somatic fibers are involved in the whole body response. In men, the processes of emission and expulsion of semen occur as part of orgasm. Emission is directed by higher centers and is not possible if the spinal cord is damaged above S_2 .

Arousal

Direct mechanical stimulation of the genitalia can produce arousal, but input from the highest central nervous regions is normally involved in initiation and continuation of the arousal states (see Figure 11–14).

Vasocongestion and Plateau

Localized vascular engorgement is caused by dilation of arteriolar inflow. A variety of fibers are involved, and the importance of nitroxidergic fibers has been recognized. They release nitric oxide, which activates guanylate cyclase and thereby increases intracellular cyclic guanosine monophosphate (cGMP). Cyclic GMP relaxes vascular smooth muscle.* In men, the initial dilatation of inflow arteries is followed by opening of shunt vessels to divert flow into the cavernous spaces of the corpora cavernosa of the penis. The extent of this dilation is such that the hydrostatic pressure in these spaces increases to near 100 mm Hg from its resting value near 20 mm Hg. Their ensuing expansion then compresses venous outflow and sustains a full erection as long as the supplying arterioles remain dilated.

Orgasm

Psychogenic factors from the central nervous system play a role. This is particularly evident in men during emission, a process that requires both secretion of seminal fluid and its transport into the urethra. Both sympathetic cholinergic and adrenergic fibers are involved and the process is dominated by centrally coordinated nervous activity.

The rhythmic local contractions that are a feature of orgasm are driven partly by sympathetic adrenergic nerves to smooth muscle and partly by somatic nerves to the labia or scrotum. The somatic nerves are under strong local control so that “expulsion” is possible even when there is no emission (dry ejaculation). As a general rule, in patients with spinal cord injuries in the sacral area, there will be emission if erection is possible. In such patients, there will also be a “feeling” of orgasm.

*Viagara® (sildenafil) is an inhibitor of phosphodiesterase type 5, the enzyme that inactivates cGMP. Thus, Viagra® sustains vasodilatation in tissues whose blood flow is governed by cGMP.

Fertilization, Pregnancy, and Lactation

FERTILIZATION

The ovum lives for about 3 days after being expelled from the graafian follicle. It is maximally fertilizable on the first day. Sperm normally require 30 to 60 minutes to reach the fallopian tubes and also have a time of maximum potency. For those wishing to conceive, the optimal time for intercourse, if it is isolated, is 2 days before ovulation.*

Fertilization occurs when the genetic material of a sperm combines with that of an oocyte. This is a three-step process involving (1) sperm activation, (2) sperm–oocyte interaction, and (3) oocyte activation.

Sperm Activation

Sperm Maturation

Spermatozoa leaving the rete testis are not mobile and are, therefore, not capable of fertilizing an ovum unless they were directly microinjected. Acquisition of motility is among the processes that occur during their passage along the epididymis. These processes are collectively called **epididymal maturation** and also include loss of the droplet of cytoplasm, changes in the physical and chemical composition of membrane lipids, and modification of the outer glycoprotein coating.

*Those who prefer to time intercourse so as not to conceive (the rhythm method) should be sobered by the observation that there are documented cases of pregnancy resulting from isolated intercourse on any one day of the menstrual cycle.

Sperm Capacitation

In addition to a requirement for motility, sperm must be able to interact with and adhere to an oocyte when they encounter it. These abilities are gained only by exposure to the female reproductive tract in a still undefined process that is called **capacitation**. It is thought to involve removal of molecules, the presence of which would shield receptors or prevent their activation.

Acrosome Reaction

The acrosome is a membrane-bound cap that covers the tip of the sperm head (Figure 12–1). It contains a large variety of enzymes, of which **hyaluronidase** and **acrosin** have been studied most. Hyaluronidase dissolves hyaluronic acid, a major component of the cumulus oophorus layer of cells that surrounds the oocyte. Acrosin is a protease. The acrosome reaction involves release of acrosome contents. It occurs as a result of physical contact between the sperm plasma membrane and the zona pellucida that surrounds the oocyte. It is believed that the zona glycoprotein ZP3 is required to trigger the reaction and that changes in H^+ , Na^+ , and Ca^{++} within the narrow band of sperm cytosol outside the acrosome are necessary intermediate steps.

Sperm–Oocyte Interaction

Each ejaculation contains between 200 and 400 million spermatozoa. Of these, many leak through the vagina, are incapacitated by the ambient acidity, are immobilized by the viscous cervical mucus, and are phagotized by intrauterine leukocytes. Only a few find the relevant fallopian tube; many

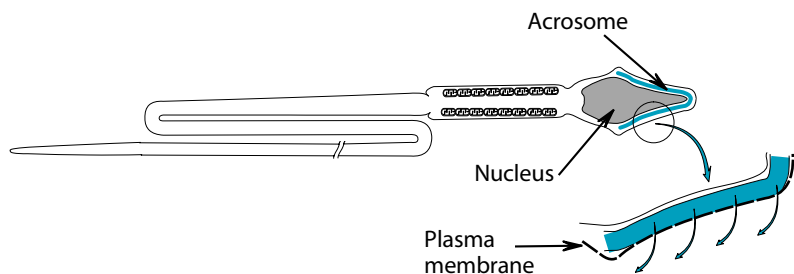


Figure 12–1 The acrosome, shown in color, is a membrane-lined structure that is positioned in the head of the spermatozoon, between the plasma membrane and the nucleus. The acrosome reaction, shown in enlargement, involves fusion of the outer acrosomal membrane with the plasma membrane and subsequent release of acrosomal contents.

of these do not experience full capacitation, and fewer still actually reach the site of fertilization.

Sperm Interaction with the Cumulus Oophorus

The cumulus mass that surrounds the oocyte contains cells and a matrix that is rich in hyaluronic acid, proteins, and carbohydrates. To move through it, sperm must (1) be capacitated and (2) not have completed their acrosome reaction. The precise nature of the interaction between sperm and cumulus is uncertain. It used to be thought that the massed acrosome reaction of many unsuccessful spermatozoa prepared a path for one successful spermatozoon. The currently preferred interpretation is that the cumulus mass is dotted with preferred pathways that facilitate sperm penetration and that this greatly limits the number of spermatozoa that will reach the zona pellucida.

Sperm Interaction with the Zona Pellucida

The zona pellucida is a few micrometers thick and consists of glycoproteins. The glycoprotein ZP3 is believed to be of major importance for recognizing and binding sperm. Its complementary receptor protein is located on the plasma membrane of the acrosome-intact sperm head (see Figure 12-1). The spermatozoon loses its acrosome content during its 2- to 15-minute transit time through the zona pellucida.

Sperm-Oocyte Fusion

Once the spermatozoon reaches the plasma membrane of the oocyte, the two membranes fuse, and a few cortical granules move from the oocyte interior to its plasma membrane and lose their content by exocytosis (Figure 12-2). Simultaneously, a variety of ion channels are activated, and the oocyte is depolarized and becomes activated.

Oocyte Activation

The first event of oocyte activation is a Ca^{++} wave that spreads over the oocyte. One of the consequences is that the oocyte plasma membrane becomes a mosaic of cortical granule membrane and oocyte plasma membrane as cortical granules spill their content toward the zona pellucida. The resulting chemical changes in the zona are thought to prevent other spermatozoa and bacteria from entering.

As the sperm enters the oocyte, its head swells under the influence of ionic and osmotic changes that accompany formation of the male **pronu-**

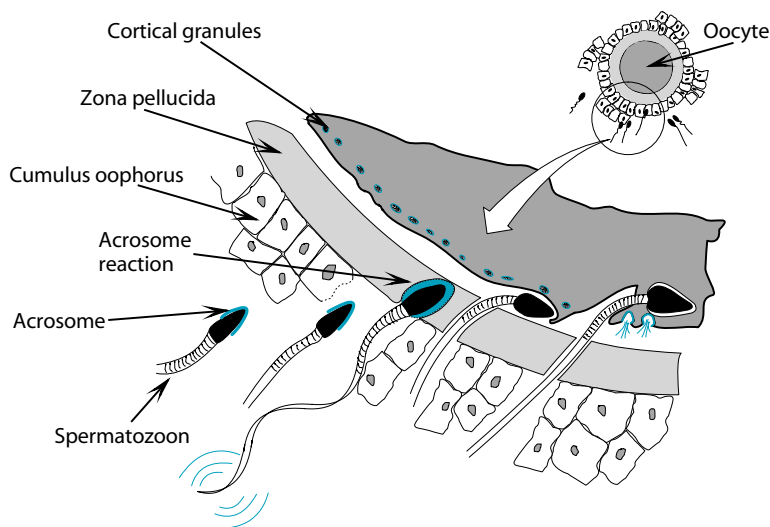


Figure 12–2 Details of the sperm–oocyte interaction. A spermatozoon, with its acrosome intact (*lower left*), approaches the zona pellucida through a preferred pathway in the cumulus mass. It loses its acrosome content during passage through the zona pellucida. Such passage is aided by vigorous beating of the tail. On fusion of the spermatozoon and oocyte plasma membranes, a few cortical granules lose their content by exocytosis.

cleus. Simultaneously, the maternal genome is condensed, and a female pronucleus is formed. Both pronuclei move toward the center of the oocyte as their nuclear membranes dissolve, causing them to decondense. The 46 chromosomes, 23 from the mother and 23 from the father, are arranged along a spindle as a new nuclear envelope, and a new diploid individual, called a **zygote**, forms. It enters into mitosis, and during the next 4 to 6 days, successive mitotic divisions produce a **blastocyst** of 8 to 16 cells (Figure 12–3).

Blastocyst Implantation

Fertilization occurs in the ampulla of the fallopian tube. Ciliary and secretory cells of the tube walls help to transport the growing blastocyst down the fallopian tube toward the uterus. There the remainder of the zona pellucida is dissolved, and implantation into the steroid-primed endometrium takes place.

Once the blastocyst has made contact with the endometrium, its trophoblast separates from the inner cell mass and differentiates into two types of cells (Figure 12–4): a surrounding outer layer of **syncytiotrophoblast** that secretes increasing quantities of steroids and an inner layer of **cytotro-**

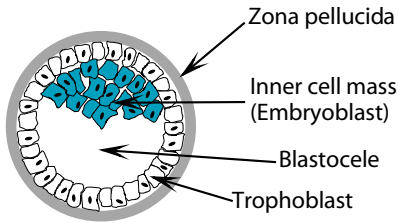


Figure 12–3 A fertilized human ovum at the early blastocyst stage. An inner cell mass and surrounding trophoblast cells are clearly recognizable. The inner cell mass becomes the embryo.

phoblast that secretes a number of (normally hypothalamic) releasing factors for the paracrine control of the syncytiotrophoblast. The syncytiotrophoblast also breaks down the endometrium as the blastocyst burrows into it and becomes implanted. A placenta then develops, and the trophoblast (see Figure 12–3) becomes the embryo's contribution to it. One important feature of trophoblast cells is that they do not express the class I and II major histocompatibility complex genes; therefore, the mother raises no antibodies against fetal proteins.

THE PLACENTA

As the syncytiotrophoblast expands unevenly along finger-like projections, it forms hollow chambers (lacunae) while the following cytotrophoblast forms villi. By about day 11, the expanding implant begins to erode maternal endometrial capillaries, and the lacunae fill with maternal blood. Fibroblast-like cells in the tissue layer next to the endometrium change into **decidual** cells, which accumulate glycogen and lipids and probably nourish the developing embryo until a connection is formed between embryonic and maternal blood vessels. Ultimately, the decidua forms a mechanical barrier against further embryonic encroachment of the uterus.

After week 12, the embryo, suspended within the fluid-filled amniotic cavity, is attached to the placenta through an umbilical cord. The amniotic cavity is bounded by the amnion and the amniotic sac, held by the umbilical stalk, and is suspended in the extraembryonic celom (chorionic cavity), the boundary of which is formed by the trophoblast.

