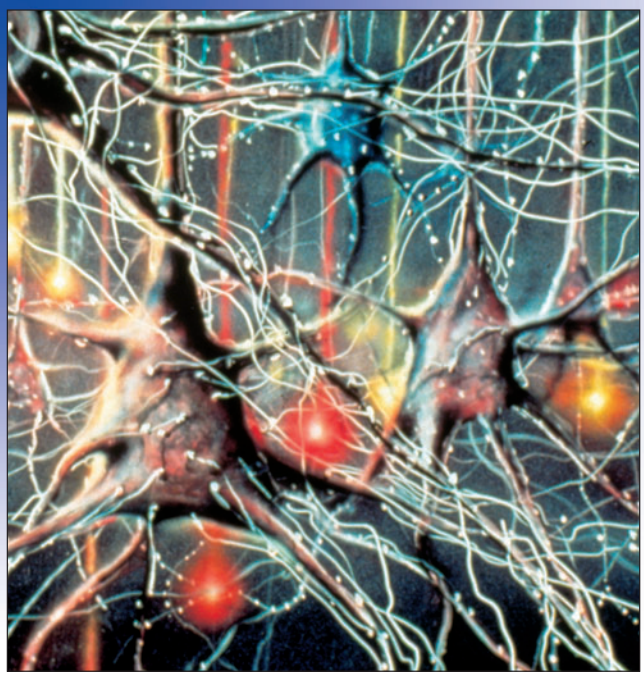

Multiple neurons of the brain "firing" (artist's conception)

CHAPTER

12

Nervous Tissue

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Brushing Up

To understand this chapter, it is important that you understand or brush up on the following concepts:
- Cations and anions (p. 60)
- Ligand- and voltage-regulated gates (p. 100)
- Cyclic AMP as a second messenger (p. 102)
- Simple diffusion (p. 106)
- Active transport and the sodium-potassium pump (p. 110)
- Basic structure of nerve cells (p. 175)

If the body is to maintain homeostasis and function effectively, its trillions of cells must work together in a coordinated fashion. If each cell behaved without regard to what others were doing, the result would be physiological chaos and death. This is prevented by two communication systems—the **nervous system** (fig. 12.1), which is specialized for the rapid transmission of signals from cell to cell, and the **endocrine system,** which is specialized for sending chemical messengers, the hormones, through the blood. The most important aspect of both systems is that they detect changes in an organ, modify its physiology, and modify that of other organs. Thus, these systems functionally coordinate the organs of the body and play a central role in maintaining homeostasis.

The scientific study of the nervous system is called **neuroscience.** It includes **neuroanatomy,** the study of structure, and **neurophysiology,** the study of function. The branch of medicine that deals with the diagnosis and treatment of neurological disorders is **neurology.**

Chapters 12 through 16 deal with neuroscience and chapter 17 with the endocrine system. This chapter is primarily concerned with how individual nerve cells work. The next four chapters are concerned with the organization and function of the nervous system at the organ level. The basic parts of a nerve cell were introduced in chapter 5 (p. 175).

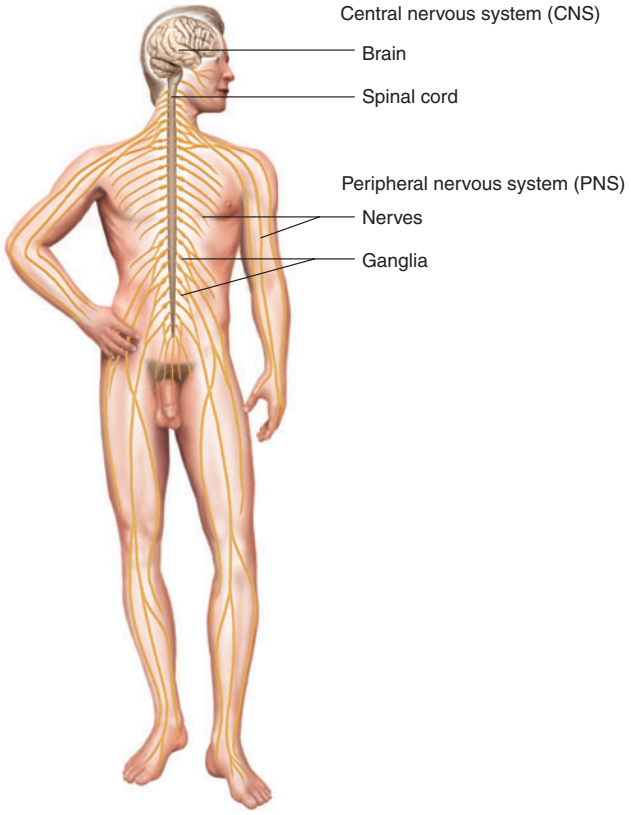


Figure 12.1 The Nervous System.

Overview of the Nervous System

Objectives

When you have completed this section, you should be able to

- describe the major anatomical subdivisions of the nervous system;
- state the general functions of the nervous system and how these relate to the general classes of nerve cells; and
- describe the basic physiological properties of nerve cells that enable them to carry out their functions.

The fundamental purpose of the nervous system is (1) to receive information from **receptors**—cells and organs specialized to detect changes in the body and its external environment; (2) to process this information and determine the appropriate response, if any—a step called **neural integration;** and (3) to issue commands to **effectors,** cells and organs (mainly muscle and gland cells) that carry out the body's responses.

The nervous system has two major anatomical subdivisions (fig. 12.2):

- The **central nervous system (CNS)** consists of the brain and spinal cord, which are enclosed and protected by the cranium and vertebral column.
- The **peripheral nervous system (PNS)** consists of all the nervous system except the brain and spinal cord. It is composed of nerves and ganglia. A **nerve** is a bundle of nerve fibers wrapped in fibrous connective tissue. Nerves emerge from the CNS through foramina of the skull and vertebral column and carry signals to

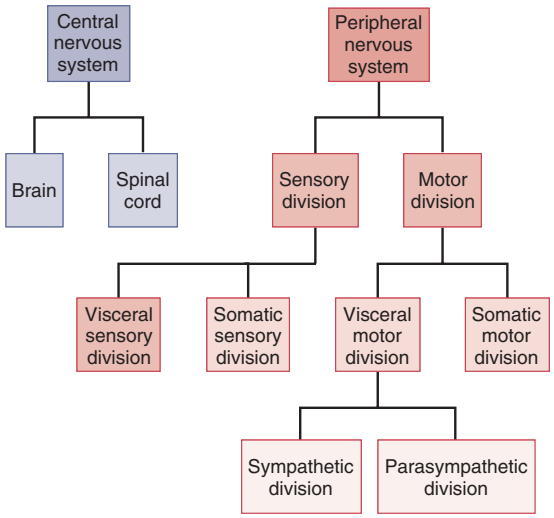


Figure 12.2 Subdivisions of the Nervous System.

and from other organs of the body. A **ganglion**[1] (plural, *ganglia*) is a knotlike swelling in a nerve where the cell bodies of neurons are concentrated.

The peripheral nervous system is functionally divided into *sensory* and *motor* divisions, and each of these is further divided into *somatic* and *visceral* subdivisions.

- The **sensory (afferent[2]) division** carries sensory signals by way of afferent nerve fibers from sensory **receptors** (cells and organs that detect stimuli) to the CNS.
  - The **visceral sensory division** carries signals mainly from the viscera of the thoracic and abdominal cavities, such as the heart, lungs, stomach, and urinary bladder.
  - The **somatic[3] sensory division** carries signals from receptors in the skin, muscles, bones, and joints.
- The **motor (efferent[4]) division** carries motor signals by way of efferent nerve fibers from the CNS to **effectors** (cells and organs that carry out the body's responses, mainly gland and muscle cells).
- The **visceral motor division (autonomic[5] nervous system)** carries signals to glands, cardiac muscle, and smooth muscle. We usually have no voluntary control over these effectors, and this system operates at an unconscious level. The responses of this system and its effectors are *visceral reflexes.* The autonomic nervous system has two further divisions:
  - The **sympathetic division** tends to arouse the body for action, for example by accelerating the heartbeat and increasing respiratory airflow, but it inhibits digestion.
  - The **parasympathetic division** tends to have a calming effect, slowing down the heartbeat, for example, but stimulating digestion.
- The **somatic motor division** carries signals to the skeletal muscles. This output produces muscular contractions that are under voluntary control as well as involuntary muscle contractions called *somatic reflexes.*

The foregoing terminology may give the impression that the body has several nervous systems—central, peripheral, sensory, motor, somatic, and visceral. These are just terms of convenience, however. There is only one nervous system, and these subsystems are interconnected parts of the whole.

[1] *gangli* = knot
[2] *af* = *ad* = toward + *fer* = to carry
[3] *somat* = body + *ic* = pertaining to
[4] *ef* = *ex* = out, away + *fer* = to carry
[5] *auto* = self + *nom* = law, governance

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. What is a receptor? Give two examples of effectors.
2. Distinguish between the central and peripheral nervous systems, and between visceral and somatic divisions of the sensory and motor systems.
3. What is another name for the visceral motor nervous system? What are the two subdivisions of this system?

Nerve Cells (Neurons)

Objectives

When you have completed this section, you should be able to

- identify the parts of a neuron;
- explain how neurons transport materials between the cell body and tips of the axon;
- name the cells that aid neuron function and state their functions;
- describe the myelin sheath that is formed around certain nerve fibers and explain its importance; and
- explain how damaged nerve fibers regenerate.

Universal Properties

The communicative role of the nervous system is carried out by nerve cells, or **neurons.** These cells have three fundamental physiological properties that are necessary to this function:

1. **Excitability (irritability).** All cells possess excitability, the ability to respond to environmental changes called **stimuli.** Neurons have developed this property to the highest degree.
2. **Conductivity.** Neurons respond to stimuli by producing traveling electrical signals that quickly reach other cells at distant locations.
3. **Secretion.** When the electrical signal reaches the end of a nerve fiber, the neuron secretes a chemical *neurotransmitter* that "jumps the gap" and stimulates the next cell.

Think About It

What basic physiological properties do a nerve cell and a skeletal muscle fiber have in common? Name a physiological property of each that the other one lacks.

Functional Classes

There are three general classes of neurons (fig. 12.3) corresponding to the three major aspects of nervous system function listed earlier:

1. **Sensory (afferent) neurons** are specialized to detect stimuli such as light, heat, pressure, and chemicals, and transmit information about them to the CNS. These neurons can begin in almost any organ of the body and end in the CNS; the word *afferent* refers to signal conduction *toward* the CNS. Some sensory receptors, such as pain and smell receptors, are themselves neurons. In other cases, such as taste and hearing, the receptor is a separate cell that communicates directly with a sensory neuron.
2. **Interneurons**[6] **(association neurons)** lie entirely within the CNS. They receive signals from many other neurons and carry out the integrative function of the nervous system—that is, they process, store, and retrieve information and "make decisions" that determine how the body responds to stimuli. About 90% of our neurons are interneurons. The word *interneuron* refers to the fact that they lie *between,* and interconnect, the incoming sensory pathways and the outgoing motor pathways of the CNS.
3. **Motor (efferent) neurons** send signals predominantly to muscle and gland cells, the effectors that carry out the body's responses to stimuli. These neurons are called *motor* neurons because most of them lead to muscle cells, and *efferent* neurons to signify the signal conduction *away from* the CNS.

[6] *inter* = between

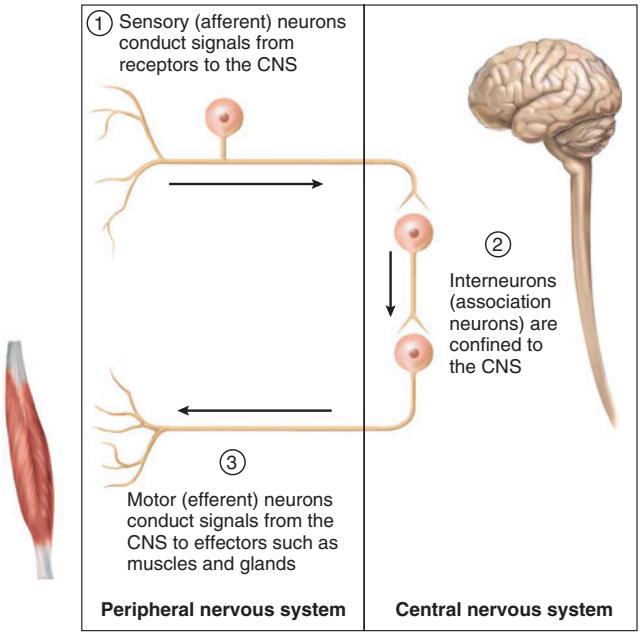


Figure 12.3 Functional Classes of Neurons. Sensory (afferent) neurons carry signals to the central nervous system (CNS); interneurons are contained entirely within the CNS and carry signals from one neuron to another; and motor (efferent) neurons carry signals from the CNS to muscles and glands.

Structure of a Neuron

There are several varieties of neurons, as we shall see, but a good starting point for discussing neuronal stucture is a motor neuron of the spinal cord (fig. 12.4). The control center of the neuron is its **soma,**[7] also called the **cell body** or **perikaryon**[8] (PERR-ih-CARE-ee-on). It has a single, centrally located nucleus with a large nucleolus. The cytoplasm contains mitochondria, lysosomes, a Golgi complex, numerous inclusions, and an extensive rough endoplasmic reticulum and cytoskeleton. The cytoskeleton consists of a dense mesh of microtubules and **neurofibrils** (bundles of actin filaments) that compartmentalize the rough ER into dark-staining regions called *Nissl*[9] *bodies* (fig. 12.4*c, d*). Nissl bodies are unique to neurons and a helpful clue to identifying them in tissue sections with mixed cell types. Mature neurons lack centrioles and apparently undergo no further mitosis after adolescence, but they are unusually long-lived cells, capable of functioning for over a hundred years. Even into old age, however, there are unspecialized *stem cells* in the CNS that can divide and develop into new neurons (see insight 4.3, p. 143).

The major cytoplasmic inclusions in a neuron are glycogen granules, lipid droplets, melanin, and a golden brown pigment called *lipofuscin*[10] (LIP-oh-FEW-sin)—an end product of lysosomal digestion of worn-out organelles and other products. Lipofuscin collects with age and pushes the nucleus to one side of the cell. Lipofuscin granules are also called "wear-and-tear granules" because they are most abundant in old neurons, but they are apparently harmless.