Anatomy of the Placenta

When it is fully developed, the placenta is a blood-filled well in which villi are suspended like inverted trees (Figure 12–5). The outside of the villi is

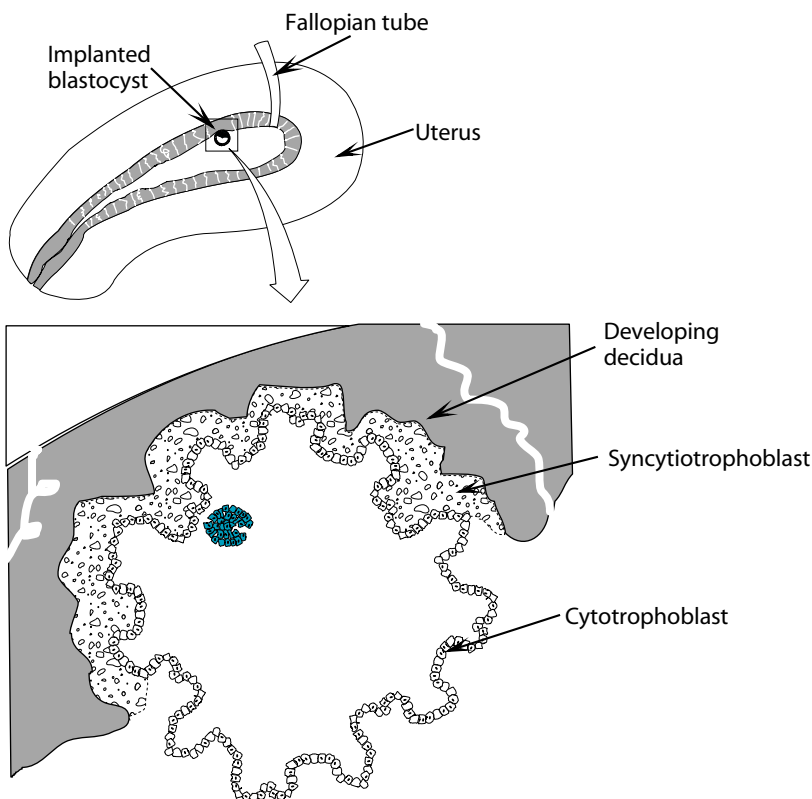


Figure 12-4 After implantation of the blastocyst, its trophoblast separates from the inner cell mass and differentiates into the syncytiotrophoblast and cytotrophoblast.

coated with a double layer of cells formed by the syncytiotrophoblast on the outside and the cytotrophoblast on the inside. The villi are filled with fetal capillaries (see Figure 12-5).

Placental Exchange of Substances

The placenta separates the fetus from the mother but allows the transport of nutrients from mother to fetus and of waste products from fetus to mother. Such transport occurs by active and passive mechanisms through the villus wall, and the mechanisms depend on whether the substance is lipid soluble (Table 12-1).

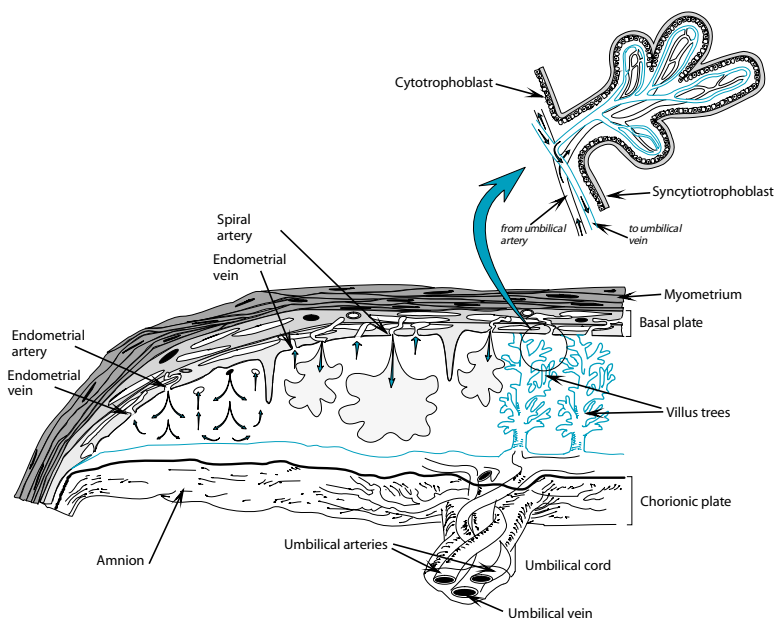


Figure 12–5 Maternal blood enters the placenta through a large number of spiral arteries that run perpendicularly through the myometrium and drain into the intervillous space. They enter the placenta through the basal plate. Maternal blood pressure spurts blood from the openings in the basal plate toward the chorionic plate. Drainage is provided by venous openings in the basal plate. Fetal blood reaches the placenta by two umbilical arteries and is finally distributed to the capillary network that inhabits the villi. It drains through a venous network that ultimately flows together into the umbilical vein. Within the placenta, the ratio of maternal blood to fetal blood is approximately 5:1.

Regulation of Amniotic Fluid and Electrolyte Composition

The fetus is surrounded by amniotic fluid. Its composition varies at different stages of gestation. During the first half of the pregnancy, its composition differs from maternal plasma only in its lower protein concentration; as the fetus grows, it swallows more amniotic fluid and voids increasing volumes into it, making the fetus the major determinant of the composition of amniotic fluid.

ENDOCRINOLOGY OF PREGNANCY

When fertilization has occurred, then the corpus luteum fails to regress because it is stimulated by human chorionic gonadotropin (hCG), a glycoprotein that is recognized by luteinizing hormone (LH) receptors.

Table 12-1

Placental Transport of Selected Substances

Substance	Requirement/ Production	Transport Mechanism
O ₂	15–20 mL/min	Passive
CO ₂	15–20 mL/min	Passive
Glucose	40 g/d	Carrier mediated
Amino acids or protein	5 g/d	Mostly active
Lipids	Negligible	
Vitamins		
• Water soluble (B group and C)		Active with some passive components
• Lipid soluble (A, D, E, and K)		Passive
Macromolecules		
• IgG		Receptor-mediated transcytosis
• IgA, IgE		Not transported; locally generated when needed
Hormones		
• Lipid soluble		Passive
• Protein bound or large (insulin)		Poorly or not at all transported

Human Chorionic Gonadotropin

The blastocyst begins to synthesize small amounts of hCG even before it is implanted. After implantation, the syncytiotrophoblast is the major source of this hormone. Its α subunit is identical to the α subunit of follicle-stimulating hormone, LH, and thyroid-stimulating hormone and is encoded by a single gene. Its β subunit is specific to hCG and derives from a locus on chromosome 19.

The major function of hCG is pregnancy maintenance by way of corpus luteum function. Human chorionic gonadotropin binds with high affinity to LH receptors in the corpus cells and thereby drives synthesis of progesterone and estrogens. It also promotes testosterone synthesis in the testes of male fetuses.

Human Chorionic Somatomammotropin

The syncytiotrophoblast also synthesizes a peptide hormone, the biologic actions of which resemble those of growth hormone. It is called one of three names: chorionic growth hormone-prolactin, human placental lactogen, and, most commonly, human chorionic somatomammotropin. It appears by the fifth week of pregnancy, and its plasma concentration rises continuously until birth, in direct proportion to the size of the placenta. Its most probable function is to increase maternal lipolysis, thereby sparing maternal glucose for the use of the growing fetus, which uses glucose exclusively.

Relaxin

Relaxin is a pregnancy-associated polypeptide that is secreted mostly from the corpus luteum. Its main biologic function is the induction of collagenase activity, which serves to soften pelvic joints and the cervical canal in preparation for birth.

Steroid Hormones

The steroids are vital for pregnancy maintenance. Important pregnancy-related interactions between the estrogens and progesterone are summarized in Figure 12–6. In addition, progesterone functions to block the positive feedback effect of estradiol on the pituitary. This prevents further ovulation by preventing the LH surge that normally occurs at mid-cycle.

Over a period of 6 to 8 weeks after fertilization and implantation, synthesis of estrogens and progesterone is shifted from the hCG-stimulated corpus luteum to the feto-placental-maternal unit (Figure 12–7). In this unit, the **fetal adrenal cortex*** is of central importance. It is rich in sulfokinase and produces sulfate conjugates of androgens that serve as substrates for estrogen production in the placenta (see Figure 12–7).

Corticotropin-releasing hormone (CRH) is produced by the fetus in steadily increasing amounts as pregnancy progresses. Its adrenocorticotrophic hormone–releasing activity in the mother is reduced by high maternal plasma levels of a specific CRH-binding protein. It is believed that high CRH levels in the fetus progressively increase estrogen synthesis, causing estrogen-dependent changes in the cervix (cervical maturing) and the myometrium.

*The adrenal cortex of the fetus is comparatively very large, and 80% of it will degenerate soon after birth. That large portion is called the fetal adrenal cortex.

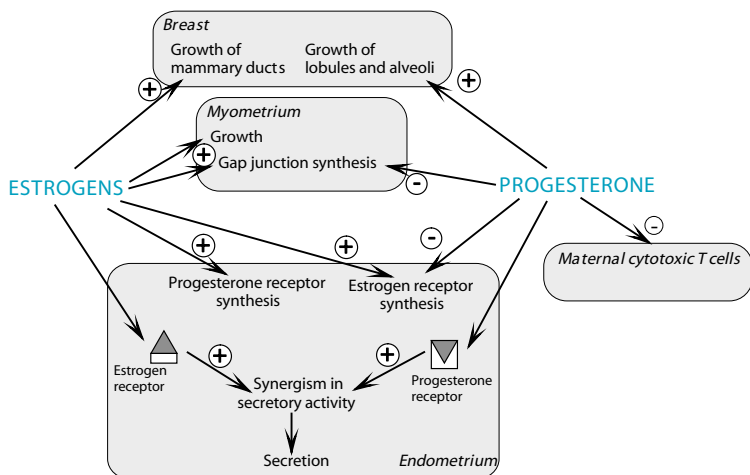


Figure 12-6 The main functions of estrogens and progesterone during pregnancy. Progesterone (1) acts on the breast to promote growth of mammary structures, (2) acts on the myometrium to ensure a quiescent uterus by inhibiting formation of gap junctions and thereby blocking spread of contractile activity, (3) inhibits estrogen receptor synthesis and thereby acts as an estrogen inhibitor, (4) induces secretory activity in estrogen-stimulated myometrial cells, and (5) inhibits maternal cytotoxic T cells to allow the mother to exhibit immunologic tolerance toward the fetus. Estrogens (1) promote growth of the mammary ducts, (2) foster continuous growth of the myometrium, (3) induce synthesis of both estrogen and progesterone receptors, and (4) prime endometrial cells for secretory activity. Toward the end of pregnancy, the steroids also act to soften and reshape genital structures so as to prepare the birth canal for parturition.

PARTURITION

Human pregnancy lasts an average of 284 days (40 weeks) from the first day of the menstrual period before conception and ends with the birth process. It is heralded by irregular uterine contractions that increase in frequency during the last month of pregnancy and progresses to labor, which is regularly occurring, strong, and painful contractions of the uterus. While the body of the uterus contracts, the cervix softens and dilates so that it can finally permit the passage of the fetus through the birth canal. These changes in the cervix are of a biochemical nature, begin long before labor, and are called **cervical maturation**.

Cervical Maturation

Cervical maturation is caused by collagen breakdown as a result of increased collagenase activity. Several factors promote collagenase activity (Figure 12-8), and progesterone is the major inhibitor of both collagenase activity

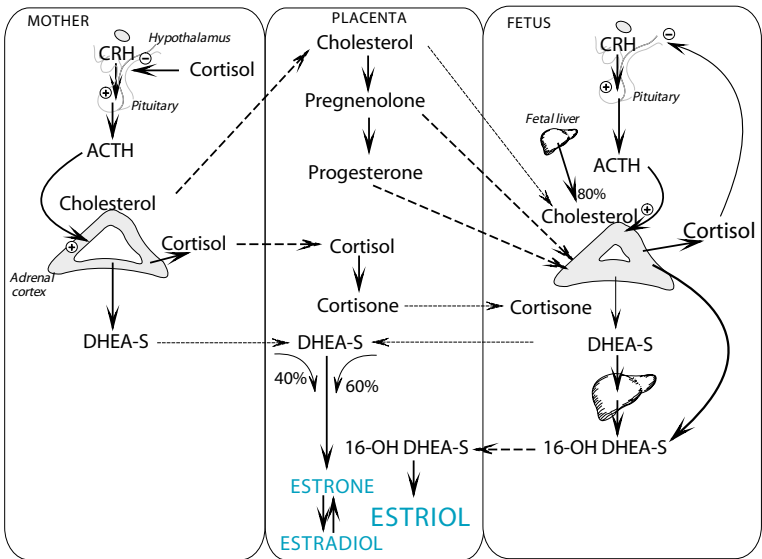


Figure 12-7 Steroid and cortisol synthesis in the feto-placental-maternal unit. Estriol is the principal estrogen formed in pregnancy and its primary substrate is fetal 16-hydroxydehydroepiandrosterone sulfate (16-OH DHEA-S). This substrate derives mostly from the fetal adrenal cortex, which uses cholesterol, pregnenolone, and progesterone as substrates. Most of the cholesterol is synthesized in the fetal liver; only 20% is of maternal origin. On the other hand, all of the pregnenolone and progesterone originates in the placenta, where they are produced from maternal cholesterol. The other estrogens, estrone and estradiol, are synthesized from DHEA-S, of which 60% comes from the fetal adrenal cortex and 40% is maternal DHEA-S. Near term, the fetus produces 75% of its circulating cortisol. Much of the maternal cortisol is converted to the inactive form, cortisone, by placental 11 β -hydroxysteroid dehydrogenase to protect the fetus from excess cortisol and its inhibitory effect on pituitary secretion of adrenocorticotrophic hormone (ACTH).

and the procollagenase action of estradiol. It is thought that inhibition of the influence of progesterone on cervical tissue is a crucial mechanism for cervical maturation. Macrophages and cytokines are involved as well, but their roles have not yet been clearly defined.