The soma of a neuron usually gives rise to a few thick processes that branch into a vast number of **dendrites**[11]—named for their striking resemblance to the bare branches of a tree in winter. The dendrites are the primary site for receiving signals from other neurons. Some neurons have only one dendrite and some have thousands. The more dendrites a neuron has, the more information it can receive from other cells and incorporate into its decision

[7] *soma* = body
[8] *peri* = around + *karyo* = nucleus
[9] Franz Nissl (1860–1919), German neuropathologist
[10] *lipo* = fat, lipid + *fusc* = dusky, brown
[11] *dendr* = tree, branch + *ite* = little

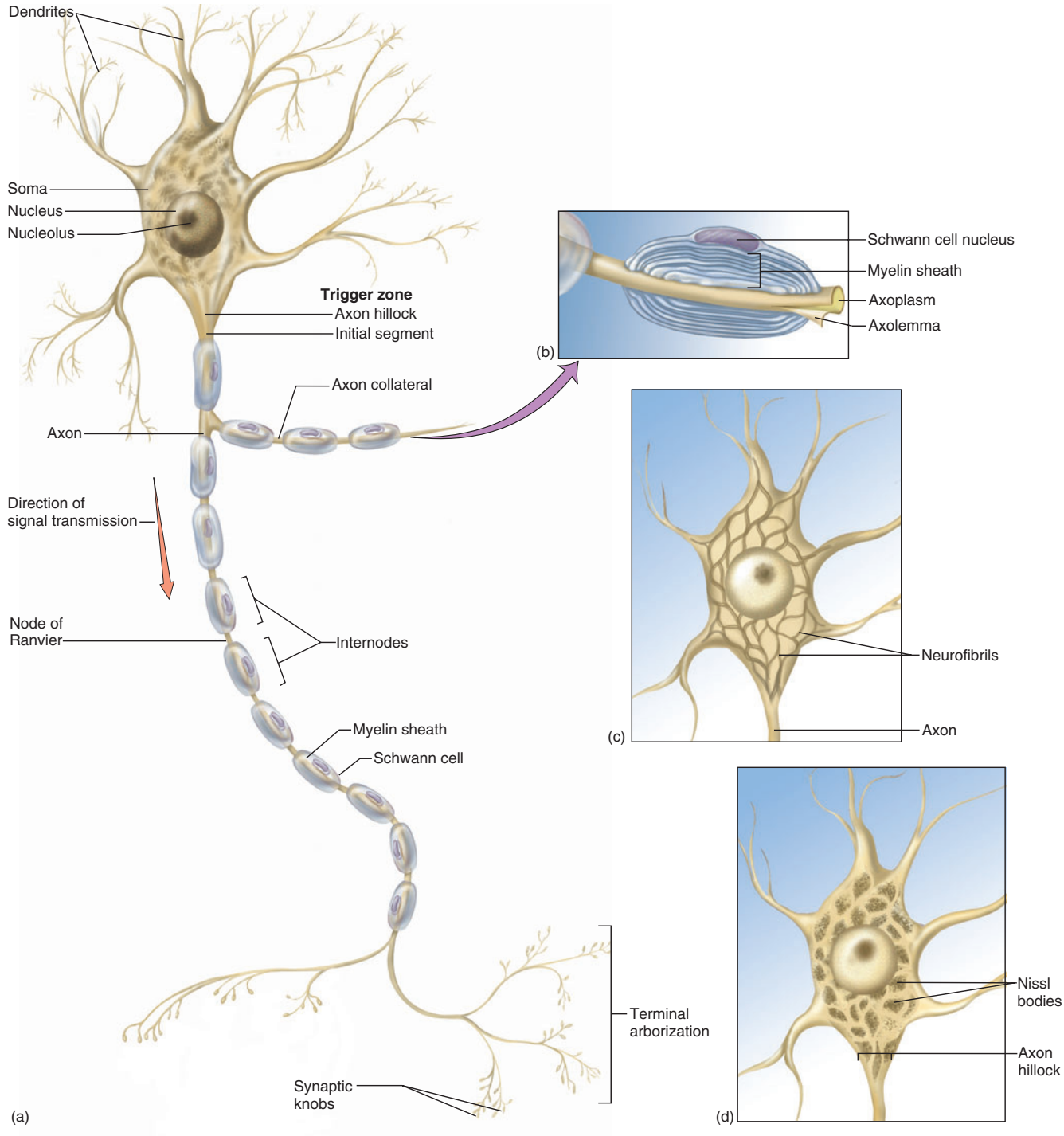


Figure 12.4 A Representative Neuron. The Schwann cells and myelin sheath are explained later in this chapter. (*a*) A multipolar neuron such as a spinal motor neuron. (*b*) Detail of myelin sheath. (*c*) Neurofibrils of the soma. (*d*) Nissl bodies, stained masses of rough ER separated by bundles of neurofibrils.

making. As tangled as the dendrites may seem, they provide exquisitely precise pathways for the reception and processing of neural information.

On one side of the soma is a mound called the **axon hillock,** from which the **axon (nerve fiber)** originates. The axon is cylindrical and relatively unbranched for most of its length, although it may give rise to a few branches called *axon collaterals* along the way, and most axons branch extensively at their distal end. An axon is specialized for rapid conduction of nerve signals to points remote from the soma. Its cytoplasm is called the **axoplasm** and its membrane the **axolemma.**[12] A neuron never has more than one axon, and some neurons in the retina and brain have none.

Somas range from 5 to 135 μm in diameter, while axons range from 1 to 20 μm in diameter and from a few millimeters to more than a meter long. Such dimensions are more impressive when we scale them up to the size of familiar objects. If the soma of a spinal motor neuron were the size of a tennis ball, its dendrites would form a huge bushy mass that could fill a 30-seat classroom from floor to ceiling. Its axon would be up to a mile long but a little narrower than a garden hose. This is quite a point to ponder. The neuron must assemble molecules and organelles in its "tennis ball" soma and deliver them through its "mile-long garden hose" to the end of the axon. How it achieves this remarkable feat is explained shortly.

At the distal end, axons usually have a **terminal arborization**[13]—an extensive complex of fine branches. Each branch ends in a **synaptic knob (terminal button).** As studied in the previous chapter, the synaptic knob is a little swelling that forms a junction **(synapse**[14]**)** with a muscle cell, gland cell, or another neuron. It contains **synaptic vesicles** full of neurotransmitter.