Myometrial Contraction

Labor requires organized contractions of the myometrium. These are possible only if electrical activity can be propagated from cell to cell. Such propagation requires **gap junctions**. High levels of progesterone during most of the pregnancy suppress gap junction formation. Gap junctions increase in number and size immediately before the onset of labor and disappear again within 24 hours after parturition. The dominant force is estrogen-

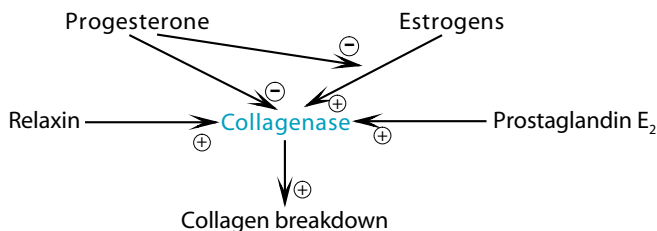


Figure 12-8 Regulation of collagenase activity in the cervix during the processes of cervical maturation. Interaction between progesterone and estrogens is of special importance. Progesterone inhibits collagenase activity and estrogen-mediated activation of collagenase. Both relaxin and prostaglandin E₂ promote collagenase activity.

mediated stimulation of the gene coding for connexin-43, a major component of gap junctions. This influence can express itself only after the local inhibitory influence of progesterone has been overcome by stimulatory influences of estrogen. Estrogen promotes additional myometrial changes conducive to strong, coordinated contractions. These include (1) increased expression of receptors for contractile agents like oxytocin, endothelin, and catecholamines; (2) increased expression of channel proteins for Ca⁺⁺ and K⁺; (3) increased synthesis of contractile proteins; and (4) increased synthesis of myosin light-chain kinase, the most important of the enzymes involved in smooth muscle contraction (see Chapter 2, “Muscle”)

Hormonal Control of Labor

Labor is not of sudden onset but progresses from one contraction every 3 hours in the 25th week of gestation to 2 per hour in the 40th week. Alpha-adrenergic and oxytocin effects play a role, but the dominant influence is metabolites of arachidonic acid, mostly prostaglandins of the E and F series.

Prostaglandins

Just before labor, the metabolism of arachidonic acid switches progressively from the lipoxygenase pathway (producing hydroxyeicosatetraenoic acids, HETE) toward the cyclooxygenase (COX) pathways (producing prostaglandins). Levels of COX-2* in particular are increased in the amnion and

*Cyclooxygenase-1 and -2 differ in their sensitivities to anti-inflammatory drugs or indomethacin. Cyclooxygenase-1 is inhibited by aspirin and indomethacin; COX-2 is not.

decidua at term, and PGE_2 and $\text{PGF}_{2\alpha}$ have been the foci of study because of their effectiveness in the induction of labor. Prostaglandin E_2 -mediated contraction occurs mostly by activation of EP_1 receptors, whereas $\text{PGF}_{2\alpha}$ works by way of both EP_1 and FP receptors. Both of these subtypes of prostaglandin receptors use the phospholipase C, inositol trisphosphate, diacylglycerol pathway to increase cytosolic $[\text{Ca}^{++}]$.

Oxytocin

The fetus produces increasing amounts of oxytocin, and under the stimulation of estrogens, the uterine myometrium increasingly synthesizes oxytocin receptors. In addition to its contractile activity, oxytocin is known to increase the incorporation of arachidonic acid into membrane phospholipids. Therefore, it may have an indirect role in the onset of labor. In the second stage of labor, which begins with full cervical dilation and ends with delivery of the baby, stretching of the lower genital tract causes reflex increases in oxytocin-dependent myometrial contractions.

Relaxin

Relaxin inhibits uterine contractions. Its levels fall progressively as the importance of the corpus luteum diminishes. A fall in relaxin is thought to promote parturition. Once labor has begun, relaxin levels increase again.

LACTATION AND LACTOGENESIS

Development of the fetal mammary glands begins by about the 8th week of gestation, rudimentary mammary ducts being formed near the beginning of the third trimester. At that time, there is a high concentration of fetal prolactin because of direct stimulation of anterior pituitary lactotropes by estrogens. Prolactin induces terminal differentiation of the ductal cells. Thereafter, the mammary glands remain in a rudimentary state until puberty. The first sign of female puberty is the growth of breasts.

The female breast is a cluster of 15 to 20 **lactiferous units** that are each composed of clusters of **alveolotubular units** and a **ductal system** (Figure 12-9).

Hormonal Control of Breast Development and Growth

Gonadal steroids and a variety of hormones are essential for mammary growth (Table 12-2). Such growth has different foci at different times during a pregnancy. During its first half, there is mainly proliferation of alve-

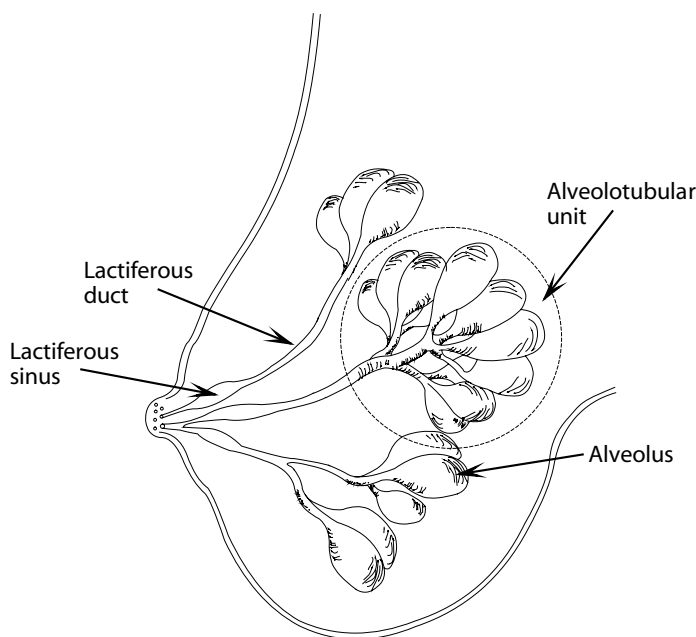


Figure 12–9 Each of the lactiferous units of the breast consists of an alveolotubular unit and a lactiferous duct. The alveoli are glands that are surrounded by secretory cells (alveolar cells). Several of them are connected to a lactiferous duct by way of short tubules. Each alveolus is surrounded by a meshwork of capillaries, contractile elements, connective tissue, and fat. The lactiferous ducts exit at the nipple.

olar cells and the duct system. During the last half, the emphasis is on promotion of secretory activity in the alveolar epithelium.

Hormonal Control of Lactogenesis

Maternal plasma levels of progesterone, estrogens, and prolactin increase progressively during pregnancy. Within 48 hours after parturition, the levels of progesterone and estrogens return precipitously to nonpregnancy values because the placenta is no longer present. Prolactin levels, however, remain elevated.

Progesterone has little effect on established lactation because lactating mammary tissue has insufficient progesterone receptors. However, it exerts a strong inhibition on the onset of milk production. Hence, lactation begins within 1 to 3 days of delivery when progesterone levels have fallen. Thereafter, maintenance of lactation requires prolactin, oxytocin, and mother–child interaction (Figure 12–10).

Table 12–2

Hormones in Mammogenesis and Lactogenesis

Hormone	Function
Estrogens	<ul style="list-style-type: none"> • Stimulate proliferation of mammary ducts • Stimulate formation of lactose and casein, provided that insulin, cortisol, T_3, and prolactin are present • Induce progesterone receptors • Stimulate prolactin mRNA in pituitary lactotropes, causing increased synthesis and release of prolactin
Progesterone	<ul style="list-style-type: none"> • Promotes differentiation of the alveolotubular system • Inhibits alveolar secretory activity
Prolactin	Stimulates duct development
Glucocorticoids	Stimulate duct development
Insulin	<ul style="list-style-type: none"> • Stimulates uptake of glucose into alveolar cells • Promotes incorporation of amino acids into alveolar cells to form proteins
IGF-1	Promotes mammary growth and development
Thyroid hormones	Promote ductal growth

T_3 = triiodothyronine; mRNA = messenger ribonucleic acid; IGF-1 = insulin-like growth factor-1.

Prolactin is essential for milk secretion. Its main functions are (1) promotion of synthesis of both casein and lactalbumin* and (2) stimulation of lipoprotein lipase activity in mammary tissue.

Oxytocin functions in lactation as a contractile stimulant to the myoepithelium that surrounds the alveoli. Such contraction propels the milk through the ductal system toward the breast nipple. It may also be involved in central nervous functions such as maternal and sexual behavior.

Lactation Amenorrhea

Prolactin inhibits gonadotropin-releasing hormone (Gn-RH) secretion from the hypothalamus and Gn-RH effects on pituitary gonadotropes. It also antagonizes the effects of gonadotropins on the ovaries. These mechanisms, in concert, inhibit ovulation and menstruation while a woman is

*Casein and lactalbumin are the major proteins in human milk. Lactalbumin is a stimulatory protein in the lactose synthetase system, which is required for lactose formation. Lactose is the major carbohydrate in human milk.

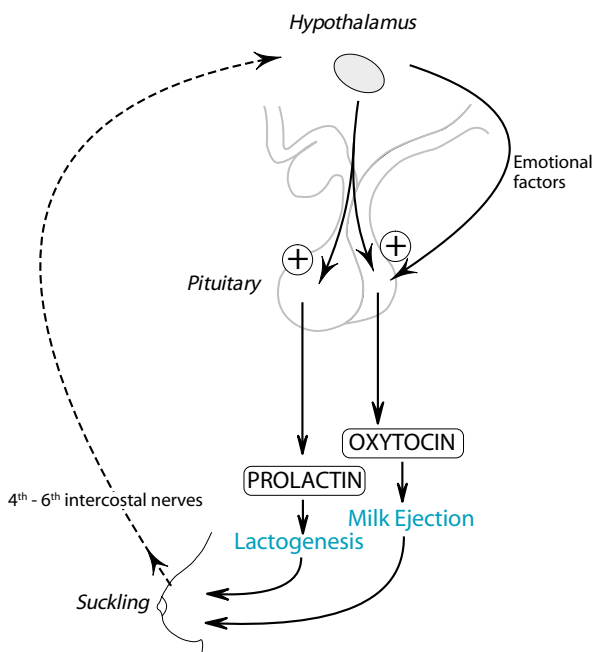


Figure 12–10 The breast is richly innervated with both sensory and efferent fibers. Sensory fibers are especially concentrated in the nipple and approach the central nervous system by way of intercostal nerves. Mechanical stimulation, especially if it is combined with the emotional correlates of nursing an infant, causes release of prolactin from lactotrophs in the anterior pituitary and of oxytocin into the capillary network of the posterior pituitary. Prolactin acts on estrogen-primed alveolar cells to promote milk secretion, and oxytocin acts on contractile units to promote milk ejection (milk letdown).

breast-feeding. Thus, women who do not breast-feed normally resume cyclic function with a menstrual period about 6 weeks after delivery; women who do breast-feed do not have a period for up to 30 weeks.

Mineral Metabolism, Bone, and Connective Tissue

MINERAL METABOLISM

Regulation of body mineral metabolism involves maintenance of (1) appropriate plasma concentrations of Ca^{++} , HPO_4^{2-} , and Mg^{++} and (2) appropriate bone mass. These two objectives are correlated because bone is the major repository for body minerals, and many of them exist as CaHPO_4 . Three hormones and three target organs are involved. The hormones are **parathyroid hormone** (PTH), **calcitonin**, and **1,25-(OH) $_2$ D $_3$ (vitamin D)**; the target organs are intestinal mucosa, nephron, and bone.

Hormones in Mineral Metabolism

Relevant actions of PTH, calcitonin, and vitamin D are summarized in Table 13–1 and more detailed descriptions of PTH and calcitonin are included in Chapter 9, “Endocrine System.”

Vitamin D

“Vitamin D” is a group of secosteroid* hormones that vary in biologic potency and are crucial for body mineral homeostasis.

Synthesis of vitamin D. Active forms of vitamin D are produced from inactive **previtamins** D $_2$ or D $_3$ (Figure 13–1). Previtamin D $_3$ is the dominant source. It is mainly produced in the skin by ultraviolet irradiation of 7-dehydrocholesterol, which causes photolysis of the bonds between C9 and

*Secosteroids are steroids with one of the rings opened.

Table 13–1

Summary of Hormonal Regulation of Mineral Metabolism

Hormone	Source	Regulation	Target Organ	Effect
PTH	Chief cells in parathyroid	<ul style="list-style-type: none"> Increased by low plasma $[Ca^{++}]$ or high plasma $[Mg^{++}]$ Decreased by $1,25-(OH)_2D_3$ 	Intestinal mucosa	Increased GI uptake of Mg^{++}
			Bone	Increased osteoclast formation. Hence, increased bone resorption
			Kidney	<ul style="list-style-type: none"> Decreased Ca^{++} excretion Increased excretion of HPO_4^{2-} and Mg^{++} Increased vitamin D activation
Calcitonin	C cells in thyroid	Increased by high plasma $[Ca^{++}]$	Bone	Depressed bone resorption as a result of (1) decreased osteolytic activity in osteocytes and (2) decreased formation of osteoclasts
			Kidney	<ul style="list-style-type: none"> Decreased Ca^{++} excretion Increased excretion of HPO_4^{2-} and Mg^{++}
Vitamin D	<ul style="list-style-type: none"> Previtamin D_3 in skin Previtamin D_2 (ergocalciferol) in saltwater fish 	<ul style="list-style-type: none"> Increased by PTH Decreased by high plasma HPO_4^{2-} 	Intestinal mucosa	Increased GI uptake of Ca^{++} and HPO_4^{2-}
			Kidney	<ul style="list-style-type: none"> Decreased Ca^{++} excretion Increased/decreased HPO_4^{2-} excretion?
			Bone	<ul style="list-style-type: none"> Increased osteoclast activity. Hence, increased bone resorption and increased plasma $[Ca^{++}]$ Slightly increased bone matrix deposition

GI = gastrointestinal.

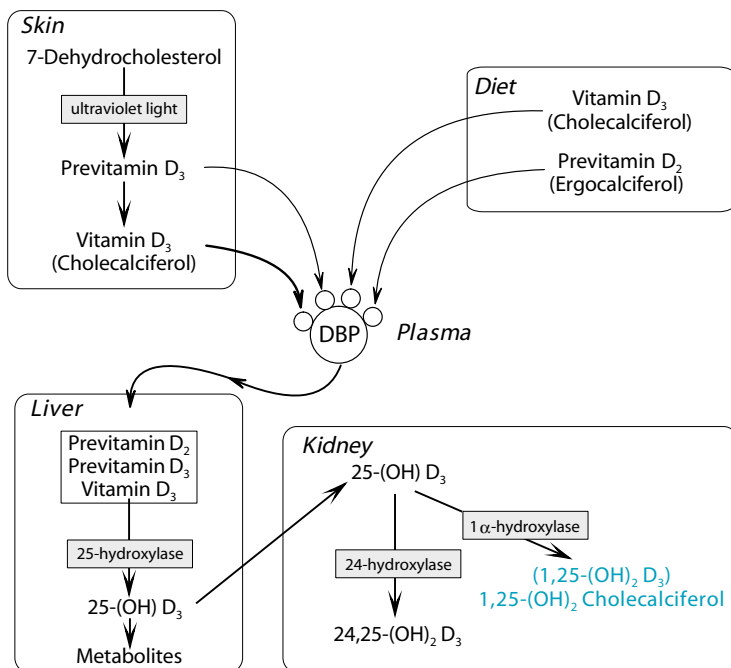


Figure 13–1 Active forms of vitamin D are produced from previtamin D₃, vitamin D₃ and previtamin D₂. The previtamins are bound to vitamin D-binding protein (DBP) and are concentrated in the liver and converted to 25-(OH)D₃, which is a biologically inactive precursor. The active hormone, 1,25-(OH)₂D₃, is produced in mitochondria of renal proximal tubular cells. These cells also produce 24,25-(OH)₂D₃, an inactive form of vitamin D.

C10 (see Figure 9–22 for numbering of the C atoms in cholesterol). The previtamin D₃ molecule spontaneously isomerizes and forms vitamin D₃ (**cholecalciferol**). Cholecalciferol can also be obtained from dietary sources like saltwater fish, liver, and egg yolk. A third possible source is previtamin D₂ (**ergocalciferol**),* which is obtained by irradiating ergosterol from yeast and is often added to milk. The previtamins and vitamin D₃ are transported to the liver by the carrier globulin, **vitamin D-binding protein** (see Figure 13–1). It binds vitamin D₃ with greater affinity than it binds the previtamins. The endoplasmic reticulum in hepatocytes hydroxylates the precursors to form **25-hydroxycholecalciferol** (25-[OH]D₃), which is the major circulating form of vitamin D. Although it is slightly more potent than its precursors, it has no significant biologic activity.

*Ergocalciferol differs from cholecalciferol by the presence of a double bond between C22 and C23 and a methyl group (-CH₃) at C24.

Vitamin D also has nongenomic effects on all its target cells. They occur within seconds to minutes and include (1) increasing Ca^{++} influx through voltage-gated channels, (2) stimulation of IP_3 production and subsequent stimulation of Ca^{++} release from intracellular stores, and (3) activation of phosphorylation processes.

Calcium Metabolism

Most of the body calcium resides in bone. Only 1% of it resides outside bone, and most of that is in the extracellular fluid. It is this small fraction that is of crucial importance in the function of nerves, muscle, blood coagulation, and intracellular communication in many tissues.

The normal total plasma calcium concentration is near 2.5 mmol/L. Of that, about 45% is bound to plasma protein, about 5% is complexed with strong anions, such as HPO_4^{2-} , SO_4^{2-} , or citrate, and about 50% exists in the ionized form, Ca^{++} . It is ionized calcium (Ca^{++}) that governs physiologic processes, such as muscle contraction or neurotransmitter release.

Regulation of Extracellular Calcium

The plasma concentration of Ca^{++} is closely regulated, presumably because of its widespread importance for cell function. Parathyroid hormone and calcitonin are the primary regulators, and regulation involves (1) an inverse relationship between plasma $[\text{Ca}^{++}]$ and the secretion of PTH and (2) a direct relationship between plasma $[\text{Ca}^{++}]$ and calcitonin (Figure 13–3). Thus, calcitonin acts as an antagonist to PTH and vitamin D in calcium homeostasis. However, its long-term effect on Ca^{++} handling is small because of the dominant influences of PTH and vitamin D.

Mechanisms of intestinal Ca^{++} absorption Ca^{++} absorption occurs mostly in the duodenum. The processes by which Ca^{++} enters on the luminal side of the enterocyte are not yet clearly defined. They are passive, driven by a concentration gradient, and slightly opposed by a cytosol-positive gradient of about 5 mV. Exit on the interstitial side is mostly by active transport via a Ca^{++} - H^+ -ATPase. The main controller of absorption is vitamin D, acting through induction of **calbindin-D**.

Mechanisms of renal Ca^{++} excretion. Ca^{++} is freely filtered at the glomerulus, and the bulk of it is reabsorbed passively in the proximal convoluted tubule and thick ascending limb of the loop of Henle (see Figure 7–28). In these segments, the main reabsorptive route is the paracellular pathway, through the tight junctions between neighboring cells. In the distal convoluted tubule and collecting duct, Ca^{++} enters epithelial cells passively

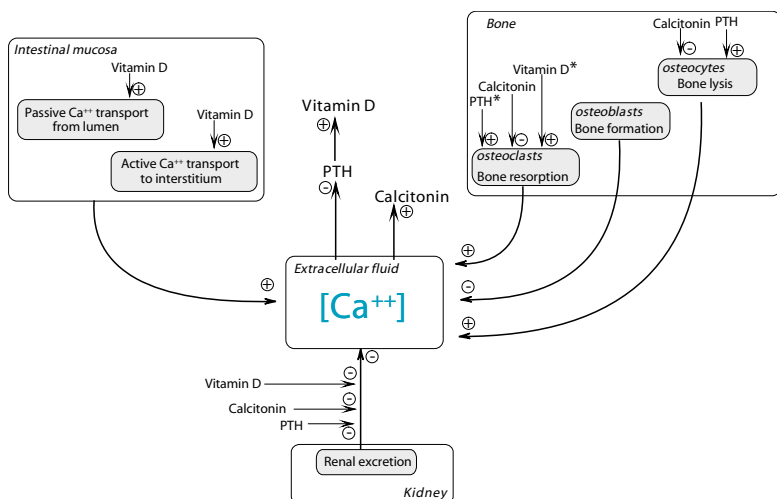


Figure 13–3 Regulation of extracellular $[Ca^{++}]$ by factors influencing intestinal absorption, bone dynamics, and renal excretion.

Dietary Ca^{++} is absorbed mainly in the duodenum. Ca^{++} also derives from bone either by transport through osteocytes or by resorptive activity in osteoclasts.

A rise in plasma $[Ca^{++}]$ will decrease PTH levels and increase calcitonin synthesis and release. Decreased PTH, in turn, will decrease vitamin D activation, decrease bone lysis by decreasing Ca^{++} influx into osteocytes, decrease bone resorption, and increase renal Ca^{++} excretion. Decreased vitamin D will decrease intestinal absorption, decrease bone resorption, and increase renal excretion. All the PTH- and vitamin D-mediated changes tend to bring about a decrease in plasma $[Ca^{++}]$. $+/-$ at arrowheads indicate the effect of an increase in the factor at the foot of the arrow.

*Effects of PTH and vitamin D on osteoclasts are not exerted directly on osteoclasts, as shown here for simplicity, but are exerted in a paracrine manner by osteoblasts. Osteoblasts are stimulated by vitamin D to increase matrix deposition, but the effect is not shown here because it is smaller than that on bone resorption by osteoclasts.

down a large electrochemical gradient. The major pathway is a PTH-modulated, dihydropyridine-sensitive channel, but voltage-gated channels are present as well. Extrusion of Ca^{++} on the basolateral side is partly by active transport (Mg^{++} -sensitive Ca^{++} ATPase) and partly by Na^{+} -driven Ca^{++} - $3Na^{+}$ exchange.

Parathyroid hormone suppresses renal Ca^{++} excretion because it increases reabsorption of filtered Ca^{++} by increasing conductance of luminal Ca^{++} channels in the distal convoluted tubule and cortical collecting duct.

Vitamin D also suppresses Ca^{++} excretion because it increases reabsorption of filtered Ca^{++} . The site of action is the distal nephron, where it induces the Ca^{++} transporting protein **calbindin-D**.

Calcitonin decreases renal Ca^{++} excretion by a cAMP-mediated mechanism in the distal convoluted tubule. This renal effect, which does not help

to reduce the rise in plasma $[Ca^{++}]$ that caused increased calcitonin release, is small compared to the homeostatically effective renal actions of PTH and vitamin D.

Phosphate Metabolism

In addition to its importance as a bone mineral, phosphate is a crucial intracellular component of the energy store ATP, the second messenger cAMP, and phosphorylation reactions by which intracellular processes are activated.

Eighty-five percent of the total body phosphorus store is in bone, and most of the remainder is in the intracellular space.

Intracellular phosphorus is mostly of the organic form, namely, phospholipid, nucleic acids, nucleotides, phosphoproteins, and metabolic intermediates. Inorganic phosphate exists mostly as the charged moieties, HPO_4^{2-} and $H_2PO_4^-$.

Only 1% of total phosphorus stores is in blood. Of that, 70% is in the organic form in red cells, leaving but a small proportion as plasma phosphate.