Not all neurons fit the preceding description. Neurons are classified structurally according to the number of processes extending from the soma (fig. 12.5):

- **Multipolar neurons** are those, like the preceding, that have one axon and multiple dendrites. This is the most common type of neuron and includes most neurons of the brain and spinal cord.
- **Bipolar neurons** have one axon and one dendrite. Examples include olfactory cells of the nasal cavity, some neurons of the retina, and sensory neurons of the inner ear.
- **Unipolar neurons** have only a single process leading away from the soma. They are represented by the neurons that carry sensory signals to the spinal cord. These neurons are also called *pseudounipolar* because they start out as bipolar neurons in the embryo, but their two processes fuse into one as the neuron

[12] *axo* = axis, axon + *lemma* = husk, peel, sheath
[13] *arbor* = tree
[14] *syn* = together + *aps* = to touch, join

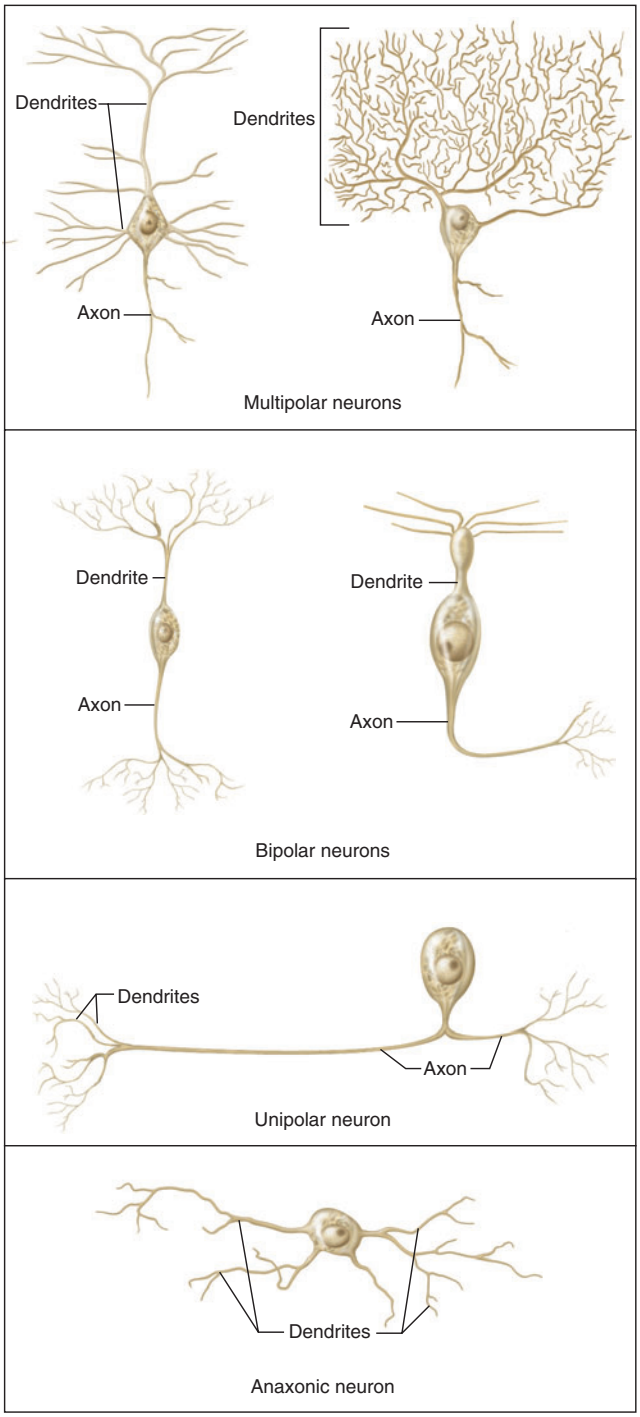


Figure 12.5 Variation in Neuronal Structure. *Top row, left to right:* Two multipolar neurons of the brain—a pyramidal cell and Purkinje cell. *Second row, left to right:* Two bipolar neurons—a bipolar cell of the retina and an olfactory neuron. *Third row:* A unipolar neuron of the type involved in the senses of touch and pain. *Bottom row:* An anaxonic neuron (amacrine cell) of the retina.

matures. A short distance away from the soma, the process branches like a T, with a *peripheral fiber* carrying signals from the source of sensation and a *central fiber* continuing into the spinal cord. In most other neurons, a dendrite carries signals toward a soma and an axon carries them away. In unipolar neurons, however, there is one long fiber that bypasses the soma and carries nerve signals directly to the spinal cord. The dendrites are the branching receptive endings in the skin or other place of origin, while the rest of the fiber is considered to be the axon (defined in these neurons by the presence of myelin and the ability to generate action potentials—two concepts explained later in this chapter).

- **Anaxonic neurons** have multiple dendrites but no axon. They communicate through their dendrites and do not produce action potentials. Some anaxonic neurons are found in the brain and retina. In the retina, they help in visual processes such as the perception of contrast.

Axonal Transport

All of the proteins needed by a neuron must be made in the soma, where the protein-synthesizing organelles such as the nucleus, ribosomes, and rough endoplasmic reticulum are located. Yet many of these proteins are needed in the axon, for example to repair and maintain the axolemma, to furnish ion gates in the membrane, or to act in the synaptic knob as enzymes and signaling molecules. Other substances are transported from the axon terminals back to the soma for disposal or recycling. The two-way passage of proteins, organelles, and other materials along an axon is called **axonal transport.** Movement from the soma down the axon is called **anterograde**[15] **transport** and movement up the axon toward the soma is called **retrograde**[16] **transport.**

Materials travel along microtubules of the cytoskeleton, which act like railroad tracks to guide them to their destination. But what is the "motor" that drives them along the tracks? Anterograde transport employs a motor protein called *kinesin,* while retrograde transport uses one called *dynein* (the same protein we encountered earlier in cilia and flagella; see chapter 3). These proteins carry materials "on their backs" while they reach out, like the myosin heads of muscle (see chapter 11), to bind repeatedly to the microtubules and crawl along them.

There are two types of axonal transport, fast and slow.

1. **Fast axonal transport** occurs at a rate of 20 to 400 mm/day and may be either anterograde or retrograde:
   - *Fast anterograde transport* moves mitochondria, synaptic vesicles, other organelles, components of the axolemma, calcium ions, enzymes such as acetylcholinesterase, and small molecules such as glucose, amino acids, and nucleotides.
   - *Fast retrograde transport* returns used synaptic vesicles and other materials to the soma and informs the soma of conditions at the axon terminals. Some pathogens exploit retrograde transport to invade neurons, including tetanus toxin and the herpes simplex, rabies, and polio viruses. In such infections, the delay between infection and the onset of symptoms corresponds to the time needed for the pathogens to reach the somas.
2. **Slow axonal transport,** also called *axoplasmic flow,* occurs at a rate of 0.5 to 10 mm/day and is always anterograde. It moves enzymes and cytoskeletal components down the axon, renews worn-out axoplasmic components in mature neurons, and supplies new axoplasm for developing or regenerating neurons. Damaged nerve fibers regenerate at a speed governed by slow axonal transport.

[15] *antero* = forward + *grad* = to walk, to step
[16] *retro* = back + *grad* = to walk, to step

Before You Go On

Answer the following questions to test your understanding of the preceding section:

4. Sketch a multipolar neuron and label its soma, dendrites, axon, terminal arborization, synaptic knobs, myelin sheath, and nodes of Ranvier.
5. Explain the difference between a sensory neuron, motor neuron, and interneuron.
6. What is the functional difference between a dendrite and an axon?
7. How do proteins and other chemicals synthesized in the soma get to the synaptic knobs? By what process can a virus that invades a peripheral nerve fiber get to the soma of that neuron?

Supportive Cells (Neuroglia)

Objectives

When you have completed this section, you should be able to

- name the cells that aid neuron function and state their functions;
- describe the myelin sheath that is formed around certain nerve fibers and explain its importance;
- describe the relationship of unmyelinated nerve fibers to their supportive cells; and
- explain how damaged nerve fibers regenerate.