Plasma Phosphate

The normal range of plasma phosphate concentration is 1.0 to 1.6 mmol/L. About 20% of plasma phosphate is bound to plasma proteins or exists in the form of phospholipids. The remaining 80% is called **acid-soluble phosphate** because it remains in plasma from which proteins and phospholipids have been precipitated by treatment with trichloroacetic acid. Acid-soluble phosphate exists in four forms: PO_4^{3-} (< 0.01%), $H_2PO_4^-$ (10%), and HPO_4^{2-} (50%), and the remaining 40% is complexed with ions such as Ca^{++} , Mg^{++} , Na^+ , and H^+ .

Regulation of plasma phosphate. Many of the phosphate-dependent reactions are only weakly sensitive to extracellular phosphate concentration because, unlike Ca^{++} , phosphate does not enter the cell through regulated channels.

As summarized in Figure 13–4, vitamin D is the primary regulator of HPO_4^{2-} . An increase in extracellular phosphate concentration inhibits renal production of biologically active vitamin D (see Figure 13–2). When vitamin D activity decreases, so will absorption of HPO_4^{2-} from intestinal mucosa and bone. Since much of the HPO_4^{2-} is complexed with Ca^{++} as $CaHPO_4$, decreased absorption of HPO_4^{2-} will also decrease Ca^{++} absorption from intestine and bone. The resulting decrease in plasma $[Ca^{++}]$ will stimulate PTH secretion (see Figures 13–2 and 13–3). Parathyroid hormone

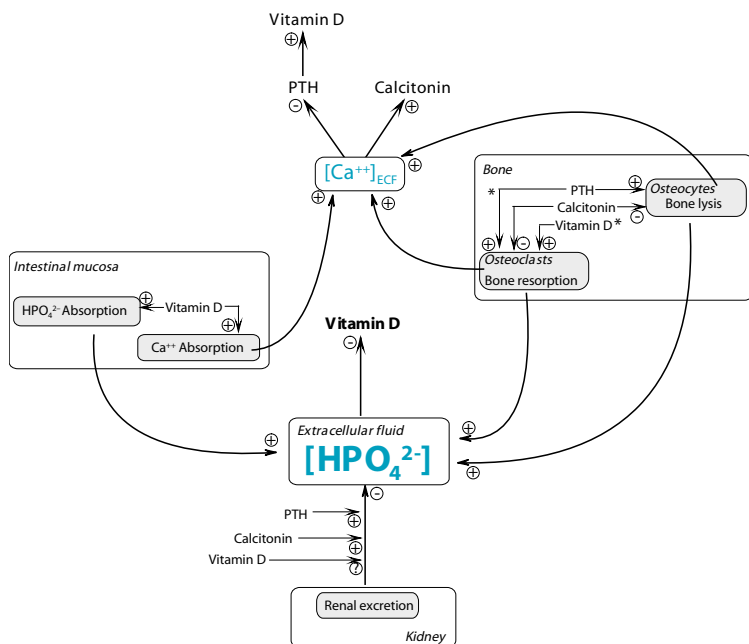


Figure 13–4 Regulation of extracellular phosphate concentration. Extracellular phosphate is mostly in the form of HPO_4^{2-} and is inversely related to activation of vitamin D. Changes in vitamin D will primarily affect intestinal absorption and bone resorption of both phosphate and calcium. The consequent changes in extracellular $[\text{Ca}^{++}]$ will then bring about changes in PTH, vitamin D, and calcitonin. The effect of PTH on vitamin D activation is opposite to that of plasma phosphate. As a result, hyperphosphatemia, for example, will suppress vitamin D, lead to a fall in plasma $[\text{Ca}^{++}]$, which will stimulate PTH, and stimulate vitamin D. +/– at arrowheads indicate the effect of an increase in the factor at the foot of the arrow.

*Effects of PTH and vitamin D on osteoclasts are not exerted directly on osteoclasts, as shown here for simplicity, but are exerted in a paracrine manner by osteoblasts.

has two significant stimulatory effects in phosphate homeostasis: (1) it increases renal phosphate excretion, and (2) it increases vitamin D activation (see Figure 13–2). In the long term, therefore, the opposing effects of similarly directed changes in extracellular $[\text{HPO}_4^{2-}]$ and $[\text{Ca}^{++}]$ on vitamin D activation tend to normalize plasma levels of vitamin D and with that normalize mineral absorption from intestine and bone.

Mechanisms of intestinal HPO_4^{2-} absorption. Ingested phosphate-containing compounds are broken down by enzymes, such as alkaline phosphatase, and the ion enters on the luminal side of enterocytes by Na^{+} -coupled co-transport. The duodenum is the major site of these passive mechanisms for absorbing phosphate.

Mechanisms of renal HPO_4^{2-} excretion. Parathyroid hormone stimulates renal HPO_4^{2-} excretion. Excretion is increased because proximal tubule reabsorption is depressed, possibly as a result of PTH-mediated, cAMP-dependent deactivation of Na^+ - HPO_4^{2-} co-transporters.

Calcitonin causes increased phosphate excretion by inhibiting its reabsorption mostly in the proximal convoluted tubule.

The effects of vitamin D on renal phosphate excretion are not yet clear because of conflicting experimental evidence that did not adequately account for simultaneous changes in plasma $[\text{Ca}^{++}]$ or PTH.

Magnesium Metabolism

Fifty to 60% of total body magnesium is in bone, and the remainder is located mostly in the intracellular fluid, where it serves as an essential cofactor in many enzymatic reactions (Table 13–2) and exists in two forms: (1) the soluble moiety is in equilibrium with diffusible Mg^{++} in plasma, and (2) the bound moiety is associated with organic compounds, mostly ATP. Mg^{++} enters cells passively down an electrochemical gradient through selective channels and is maintained in balance by active extrusion through a Mg^{++} ATPase.

Regulation of Plasma Magnesium

The normal total extracellular concentration of Mg^{++} is between 0.8 and 1.3 mmol/L, of which about 30% is bound to plasma proteins, about 50% is in the ionized form, and the remainder is complexed with the same anions that bind Ca^{++} , namely, HPO_4^{2-} , SO_4^{2-} , and citrate.

Plasma $[\text{Mg}^{++}]$ is regulated by way of PTH (Figure 13–5) and its simultaneous promotion of Mg^{++} absorption from gut and bone and Mg^{++} excretion in the urine. Mg^{++} is an important stimulus for PTH secretion and, therefore, has secondary effects on plasma $[\text{Ca}^{++}]$. Accordingly, the clinical signs of magnesium deficiency are due mostly to the attendant lack of Ca^{++} because lack of Mg^{++} depresses PTH, which, in turn, depresses vitamin D activation in the kidney. Lack of PTH and vitamin D inhibit Ca^{++} absorption and promote renal Ca^{++} excretion (see Figure 13–3).

Mechanisms of Intestinal Mg^{++} Absorption

Mg^{++} is absorbed in the jejunum and ileum by processes that mirror Mg^{++} transport in other cells, namely, passive entry on the luminal side and active pumping on the basolateral side. Since passive entry is by way of selective channels, reabsorption is inhibited by such factors as phosphate, oxalate,

Table 13–2

Examples of Mg^{++} -Dependent Enzymes

Enzyme	Location	Action
Alkaline phosphatase	Anchored to exterior of plasma membrane	Helps to digest organic phosphates
Acid phosphatase*	Inside lysosomes	Variety of dephosphorylation reactions
Creatine kinase	Muscle cytosol	Catalyzes transfer of phosphate from phosphocreatine to ADP so as to form ATP
Pyruvate kinase	Cytosol	Catalyzes formation of pyruvate from phosphoenolpyruvate
Phosphodiesterases	Cytosol	Inactivate cAMP and cGMP
Na^+K^+ -ATPase	Plasma membrane	Activates Na^+/K^+ transport
Ca^{++} -ATPase	Plasma membrane; longitudinal sarcoplasmic reticulum in muscle	Activates Ca^{++} transport
Adenylate cyclase	Plasma membrane	Catalyzes formation of cAMP from ATP
Myosin ATPase	Cytosol of muscle	Hydrolyzes ATP to cause muscle contraction
DNA/RNA polymerase	Nucleus	Replication of DNA/RNA

*High plasma levels are associated with prostate cancer.

and others that complex the Mg^{++} ion. Absorption is stimulated by PTH and vitamin D by mechanisms that have not yet been explained.

Mechanisms of Renal Mg^{++} Excretion

The thick ascending limb of the loop of Henle is the major site of Mg^{++} reabsorption. The mechanism involves the paracellular pathway and the driving force is the lumen-positive electrical potential that is set up by K^+ movements resulting from both the furosemide-sensitive $Na^+-2Cl^--K^+$ co-transporter and the $3Na^+-2K^+$ pump (see Figure 7–18). The mechanisms by which PTH and calcitonin promote renal Mg^{++} excretion are not clear yet.

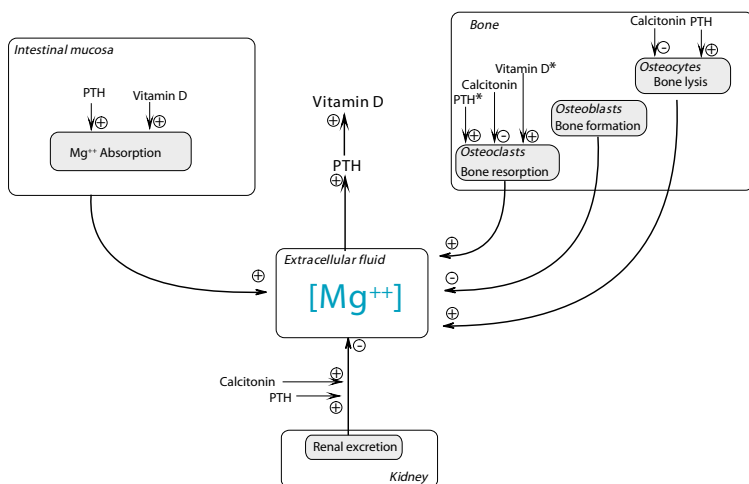


Figure 13–5 Regulation of extracellular $[Mg^{++}]$ is driven by PTH. Its promotion of renal Mg^{++} excretion provides the opposition to increased absorption from the GI tract and bone. +/– at arrowheads indicate the effect of an increase in the factor at the foot of the arrow.

*Effects of PTH and vitamin D on osteoclasts are not exerted directly on osteoclasts, as shown here for simplicity, but are exerted in a paracrine manner by osteoblasts.

CARTILAGE AND BONE

Cartilage and bone are the supportive tissues of the body. They are built upon a collagen fiber matrix and differ from other tissues in that their biologic purpose resides in the matrix rather than in the cells. Cartilage is characterized by deposits of **glycosaminoglycans** (mostly chondroitin sulfate) in the collagen matrix, whereas bone is characterized by mineral deposits.

Cartilage

Cartilage is a semirigid connective tissue that functions to provide firm, flexible support. This mechanical feature derives mostly from the high fluid content, which also provides an avenue for rapid diffusion of nutrients and metabolic products. Diffusion is important because cartilage contains no blood vessels.

Cartilage is classified on the basis of its fiber content into one of three types: **hyaline**, **elastic**, or **fibrous**. Hyaline cartilage is the most abundant of the three types. Their properties are summarized in Table 13–3.

Table 13–3

Properties of Cartilage

Type of Cartilage	Location	Properties
Hyaline	<ul style="list-style-type: none"> • Ventral ends of ribs • On the joint surfaces of bones 	Glassy appearance because high proportions of collagen and glycosaminoglycans allow no fibers to be seen macroscopically
Elastic	External ear	Contains a large number of branching elastin fibers and is, therefore, more flexible than hyaline cartilage
Fibrous	<ul style="list-style-type: none"> • Intervertebral discs • At the attachment sites of some tendons to bone 	<ul style="list-style-type: none"> • Does not exist on its own but forms a bridge between hyaline cartilage and dense connective tissue • Fibers are visible to the naked eye because it has a high proportion of collagen and a low content of glycosaminoglycans • Contributes tensile strength and flexibility

Cartilage Structure

The basic structural element of all connective tissues is formed by collagen fibers, 20 to 60 nm in diameter and arranged in a fine net. The inter-fiber spaces of the net contain a variety of noncollagenous proteins and mineral precipitates. They also contain two cell types: **chondroblasts** and **chondrocytes**.

Cartilage is bounded either by **perichondrium**, a calcified surface, or by a smooth articular margin.