Types of Neuroglia

There are about a trillion (10^{12}) neurons in the nervous system—10 times as many neurons in your body as there are stars in our galaxy! Yet the neurons are outnumbered as much as 50 to 1 by supportive cells called **neuroglia** (noo-ROG-lee-uh), or **glial** (GLEE-ul) **cells.** Glial cells protect the neurons and aid their function. The word *glia,* which means "glue," implies one of their roles— they bind neurons together and provide a supportive framework for the nervous tissue. In the fetus, glial cells form a scaffold that guides young migrating neurons to their destinations. Wherever a mature neuron is not in synaptic contact with another cell, it is covered with glial cells. This prevents neurons from contacting each other except at points specialized for signal transmission, and thus gives precision to their conduction pathways.

There are six kinds of neuroglia, each with a unique function (table 12.1). Four types occur in the central nervous system (fig. 12.6):

1. **Oligodendrocytes**[17] (OL-ih-go-DEN-dro-sites) somewhat resemble an octopus; they have a bulbous body with as many as 15 armlike processes. Each process reaches out to a nerve fiber and spirals around it like electrical tape wrapped repeatedly around a wire. This spiral wrapping, called the *myelin sheath,* insulates the nerve fiber from the surrounding extracellular fluid. For reasons explained later, it speeds up signal conduction in the nerve fiber.
2. **Astrocytes**[18] are the most abundant and functionally diverse glia in the CNS and constitute over 90% of the tissue in some areas of the brain. They are many-branched and have a somewhat starlike shape. Astrocytes cover the entire brain surface and most nonsynaptic regions of the neurons in the gray matter of the CNS. They form a supportive framework for the nervous tissue. They issue numerous extensions, called *perivascular feet,* that contact the endothelial cells of the blood capillaries and stimulate them to form tight junctions. These junctions contribute to a *blood-brain barrier* that strictly controls which substances are able to get from the bloodstream into the brain tissue (see chapter 14). Astrocytes convert blood glucose to lactate and supply this to the neurons for nourishment. They secrete growth factors that promote neuron growth and synapse formation. They communicate electrically with neurons and may influence future synaptic signalling between neurons. Astrocytes also regulate the chemical composition of the tissue fluid—when neurons transmit signals, they release neurotransmitters and potassium ions; astrocytes absorb these substances and prevent them from reaching excessive levels in the tissue fluid. When neurons are damaged, astrocytes form hardened masses of scar tissue and fill space formerly occupied by neurons. This process is called *astrocytosis* or *sclerosis.*
3. **Ependymal**[19] (ep-EN-dih-mul) **cells** resemble a cuboidal epithelium lining the internal cavities of the brain and spinal cord. Unlike epithelial cells, however, they have no basement membrane and they exhibit rootlike processes that penetrate into

[17] *oligo* = few + *dendro* = branches + *cyte* = cell
[18] *astro* = star + *cyte* = cell
[19] *ependyma* = upper garment

Chapter 12

Table 12.1 Types of Glial Cells

Types	Functions
Neuroglia of CNS	
Oligodendrocytes	Form myelin in brain and spinal cord
Astrocytes	Cover brain surface and nonsynaptic regions of neurons; form supportive framework in CNS; induce formation of blood-brain barrier; nourish neurons; produce growth factors that stimulate neurons; communicate electrically with neurons and may influence synaptic signalling; remove neurotransmitters and K^+ from ECF of brain and spinal cord; help to regulate composition of ECF; form scar tissue to replace damaged nervous tissue
Ependymal cells	Line cavities of brain and spinal cord; secrete and circulate cerebrospinal fluid
Microglia	Phagocytize and destroy microorganisms, foreign matter, and dead nervous tissue
Neuroglia of PNS	
Schwann cells	Form neurilemma around all PNS nerve fibers and myelin around most of them; aid in regeneration of damaged nerve fibers
Satellite cells	Surround somas of neurons in the ganglia; function uncertain

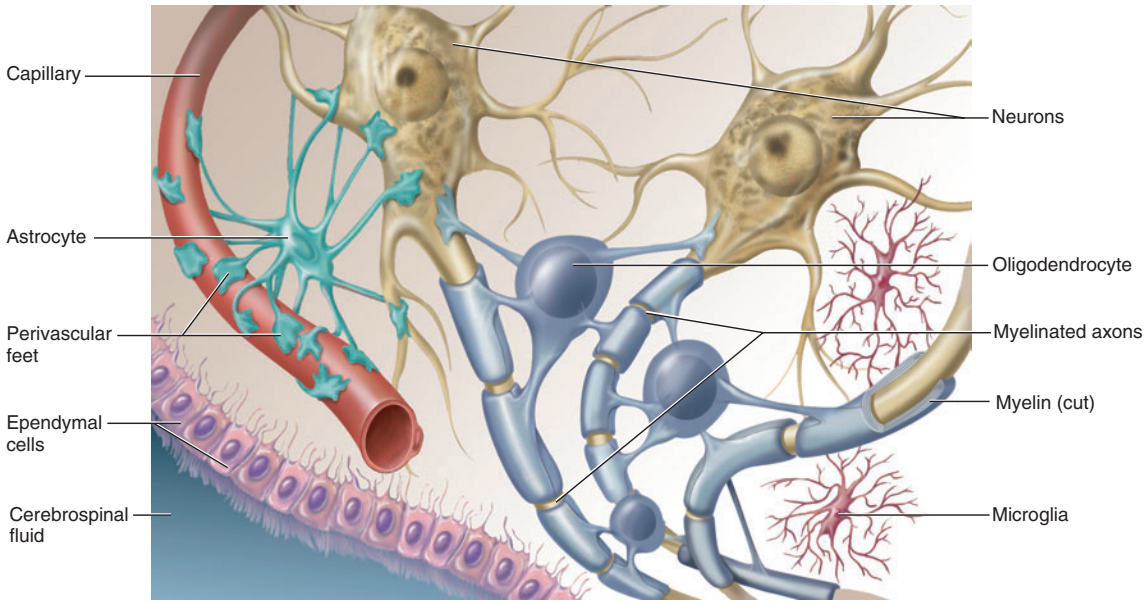


Figure 12.6 **Neuroglia of the Central Nervous System.**

the underlying nervous tissue. Ependymal cells produce cerebrospinal fluid (CSF), a clear liquid that bathes the CNS and fills its internal cavities. They have patches of cilia on their apical surfaces that help to circulate the CSF. Ependymal cells and CSF are considered in more detail in chapter 15.

4. **Microglia** are small macrophages that develop from white blood cells called monocytes. They wander through the CNS and phagocytize dead nervous tissue, microorganisms, and other foreign matter. They become concentrated in areas damaged by infection, trauma, or stroke. Pathologists look for clusters of microglia in brain tissue as a clue to sites of injury.

The other two types of glial cells occur in the peripheral nervous system:

5. **Schwann**[20] (shwon) **cells** envelop nerve fibers of the PNS. In most cases, a Schwann cell winds repeatedly around a nerve fiber and produces a myelin sheath similar to the one produced by oligodendrocytes in the CNS. There are some important differences between the CNS and PNS in the way myelin is produced, which we consider shortly. In addition to myelinating peripheral nerve fibers, Schwann cells assist in the regeneration of damaged fibers, which also is discussed later.
6. **Satellite cells** surround the neuron cell bodies in ganglia of the PNS. Little is known of their function.

[20]Theodor Schwann (1810–82), German histologist

Insight 12.1 Clinical Application

Glial Cells and Brain Tumors

A tumor consists of a mass of rapidly dividing cells. Mature neurons, however, have little capacity for mitosis and seldom form tumors. Some brain tumors arise from the meninges (protective membranes of the CNS) or arise by metastasis from tumors elsewhere, such as malignant melanoma and colon cancer. Most adult brain tumors, however, are composed of glial cells, which are mitotically active throughout life. Such tumors are called *gliomas*.[21] Gliomas usually grow rapidly and are highly malignant. Because of the blood-brain barrier (see chapter 14), brain tumors usually do not yield to chemotherapy and must be treated with radiation or surgery.

[21]*glia* = glial cells + *oma* = tumor

Myelin

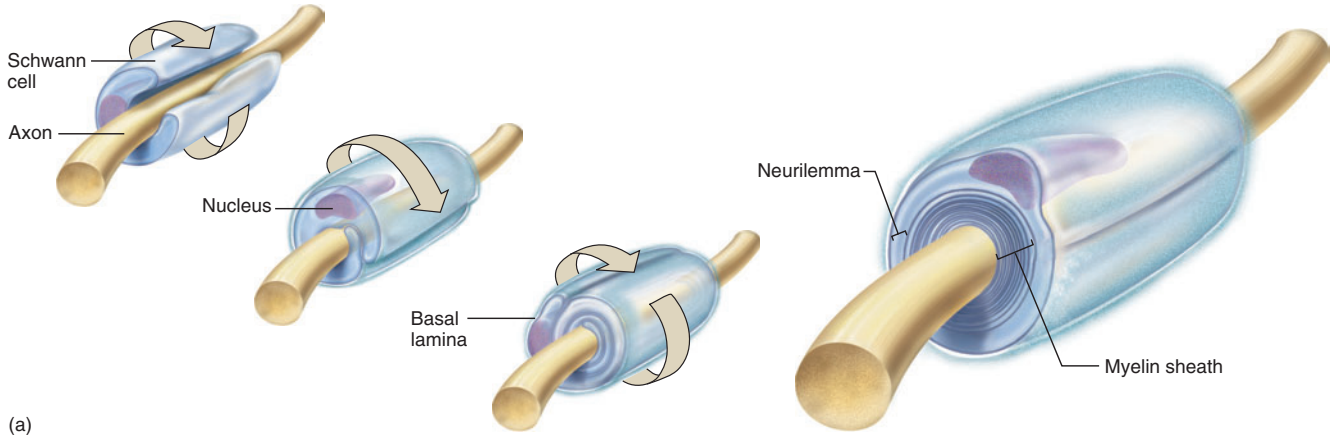
The **myelin** (MY-eh-lin) **sheath** is an insulating layer around a nerve fiber, somewhat like the rubber insulation on a wire. It is formed by oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. Since it consists of the plasma membranes of these glial cells, its composition is like that of plasma membranes in general. It is about 20% protein and 80% lipid, the latter including phospholipids, glycolipids, and cholesterol. Myelination of the nervous system begins in the fourteenth week of fetal development, yet hardly any myelin exists in the brain at the time of birth. Myelination proceeds rapidly in infancy

and isn't completed until late adolescence. Since myelin has such a high lipid content, dietary fat is important to early nervous system development. Well-meaning parents can do their children significant harm by giving them the sort of low-fat diets (skimmed milk, etc.) that may be beneficial to an adult.

In the CNS, each oligodendrocyte reaches out to several nerve fibers in its immediate vicinity. The armlike process of the oligodendrocyte spirals repeatedly around the nerve fiber, laying down many compact layers of its own membrane with almost no cytoplasm between the membranes. These layers constitute the myelin sheath. A nerve fiber is much longer than the reach of a single oligodendrocyte, so it requires many oligodendrocytes to cover one nerve fiber.

In the PNS, a Schwann cell spirals around a single nerve fiber, putting down as many as a hundred layers of membrane (fig. 12.7). External to the myelin sheath is the **neurilemma**[22] (noor-ih-LEM-ah), the outermost coil of the Schwann cell. Here, the bulging body of the Schwann cell contains its nucleus and most of its cytoplasm. To

[22] *neuri* = nerve + *lemma* = husk, peel, sheath



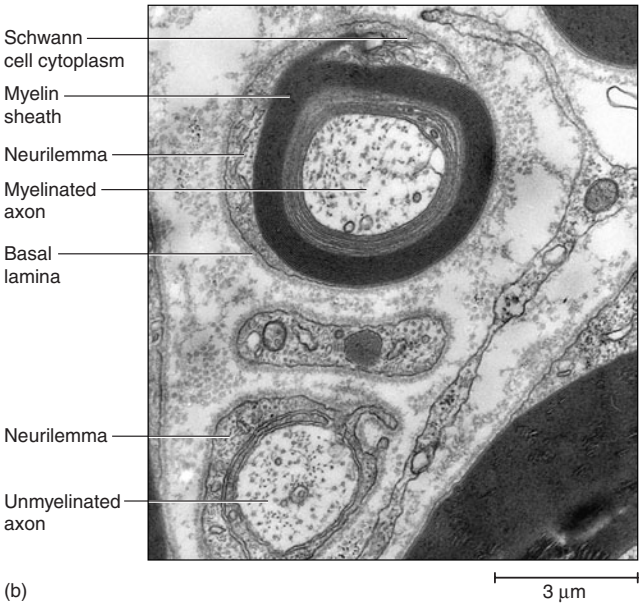


Figure 12.7 Schwann Cells and Myelin. (*a*) The repetitive wrapping of a Schwann cell around an axon, forming the multilayered myelin sheath. (*b*) A myelinated axon (*top*) and unmyelinated axon (*bottom*) (TEM).

visualize this, imagine that you wrapped an almost-empty tube of toothpaste tightly around a pencil. The pencil represents the axon, and the spiral layers of toothpaste tube (with the toothpaste squeezed out) represent the myelin. The toothpaste would be forced to one end of the tube, which would form a bulge on the external surface of the wrapping, like the body of the Schwann cell.

External to the neurilemma is a basal lamina and then a thin sleeve of fibrous connective tissue called the *endoneurium.* Nerve fibers of the CNS have no neurilemma or endoneurium.

Since each glial cell (Schwann cell or oligodendrocyte) myelinates only part of an axon, the myelin sheath is segmented. The gaps between the segments of myelin are **nodes of Ranvier**[23] (RON-vee-AY), and the myelin-covered segments from one gap to the next are called **internodes** (see fig. 12.4). The internodes are about 0.2 to 1.0 mm long in the PNS. The short section of nerve fiber between the axon hillock and the first glial cell is called the **initial segment.** Since the axon hillock and initial segment play an important role in initiating a nerve signal, they are collectively called the **trigger zone.**

[23]L. A. Ranvier (1835–1922), French histologist and pathologist

Insight 12.2 Clinical Application

Diseases of the Myelin Sheath

Multiple sclerosis and Tay-Sachs disease are degenerative disorders of the myelin sheath. In *multiple sclerosis (MS),* the oligodendrocytes and myelin sheaths of the CNS deteriorate and are replaced by hardened scar tissue, especially between the ages of 20 and 40. Nerve conduction is disrupted with effects that depend on what part of the CNS is involved—double vision, blindness, speech defects, neurosis, tremors, and numbness. Patients experience variable cycles of milder and worse symptoms until they eventually become bedridden. Most die from 7 to 32 years after the onset of the disease. The cause of MS remains uncertain; most theories suggest that it results from an immune disorder triggered by a virus in genetically susceptible individuals. There is no cure.