The perichondrium consists of two layers; the outer layer blends smoothly with surrounding connective tissue, and the inner layer blends with cartilage. The inner layer also contains cells, called the **chondrogenic** cells, which are capable of differentiating into **chondroblasts**.

Chondroblasts. These are dividing cells that participate in synthesizing activity. As they enlarge and differentiate, they secrete around themselves the components that quickly form cartilage matrix. Type II collagen makes up the bulk of their secretions, and growth hormone is the major stimulus for their activity.

The continuing secretory activity of chondroblasts causes the increasing amount of matrix to push apart the cells that are secreting it. Eventually, each cell becomes isolated in its own lacuna and acquires the structural and functional characteristics of **chondrocytes**.

Chondrocytes. Chondrocytes are mature cartilage cells. They no longer participate in the synthesis of structural elements. However, they continue to mitose, and the daughter cells either do or do not differentiate into chondroblasts. If they do not differentiate, then they remain as **nests** of nonsecreting chondrocytes. On the other hand, if they do differentiate into chondroblasts, then they will increase the bulk of the cartilage by the process of **interstitial growth**.

Growth of Cartilage

Interstitial growth. Interstitial growth is the main mechanism of growth in mature cartilage. It resides in chondroblasts that have differentiated from dividing chondrocytes. Each such chondroblast surrounds itself with matrix material and, thereby, causes cartilage to grow from within as each chondroblast gets pushed away from its neighbors by the expanding matrix.

Appositional growth. Appositional growth proceeds by layering of new cartilage on old and, therefore, adds volume. It originates in the perichondrium in chondrogenic cells that have differentiated into chondroblasts and are secreting matrix material.

Cartilage Function

The embryo contains relatively much more cartilage than the adult because in prenatal life cartilage serves as a precursor for bone. In the adult, cartilage is found at different sites, performing three different functions: (1) flexible support, (2) low-friction contact, or (3) impact resilience. Each of them derives from the special structure of cartilage:

- Bending deformation is possible because of the high elastic fiber content. The associated flexibility is of advantage in providing (1) flexible support in structures like the trachea or external ear or (2) flexible attachment in structures like the rib cage.
- Compressive deformation and the ability to absorb compressive mechanical loads are possible because of the high water content associated particularly with hyaline cartilage. Under a compressive load, such as would occur at the articular surface in the joint between two bones, the water can be slowly expressed through the cartilage surface and then be reabsorbed after the load has been removed.

- Low-friction contact is provided by cartilage at the ends of articulating bones where they meet in a joint.

Bone

Bone is a specialized, rigid form of connective tissue. It differs from cartilage in two respects: (1) the collagen matrix of bone holds precipitates of calcium, magnesium, and phosphate, rather than glycosaminoglycans, and (2) bone has a blood supply, whereas cartilage does not.

Most of the bones of the skeleton are classified as **long bones**. Within them bone exists as trabecular (spongy; cancellous) or compact (dense) bone (Figure 13–6). At a magnification greater than that of Figure 13–6, it can be seen that each osteon lamella contains numerous irregularly shaped spaces, the **lacunae**, with minute channels, called **canaliculi**, radiating out from them and traversing the bone. Each lacuna is occupied by an **osteocyte** and the canaliculi are filled with osteocyte processes (Figure 13–7). The canaliculae allow contact among bone cells and also provide a very large surface area for mineral exchange with extracellular fluid.

Bone Cells

The internal and external surfaces of mineralized bone are covered with a layer that contains two types of specialized cells: **osteoblasts** and **osteoclasts**. In young, growing bone, the osteoblast/osteoclast layer is about three cells thick. In older bone, it is only one cell thick. The third type of bone cell, the **osteocyte**, is found imprisoned in the lacunae.

Osteoblasts. Osteoblasts originate from a distinct line of pluripotent stem cells of the bone marrow. These common progenitors are called fibroblast colony-forming units and give rise to fibroblasts, muscle cells, adipocytes, chondrocytes, or osteoblasts. Osteoblasts have two important functions (Figure 13–8): (1) they secrete substances that initiate formation of new bone, and (2) they respond to PTH, vitamin D, and other factors to modulate the differentiation and activity of **osteoclasts**.

Osteoblasts secrete collagen (mostly type I) and **ground substance**, which is composed mostly of chondroitin sulfate and hyaluronic acid. The collagen polymerizes rapidly to form collagen fibers and **osteoid**, a cartilage-like material but differing from cartilage in that calcium salts precipitate in it.

Within a few days after the osteoid is formed and in response to **alkaline phosphatase** of osteoblast origin, calcium salts begin to precipitate on the surfaces of the collagen fibers. The precipitates appear at regularly placed intervals along each collagen fiber, forming minute *nidi* that gradually, over a period of days and weeks, grow into the finished product, **hydroxyapatite**.

Osteoblasts eventually differentiate into osteocytes.

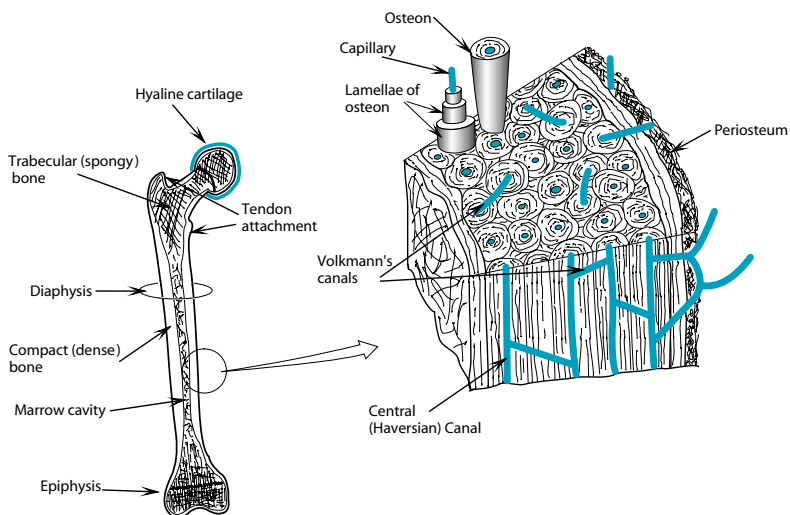


Figure 13-6 Structure of a typical long bone. The midregion is called the diaphysis or shaft, and the end regions are called the epiphyses. Most bones have protuberances that serve as attachment points for tendons. The articulated end, where joints occur, is covered by a layer of hyaline cartilage and the remainder is covered by a sheath of connective tissue, called the periosteum. The periosteum and the underlying bone are perforated at several places by channels that contain blood vessels.

Bone is either trabecular (spongy) or compact (dense). Trabecular bone is surrounded by compact bone and consists of thin spikes that interconnect like a three-dimensional mechano set. The open spaces in the meshwork of trabeculae are filled with highly vascularized red marrow and are the site of blood cell formation. Cortical bone consists of densely packed cylindrical units, called osteons. Each osteon is arranged in concentric layers around a central haversian canal. Each canal holds a capillary. Larger canals (Volkmann's canals) allow blood-vessel interconnections among neighboring haversian canals.

Osteoclasts. Osteoclasts are large cells containing up to 50 nuclei. They are rich in **tartrate-resistant acid phosphatase (TRAP)**, which is contained in microvesicles and is widely used as their specific histochemical marker. Osteoclasts derive from the granulocyte-macrophage line of colony-forming units. Their differentiation and development are promoted by factors that are produced by osteoblasts (see Figure 13-8). Estrogen inhibits osteoblasts, particularly in their production of interleukin-6 (IL-6), an important osteoclast differentiating factor. Lack of this estrogen-mediated inhibition leads to **osteoporosis** in menopausal women.

Osteoclasts are highly mobile. They attach to bone by means of integrins, form a tight seal with the bone surface (the **sealing zone**), and create **resorption pits**, which are hollowed-out areas where bone has been resorbed. The edge of the cell facing into such a pit forms an uneven **ruf-**

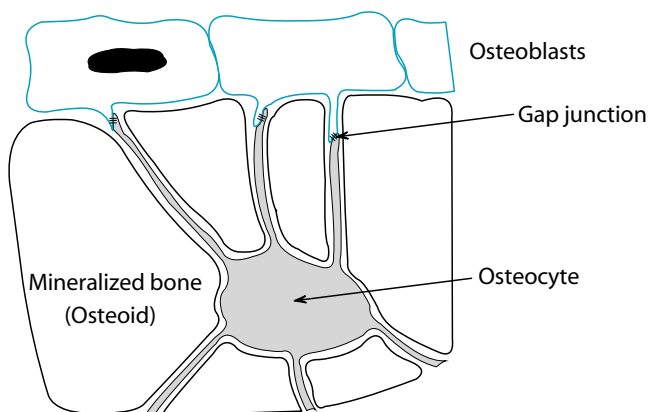


Figure 13-7 Osteocytes communicate through gap junctions with neighboring osteocyte processes and with surface osteoblasts.

fled border from which collagenases, phosphatases, and lysosomal enzymes are secreted so as to loosen, fragment, and dissolve bone. The dissolution products are endocytosed and move across the osteoclast to be released into the interstitial fluid.

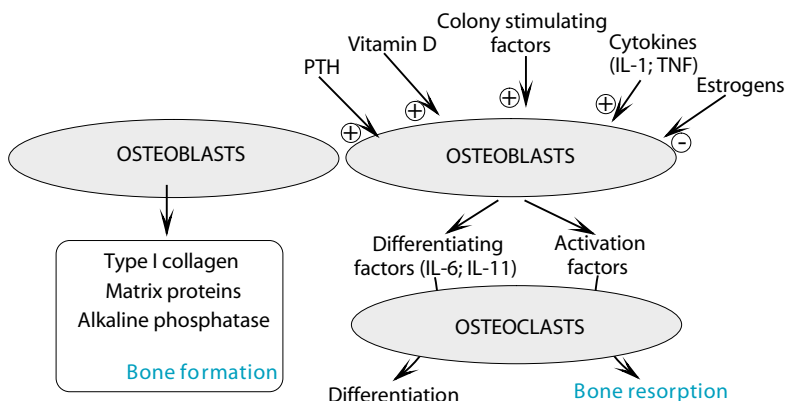


Figure 13-8 Osteoblasts are responsible for bone formation and accomplish this by secreting type I collagen and other factors. In addition, they respond to parathyroid hormone (PTH), vitamin D [$1,25-(\text{OH})_2\text{D}_3$], a variety of colony-stimulating factors, and cytokines, such as IL-1 and tumor necrosis factor (TNF), by expressing, on their plasma membrane, such factors as IL-6 and IL-11 that influence the differentiation and subsequent activity of **osteoclasts**. This second aspect of osteoblast activity is inhibited by estrogens. IL-1, -6, -11 = interleukin-1, -6, and -11.

Osteocytes. Osteocytes are former osteoblasts, buried by freshly formed matrix. They are covered by fine branching projections that extend through the canaliculi to communicate, via gap junctions, with neighboring osteocyte processes and with surface osteoblasts (see Figure 13–7). Such junctions allow the flow of ions between neighboring cells. The osteocyte network is closely adjacent to the bone capillary network and communicates directly with the interfibrillar spaces of the bone matrix. This morphologic feature and the observation that osteocytes are stimulated by PTH to lyse surrounding bone matrix suggest that they form a link in the transfer of calcium from bone to blood.

Bone Development and Growth

Mature bone can grow only by the deposition of new layers of bony material on preformed surfaces. However, in the embryo, there is a need for bone formation, and thereafter, up to puberty, there is a need for increasing bone length.

Bone is formed from undifferentiated mesenchymal tissue by two processes: **intramembranous** and **endochondral ossification**. Intramembranous ossification forms bone directly from the mesenchyme. Only the calvaria and clavicle are formed by this process. Most of the fetal skeleton is formed by endochondral ossification, a process that involves the formation of cartilage as an intermediate step.

Endochondral ossification. Adult bones have their beginning in a minute set of scale models made of cartilage in the embryo. These models grow initially by proliferation of chondrocytes. In long bones, ossification starts in the mid-diaphysis region in a **primary ossification center** (Figure 13–9).

Bone lengthening. **Epiphyseal plates** separate bony epiphysis from bony diaphysis (Figure 13–10). During longitudinal growth, which continues until adulthood is reached, somatomedins stimulate each plate to deposit cartilage toward the epiphyseal surface and to mineralize the cartilage into bone on the diaphyseal surface (see Figure 13–10).

When adult height is reached, longitudinal growth stops, and the cartilage of the epiphyseal plates is resorbed and replaced by bony trabeculae. All newly formed bone is trabecular. It is subsequently transformed into cortical bone by the processes of **remodeling**.

Bone remodeling. Living bone is never at rest. Both its matrix and mineral stores are constantly turning over, being remodeled along lines of mechanical stress. Normally, the processes of bone removal and bone formation are balanced so that there is no change in adult bone mass.

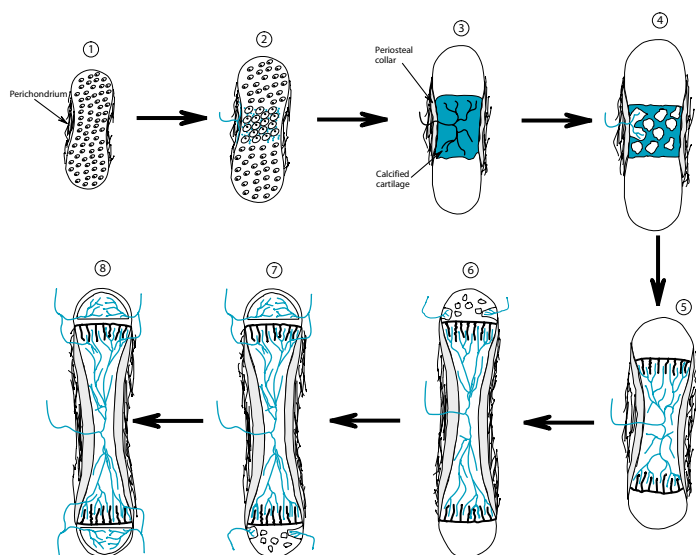


Figure 13-9 Bone growth in the embryo by endochondral ossification.

1. Cartilage model of a long bone.
2. Blood vessels begin to invade the cartilage, chondrocytes hypertrophy in the primary ossification center and secrete **alkaline phosphatase**. This causes precipitation of calcium phosphate within the matrix.
3. Blood vessels grow into the center of the cartilage, chondrocytes proliferate, and progressive deposition of CaHPO_4 within the matrix impairs diffusion and kills chondrocytes. Calcium phosphate is then slowly transformed into hydroxyapatite, an insoluble, crystalline mineral. As a result of these events, thin trabeculae of calcified matrix are formed and a bone sleeve (periosteal collar) begins to be deposited around the midshaft.
4. Some of the mesenchymal cells differentiate into osteoclasts. In addition, macrophages enter from the newly proliferated blood vessels. Osteoclasts and macrophages remove calcified matrix and cellular debris converting the cartilage model into a hollow cylinder and allowing **marrow** (capillaries and undifferentiated tissue) to proliferate into the space.
5. Other mesenchymal cells differentiate into osteoblasts, and they enter the cartilage along with the advancing capillaries, deposit bone matrix, and expand the primary ossification center toward the epiphyses.
6. A secondary ossification center forms proximally.
7. Another secondary ossification center forms distally. At the secondary ossification centers, chondrocytes grow in long columns that are surrounded by cartilaginous matrix.
8. Eventually, the matrix calcifies, chondrocytes die, and blood vessels as well as mesenchyme invade, and bone is deposited on the surface of the matrix cores. Most of the growth of bones before puberty occurs at the ends of bones in a cylinder of cartilage known as the epiphyseal plate. Both vertical and horizontal growths occur and account for lengthening of bones and the greater diameter of the epiphyses than the shaft.

Remodeling is initiated when a local osteocyte effect alters adjacent bone in such a way that it can be recognized by circulating mononuclear phagocytes and osteoclasts. They accumulate on the interior bone surface, fuse, and begin resorption. Over the course of about 3 weeks, the resorp-

tion forms a small tunnel of up to 1 mm in diameter. The tunnel is then invaded by osteoblasts, and their activity over the next several months fills the tunnel with new bone.

Bone thickening. If bone resorption is not exactly balanced by bone rebuilding, then there is a change in bone mass.

Bone thickening or bone expansion (in the case of the flat bones of the skull) occurs by removal of bone along the inner surface and concurrent deposition along the outer surface (see Figure 13–10).

Regulation of bone homeostasis. The activity of osteoblasts and osteoclasts is regulated by mechanical and a variety of hormonal factors (Figure 13–11). Somatomedins and mechanical stress are the major long-term regulators, whereas PTH, vitamin D, and calcitonin are the major short-term regulators. Only osteoblasts have PTH receptors, and the effect of the hormone is to increase osteoblast production of differentiating factors

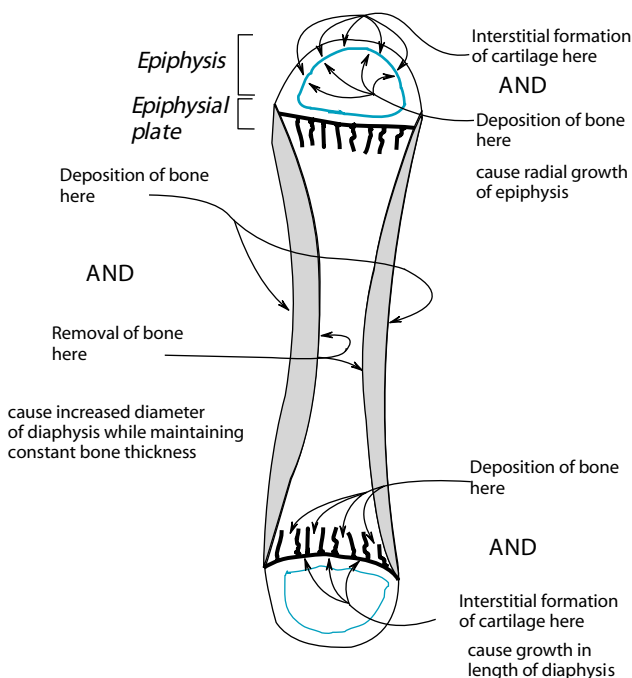


Figure 13–10 Bone growth and remodeling occur potentially at three places. Before puberty, while bones still grow in diameter and length, the epiphyses can grow in radius, and the shaft can grow in diameter, thickness, and length. After puberty, the epiphyseal plates disappear, and then there is only remodeling.

for osteoclasts (see Figure 13–11). Vitamin D acts on bone mostly by stimulating osteoblast production of differentiating factors for osteoclasts. Calcitonin acts directly on membrane receptors in osteocytes and osteoclasts. Its action in osteocytes inhibits bone demineralization, and its action in osteoclasts inhibits their resorptive activity.

Estrogen plays a vital role in the local coupling of bone resorption and formation. Estrogen and, to some extent, testosterone act on osteoblasts and peripheral monocytes to inhibit particularly the formation of IL-6, an important osteoclast differentiation factor. As a result, the presence of estrogen ensures a low rate of bone resorption and precise coupling between osteoblast and osteoclast activities. Lack of estrogen promotes osteoclast formation and activity and leads to reduction of bone mass (**osteoporosis**).

Functions of Bone

Bone has (1) mechanical function in that it provides support for the soft tissues of the body, protection for internal organs, and attachment points for tendons; (2) regulatory function in that it acts as a storage depot for minerals; and (3) germinal function in that it contains blood-forming tissues.

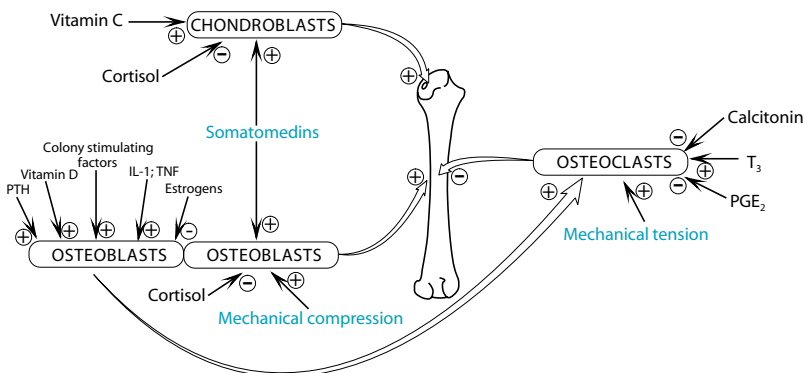


Figure 13–11 Chondroblasts increase the mass of cartilage; osteoblasts increase bone mass and also produce factors that promote differentiation of osteoclasts. Osteoclasts tend to reduce bone mass. The most important long-term regulators of bone mass are the somatomedins and mechanical loading. The major effect of PTH on bone is osteoclast stimulation. However, this effect is indirect and requires the presence of osteoblasts because osteoclasts have no PTH receptors. Although vitamin D stimulates both bone formation and resorption, its net effect on bone, in most physiologic settings, is resorption. Vitamin D also acts only through osteoblasts because osteoclasts lack vitamin D receptors. Estrogen is significantly involved because it inhibits release of the osteoblast-derived factors that stimulate osteoclast formation and action. Vitamin C is required for hydroxylation of proline and lysine in the formation of collagen, which stabilizes the matrix. IL-1 = interleukin-1; TNF = tumor necrosis factor; PTH = parathyroid hormone; vitamin D = 1,25-(OH)₂D₃.

Mechanical Support

The mechanical support provided by bone is related to its length, circumference, thickness, and composition.

Longitudinal bone growth stops when adult height is reached, and the epiphyseal plates have been sealed. However, bone changes in circumference throughout life as it responds to mechanical stresses. Compression, such as results from the force of gravity on the skeleton, causes bone thickening and this makes load-bearing exercises (walking as opposed to swimming) important for the building of bone mass.

Bone as a Reservoir for Minerals

Bone is the major reservoir for body calcium, phosphate, and magnesium. The minerals are deposited there by the action of osteoblasts and are released to the extracellular fluid by the action of osteocytes or osteoclasts.

Osteocyte enzymes or changes in osteocyte membrane permeability access the most recently formed bone crystals, which form a small but rapidly exchanging pool for Ca^{++} , Mg^{++} , and HPO_4^{2-} . This process is called **osteolysis**.

Osteoclast activity accesses the large, but slowly exchanging, compartment that is represented by mineralized bone.

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Web Links

General Interest

Washington State College of Veterinary Medicine Image Database

Harvey Project Home Page

Integrated Medical Curriculum – Homepage

Virtual Frog Dissection Kit Version 2.0

<http://www.critcon.com/>

Welcome to APS

Physiology Online - from The Physiological Society

Canadian Physiological Society

Biology Animations

Ch 1 - General Physiologic Processes

IP3 and calcium ion wave production after ligand binds receptor

CELLS alive!

Biology Animations

Ch2 – Muscle

SDSU Biology 590 - Actin Myosin Crossbridge 3D Animation

Muscle contraction

Calcium accumulation in Sarcoplasmic Reticulum

Muscle Physiology

Muscle Animation

Biology Animations

Ch 3 – Blood

Physiology of Blood

CELLS alive!