Tay-Sachs[24] *disease* is a hereditary disorder seen mainly in infants of Eastern European Jewish ancestry. It results from the abnormal accumulation of a glycolipid called GM_2 (ganglioside) in the myelin sheath. GM_2 is normally decomposed by a lysosomal enzyme, but this enzyme is lacking from people who are homozygous recessive for the Tay-Sachs allele. As GM_2 accumulates, it disrupts the conduction of nerve signals and the victim typically suffers blindness, loss of coordination, and dementia. Signs begin to appear before the child is a year old and most victims die by the age of three or four. Asymptomatic adult carriers can be identified by a blood test and advised by genetic counselors on the risk of their children having the disease.

[24]Warren Tay (1843–1927), English physician; Bernard Sachs (1858–1944), American neurologist

Unmyelinated Nerve Fibers

Many nerve fibers in the CNS and PNS are unmyelinated. In the PNS, however, even the unmyelinated fibers are enveloped in Schwann cells. In this case, one Schwann cell harbors from 1 to 12 small nerve fibers in grooves in its surface. The Schwann cell's plasma membrane does not spiral repeatedly around the fiber as it does in a myelin sheath, but folds once around each fiber and somewhat overlaps itself along the edges (fig. 12.7*b*). This wrapping is the neurilemma. A basal lamina surrounds the entire Schwann cell along with its nerve fibers.

Conduction Speed of Nerve Fibers

The speed at which a nerve signal travels along a nerve fiber depends on two factors: the diameter of the nerve fiber and the presence or absence of myelin. Signal conduction occurs along the surface of a fiber, not deep within its axoplasm. Larger fibers have more surface area and conduct signals more rapidly than smaller fibers. Myelin further speeds signal conduction for reasons discussed later. Nerve signals travel about 0.5 to 2.0 m/sec in small unmyelinated fibers (2–4 μm in diameter) and 3 to 15 m/sec in myelinated fibers of the same size. In large myelinated fibers (up to 20 μm in diameter) they travel as fast as 120 m/sec. One might wonder why all of our nerve fibers are not large, myelinated, and fast, but if this were so, our nervous system would be either impossibly bulky or limited to far fewer fibers. Slow unmyelinated fibers are quite sufficient for processes in which quick responses are not particularly important, such as secreting stomach acid or dilating the pupil. Fast myelinated fibers are employed where speed is more important, as in motor commands to the skeletal muscles and sensory signals for vision and balance.

Regeneration of Nerve Fibers

Nerve fibers of the PNS are vulnerable to cuts, crushing injuries, and other trauma. A damaged peripheral nerve fiber can regenerate, however, if its soma is intact and at least some neurilemma remains. Within the first few weeks after injury, the severed distal end of an axon and its myelin sheath degenerate and macrophages remove the debris (fig. 12.8). A **regeneration tube,** formed by the neurilemma and endoneurium, is necessary for regeneration. The axon stump puts out several sprouts until one of them finds its way into the tube. This sprout begins to grow rapidly (about 3–5 mm/day), possibly under the influence of chemicals secreted by the tube (see insight 12.3), while the other sprouts are reabsorbed. The regeneration tube guides the growing axon back to its original destination until the neuron reestablishes a connection with the cells that it originally innervated. Skeletal muscle fibers atrophy

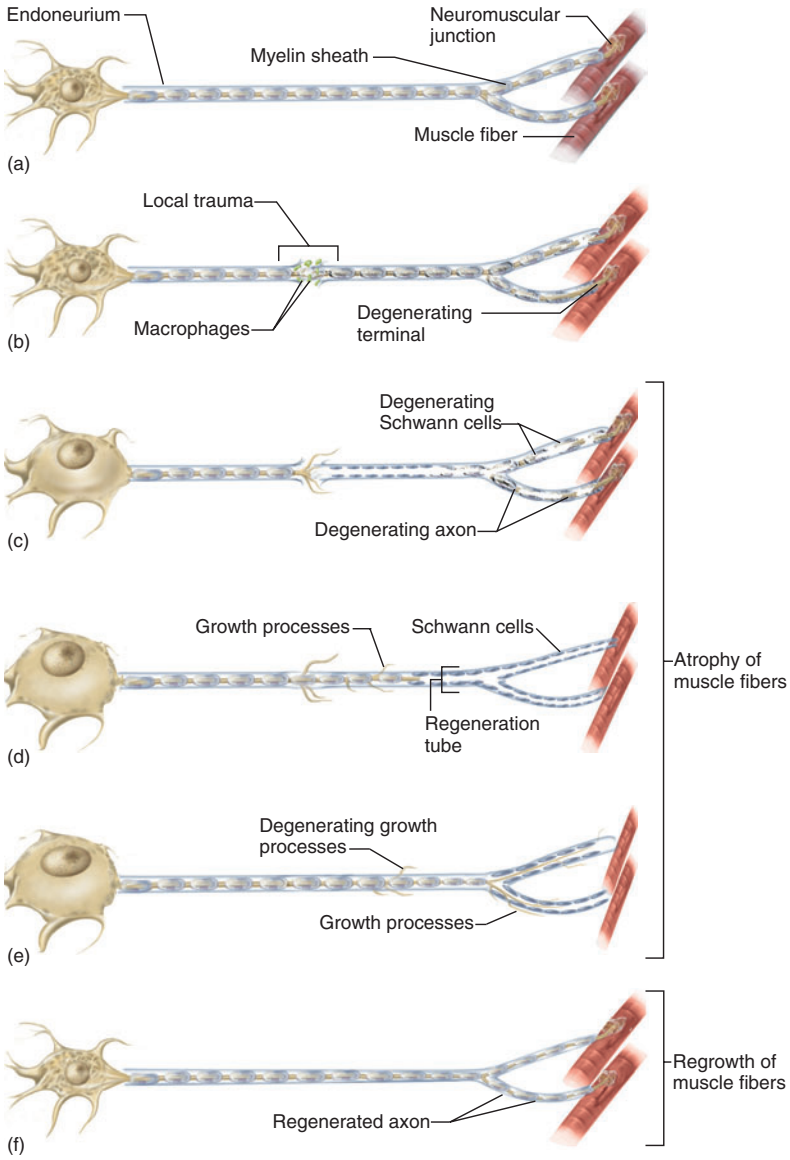


Figure 12.8 Regeneration of a Damaged Nerve Fiber. (*a*) Normal nerve fiber. (*b*) Injured fiber with macrophages cleaning up tissue debris at the point of injury, and with early degeneration of the nerve fiber, myelin sheath, and axon terminals distal to that. (*c*) Early regeneration; the soma is swollen, the Nissl bodies have dispersed, and the axon stump has begun producing multiple growth processes, while the severed distal part of the nerve fiber shows further degeneration. In the case of somatic motor neurons, muscle fibers atrophy for lack of innervation. (*d*) Continued regeneration; the Schwann cells, basal lamina, and neurilemma form a regeneration tube, one growth process grows into the tube, and the other growth processes are reabsorbed. (*e*) Continued regeneration; the growth processes have almost reestablished contact with the muscle fibers. (*f*) Regeneration complete; the muscle fibers are reinnervated and have regrown, and the soma of the neuron has returned to its original appearance.

when their nerve fiber is severed *(denervation atrophy),* but regrow after the connection is reestablished. Damaged neurons in the CNS cannot regenerate, but since the CNS is enclosed in bone, it suffers less trauma than the PNS.