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Ch 5 – Respiration

Physiology of Blood

LUNG TOUR – HomePage

Biology Animations

Ch 6 - Cardiovascular Physiology

Physiology or Medicine for 1998 – Animation

EKG Tutorial-Menu

Animation

Biology Animations

Ch7 - Body Fluids and Electrolytes

Biology Animations

Ch8 - Gastrointestinal System

The Parietal Cell: Mechanism of Acid Secretion

Biology Animations

Ch9 - Endocrine System

Insulin Pathway

Insulin in Glucose Metabolism

Animation for Hypothalamus-Anterior Pituitary Axis

Steps in Insulin Receptor Signal Transduction

Diabetes

Biology Animations

Ch10 - Fuel Metabolism and Nutrition

Biology Animations

Ch11 - Reproduction and Sexual Function

Régulation hypothalamus et hypophyse

Biology Animations

Ch12 - Fertilization, Pregnancy, and Lactation

When Sperm Meets Egg

Fertilization

Biology Animations

Ch13 - Mineral Metabolism, Bone, and Connective Tissue

Physiology

Bone Physiology

Biology Animations

Glossary

1,25-(OH) ₂ D ₃	1,25-dihydroxycholecalciferol
2,3-DPG	2,3-diphosphoglycerate
16-OH DHEA-S	16-hydroxy dehydroepiandrosterone sulfate
AI, II	Angiotensin I, II
AA	Aachidonic acid
ABP	Arterial blood pressure
ACE	Converting enzyme
Acetyl-CoA	Acetyl-coenzyme A
ACTH	Adrenocorticotrophic hormone
ADH	Vasopressin; antidiuretic hormone
ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ANP	Atrial natriuretic peptide
ASA	Acetyl salicylic acid
AT _{1,2}	Angiotensin type 1, 2 receptor
ATP	Adenosine 5'-triphosphate
ATPase	Adenosine triphosphatase
AV3V	Antero ventral region of the third cerebral ventricle
aV _{EL,R}	Auxiliary leads in the standard 12-lead ECG
AVP	Arginine vasopressin
β, γ-LPH	Beta-, gamma-lipotrophic hormone
BMR	Basal metabolic rate
BNP	Brain natriuretic peptide
C1 to -9	Complement factors 1 to 9
CAM	Cellular adhesion molecules
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
CD	Cluster of differentiation
CFU	Colony-forming unit
cGMP	Cyclic guanosine monophosphate
CGRP	Calcitonin gene-related peptide
cis	On this side; the near side; the same side

FABP	Fatty acid binding protein
FAD	Flavin adenine dinucleotide
FADH ₂	Reduce flavin adenine dinucleotide
FBPase 2	Fructose bisphosphatase 2
FF	Filtration fraction
FFA	Free fatty acid
FGF	Fibroblast growth factor
FRC	Functional residual capacity
FSH	Follicle stimulating hormone
FVC	Functional vital capacity
GCSF	Granulocyte colony stimulating factor
GDP	Guanosine diphosphate
GFR	Glomerular filtration rate
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GnRH	Gonadotropin releasing hormone
GI	Gastrointestinal
GIP	Gastric inhibitory peptide a.k.a. glucose-dependent insulin-releasing peptide
GLP	Glucagon like peptide
GMCSF	Granulocyte-monocyte colony stimulating factor
GRP	Gastrin releasing peptide (= bombesin)
GTP	Guanosine triphosphate
Hb	Hemoglobin
Hb•NH•COO ⁻	Carbamino hemoglobin
HbO ₂	Oxygenated hemoglobin
hCG	Human chorionic gonadotropin
HCP	Histidine-rich calcium-binding protein
hCS	Human chorionic somatomammotropin
HDL	High density lipoprotein
HETE	Hydroxyeicosatetraenoic acid
Hg	Mercury
HHb	Deoxygenated hemoglobin
HMG	3-hydroxy-3-methylglutaryl
HR	Heart rate
hsd	Hydroxysteroid dehydrogenase
HVA	Homovanillic acid
Hz	Hertz (a measure of frequency) = cycles per second
I, II, III	Bipolar limb leads in the standard 12-lead ECG
I _{Ca-L}	Ca ⁺⁺ current, L-type channel
I _{Ca-T}	Ca ⁺⁺ current, T-type channel
I _f	Mixed Na ⁺ /K ⁺ current in pacemaker cells
I _{K1}	An inwardly rectifying K ⁺ current
I _{K (Ach)}	Acetylcholine-activated K ⁺ current
I _{KATP}	ATP-inhibited K ⁺ current
I _{Kr}	Rapid component of the delayed rectifier K ⁺ current
I _{Ks}	Slow component of the delayed rectifier K ⁺ current

CNP	C-type natriuretic peptide
CNS	Central nervous system
CoA	Coenzyme A
COMT	Catecholamine O-methyltransferase
COX	Cyclo-oxygenase
COX-1	Cyclo-oxygenase-1
CRH	Corticotropin releasing hormone
CTP	Cytosine triphosphate
CVLM	Caudal ventro-lateral medulla
DA	Dopamine
DAG	Diacylglycerol
DBP	Vitamin D-binding protein
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
DHP	Dihydropyridine
DHPG	3,4-dihydroxy-phenylglycol
DHT	Dihydrotestosterone
DIT	Di-iodotyrosine
DNA	Deoxyribonucleic acid
DOMA	3,4-dihydroxy-mandelic acid
DOPA	Dihydroxyphenylalanine
DOPAC	3,4-dihydroxyphenyl acetic acid
DOPAMINE	Dihydroxyphenylethyl-amine
dP/dt	Rate of change of pressure
dP/dt _{max}	Maximum rate of change of pressure
DPG	Diphosphoglycerate
E _{ion}	Equilibrium potential for a specific ion
E _K	Potassium equilibrium potential
E _m	Membrane potential
E _{NaCaX}	Reversal potential for the Na ⁺ /Ca ⁺⁺ exchanger
E _{rest}	Resting membrane potential
E _x	Ion equilibrium voltage potential for ion species "x"
E	Epinephrine (adrenaline)
ECG	Electrocardiogram
EDCF	Endothelium-derived contracting factor
EDHF	Endothelium-derived hyperpolarizing factor
EET	Epoxyecosatrienoic acid
EMG	Electromyogram
END	Endorphins
eNOS	Endothelial nitric oxide synthase
EP _{2,3}	Prostaglandin type 2, 3 receptor
EPO	Erythropoietin
EPSP	Excitatory postsynaptic potential
ER	Endoplasmic reticulum
ERV	Expiratory reserve volume
ETA	Endothelin type A receptor
F-1(or-2), 6 BP	Fructose 1 (or -2), 6 Biphosphate
F ₁ F ₀ -ATPase	ATP synthase

I_{Kur} , I_{Kq}	Ultrarapid component of the delayed rectifier K^+ current
I_{Na}	Current carried by Na^+ ions
I_{NaCaX}	Na^+/Ca^{++} exchange current
I_{to}	Transient outward current
IC	Inspiratory capacity
ICAM	Intercellular cellular adhesion molecules
IDL	Intermediate density lipoprotein
IgA, -D, -E, -G, -M	Immunoglobulin A to -M
IGF-1,2	Insulin-like growth factor-1 or -2
IL-X	Interleukin -X where X=1 to 10
IMP	Imidazole monophosphate
IP_3	Inositol 1,4,5'-triphosphate
IP_4	Inositol 1,3,4,5'-tetrakisphosphate
IPSP	Inhibitory postsynaptic potential
IRV	Inspiratory reserve volume
ITP	Inosine triphosphate
K_{ATP}	ATP-sensitive potassium channel
KPA	Kilo Pascal
LCAT	Lecithin-cholesterol acyltransferase
LDL	Low density lipoprotein
LH	Luteinizing hormone
LMM	Light meromyosin
LTB4	Leukotriene B4
LVEDP	Left ventricular end diastolic pressure
LVEDV	Left ventricular end diastolic volume
LVESp	Left ventricular end systolic pressure
LVESV	Left ventricular end systolic volume
LVET	Left ventricular ejection time
M_{1-5}	Muscarinic receptors; types 1 to 5
MAG	Myelin-associated glycoprotein
MAO	Monoamine oxidase
MELC	Myosin essential light chain
MHC	Myosin heavy chain
MHC 1; - α ; - β , -2A; -2B; -2X; -emb; -exoc; -neo	Isoforms of myosin heavy chain
MHC-I or -II	Major histocompatibility complex-I or -II
MHPG	3-methoxy-4-hydroxy-phenylglycol
MIT	Mono iodotyrosine
MLC	Myosin light chain
MLCK	Myosin light chain kinase
MLRC	Myosin regulatory light chain
MMC	Migrating motor complex
mRNA	Messenger ribonucleic acid
MSH	Melanocyte stimulating hormone
MTA	3-methoxytyramine
MVO ₂	Myocardial oxygen consumption rate

MW	Molecular weight
NaCaX	Na ⁺ /Ca ⁺⁺ exchange
NAD	Nicotinamide adenine dinucleotide
NADH	Reduced nicotinamide adenine dinucleotide
NADP ⁺	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NANC	Non-adrenergic/non-cholinergic
NCAM	Neural cellular adhesion molecules
NE	Norepinephrine (noradrenaline)
NO	Nitric oxide
NPY	Neuropeptide Y
NSF	N-ethylmaleimide-sensitive factor
NTS	Nucleus tractus solitarius
O ₂ ⁻	Free oxygen radical
Osm	Osmole
OVL	Organum vasculosum of the lamina terminalis
P-450scc	P-450 side chain cleavage enzyme
P _A	Alveolar pressure
P _i	Inorganic phosphate
P _{IN}	Plasma inulin concentration
P _{O₂} , CO ₂ , N ₂	Partial pressure of oxygen, carbon dioxide, or nitrogen
P _{PA}	Pulmonary arteriolar pressure
P _{PV}	Pulmonary venular pressure
P	P-wave of the ECG
P	Pressure
Pa	Pascal
PAF	Platelet activating factor
PAH	Para-amino hippuric acid
pCO ₂	Partial pressure of CO ₂
PDE III	Phosphodiesterase III
PDGF	Platelet-derived growth factor
PEP	Pre-ejection period
PFK-2	Phosphofructokinase-2
PGC	Particulate guanylate cyclase
PGE ₂	Prostaglandin E ₂
PGF _{2α}	Prostaglandin F _{2α}
PGH ₂ , -I ₂ , -G ₂	prostaglandin
PGI ₂	Prostaglandin I ₂
PHI	Peptide histidine isoleucine amide (a neurotransmitter co-released with VIP in humans)
PHM	Peptide histidine methionine amide (a neurotransmitter co-released with VIP in humans)
PIF	Prolactin inhibiting factors
PKA	Protein kinase A
PLP-C	Phospholipase-C
PMN	Polymorphonuclear leukocytes
PNMT	Phenylethanolamine-N-methyltransferase

pO ₂	Partial pressure of O ₂
POMC	Pro-opiomelanocortin
PP	Pancreatic polypeptide
PRF	Prolactin releasing factors
PSTI	Pancreatic secretory trypsin inhibitor
PTH	Parathyroid hormone
PTHrH	PTH-related protein
PVN	Paraventricular nucleus
PVP	Time to peak ventricular pressure
P _x	Membrane permeability coefficient for ion species x
Q	Blood flow (perfusion) (in L/min)
Q	Q-wave of the ECG
R	R-wave of the ECG
R _{AW}	Airway resistance
R _{GC(B)}	Guanylate cyclase receptor, type B
Re	Reynold's number
RNA	Ribonucleic acid
RPF	Renal plasma flow
RQ	Respiratory quotient
RV	Residual volume
RVD	Regulatory volume decrease
RVI	Regulatory volume increase
RVL	Rostral ventrolateral medulla
RVLM	Rostral ventro-lateral medulla
S ₁ ; S ₂	Subfragments 1 or 2 or myosin heavy chain
S _{aO2}	Oxygen saturation of hemoglobin
S	S-wave of the ECG
SA	Serum albumin
SFO	Subfornical organ
sGC	Soluble guanylate cyclase
SGLT1	Na ⁺ -glucose cotransporter 1
SNAP	Synaptosomal-associated protein
SON	Supraoptic nucleus
SR	Sarcoplasmic reticulum
SS	Somatostatin
SV	Stroke volume
T ₃	L-3,5,3'-tri-iodothyronine
T3	Tri-iodothyronine
T ₄	L-thyroxine
T _C	Cytotoxic T-lymphocytes
T _H	Helper T-lymphocytes
T _m	Tubular maximum reabsorption rate
T	T-wave of the ECG
TBG	Thyroxine-binding globulin
TBPA	Thyroxine-binding pre albumin
TG	Thyroglobulin
TLC	Total lung capacity

t-PA	Tissue-type plasminogen activator
TFN- α	Tumor necrosis factor-alpha
TFPI	Tissue factor pathway inhibitor
TGL	Thyroglobulin
Tn-C; -I; -T	Troponin-C; -I; -T
TPR	Total peripheral resistance
trans	On that side; the far side; the opposite side
TRAP	Thyroid receptor auxiliary protein
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone; thyrotropin
TTR	Transthyretin
TXA ₂	Thromboxane A ₂
TYR	Tyrosine
U _{IN}	Urine inulin concentration
u-PA	Urokinase-type plasminogen activator
UTP	Uridine triphosphate
V _{1 to 6}	Unipolar chest leads in the standard 12-lead ECG
V _{1,2}	Vasopressin type 1, 2 receptor
V _A	Alveolar ventilation (in L/min)
V _{O₂ max}	Maximum oxygen uptake (in mL.kg.min)
V _T	Tidal volume
v	Rate of urine volume excretion
VAMP	Vesicle-associated membrane protein
VC	Vital capacity
VCAM	Vascular cellular adhesion molecules
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal polypeptide
VLDL	Very low density lipoprotein
VMA	Vanillylmandelic acid
VMAT-1, -2	Vesicular monoamine transporter-1 or -2
VSM	Vascular smooth muscle
z	Valence