Insight 12.3 Clinical Application

Nerve Growth Factor

Nerve growth factor (NGF) is a protein involved in the development of sympathetic nerve fibers and some sensory fibers. It is secreted by effector (gland and muscle) cells, picked up by axon terminals, and carried back to the soma by retrograde axonal transport. NGF guides developing nerve fibers to the appropriate target cells and thus plays a key role in the proper "wiring" of the nervous system to its effectors. The study of NGF and other growth factors is one of the most rapidly developing areas of biomedical research today, especially since recombinant DNA technology has made it possible to produce large quantities of these chemicals for study and clinical use. The use of NGF to treat Alzheimer disease is discussed in insight 12.4 on page 475.

Think About It

What features essential to regeneration, present in the PNS, are lacking from the CNS?

Before You Go On

Answer the following questions to test your understanding of the preceding section:

8. How is a glial cell different from a neuron? List the six types of glial cells and discuss their functions.
9. How is myelin produced? How does myelin production in the CNS differ from that in the PNS?
10. How can a severed peripheral nerve fiber find its way back to the cells it originally innervated?

Electrophysiology of Neurons

Objectives

When you have completed this section, you should be able to

- explain why a cell has an electrical charge difference (voltage) across its membrane;
- explain how stimulation of a neuron causes a local electrical change in its membrane;
- explain how local electrical changes generate a nerve signal; and
- explain how the nerve signal is transmitted down an axon.

The nervous system has intrigued scientists and philosophers since ancient times. The Roman physician Galen thought that the brain pumped a vapor called *psychic pneuma* through hollow nerves and squirted it into the muscles to make them contract. The French philosopher René Descartes still argued for this theory in the seventeenth century. It finally fell out of favor in the eighteenth century, when Luigi Galvani discovered the role of electricity in muscle contraction. When microscopes and histological staining methods were better developed, the Spanish histologist Santiago Ramón y Cajal (1852–1934) was able, with great effort, to trace the course of nerve fibers through tissue sections. He demonstrated that the nervous pathway was not a continuous "wire" or tube, but a series of separate cells separated by synapses. His theory, now called the *neuron doctrine,* suggested another direction for research—how do neurons communicate? The two key issues in neurophysiology are (1) How does a neuron generate an electrical signal and (2) How does it transmit a meaningful message to the next cell? These are the questions to which this section and the next are addressed.

Electrical Potentials and Currents

Neuronal communication, like muscle excitation, is based on electrophysiology—cellular mechanisms for producing electrical potentials and currents. An **electrical potential** is a difference in the concentration of charged particles between one point and another. It is a form of potential energy that, under the right circumstances, can produce a current. An electrical **current** is a flow of charged particles from the one point to the other. A new flashlight battery, for example, typically has a potential, or charge, of 1.5 volts (V). If the two poles of the battery are connected by a wire, electrons flow through the wire from one pole of the battery to the other, creating a current that can be used to light a bulb. As long as the battery has a potential, we say it is **polarized.**

Living cells are also polarized. As we saw in chapter 11, the charge difference across the plasma membrane is called the **resting membrane potential (RMP).** It is much less than the potential of a flashlight battery—typically about −70 millivolts (mV) in an unstimulated, "resting" neuron. The negative value means there are more negatively charged particles on the inside of the membrane than on the outside.

We do not have free electrons in the body as we do in an electrical circuit. Electrical currents in the body are created, instead, by the flow of ions such as Na^+ and K^+ through channels in the plasma membrane. As we saw in chapters 3 and 11, gated channels can be opened and closed by various stimuli. This enables cells to turn electrical currents on and off.

The Resting Membrane Potential

The reason that a cell has a resting membrane potential is that electrolytes are unequally distributed between the

extracellular fluid (ECF) on the outside of the plasma membrane and the intracellular fluid (ICF) on the inside. The RMP results from the combined effect of three factors: (1) the diffusion of ions down their concentration gradients through the plasma membrane; (2) selective permeability of the plasma membrane, allowing some ions to pass more easily than others; and (3) the electrical attraction of cations and anions to each other.

Potassium ions (K^+) have the greatest influence on the RMP because the plasma membrane is more permeable to K^+ than to any other ion. Imagine a hypothetical cell in which all the K^+ starts out in the ICF, with none in the ECF. Also in the ICF are a number of cytoplasmic anions that cannot escape from the cell because of their size or charge—phosphates, sulfates, small organic acids, proteins, ATP, and RNA. Assuming K^+ can diffuse freely through channels in the plasma membrane, it diffuses down its concentration gradient and out of the cell, leaving these cytoplasmic anions behind. As a result, the ICF grows more and more negatively charged. But as the ICF becomes more negative, it exerts a stronger and stronger attraction for the positive potassium ions and attracts some of them back into the cell. Eventually an *equilibrium* (balance) is reached in which K^+ is moving out of the cell (diffusion down its concentration gradient) and into the cell (by electrical attraction) at equal rates. The *net* diffusion of K^+ then stops. At the point of equilibrium, K^+ is about 40 times as concentrated in the ICF as in the ECF (fig. 12.9).

If K^+ were the only ion affecting the RMP, it would give the membrane a potential of about −90 mV. However, sodium ions (Na^+) also enter the picture. Sodium is about 12 times as concentrated in the ECF as in the ICF. The resting plasma membrane is much less permeable to Na^+ than to K^+, but Na^+ does diffuse down its concentration gradient into the cell, attracted by the negative charge in the ICF. This sodium leak is only a trickle, but it is enough to neutralize some of the negative charge and reduce the voltage across the membrane.

Sodium leaks into the cell and potassium leaks out, but the sodium-potassium (Na^+-K^+) pump described in chapter 3 continually compensates for this leakage. It pumps 3 Na^+ out of the cell for every 2 K^+ it brings in, consuming 1 ATP for each exchange cycle. By removing more cations from the cell than it brings in, it contributes about −3 mV to the resting membrane potential. The net effect of all this—K^+ diffusion out of the cell, Na^+ diffusion inward, and the Na^+-K^+ pump—is the resting membrane potential of −70 mV.

The Na^+-K^+ pump accounts for about 70% of the energy (ATP) requirement of the nervous system. Every signal generated by a neuron slightly upsets the distribution of Na^+ and K^+, so the pump must work continually to restore equilibrium. This is why nervous tissue has one of the highest rates of ATP consumption of any tissue in the body, and why it demands so much glucose and oxygen. Although a neuron is said to be resting when it is not producing signals, it is highly active maintaining its RMP and "waiting," as it were, for something to happen.

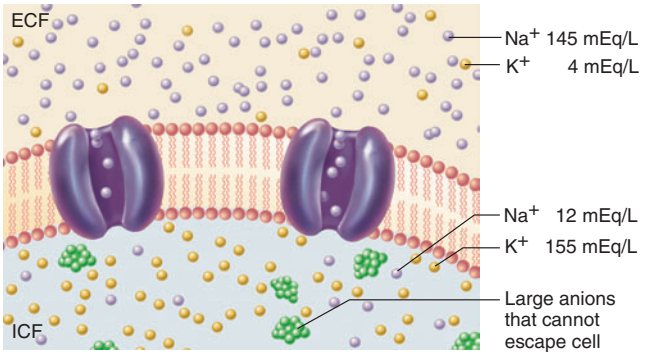


Figure 12.9 Ionic Basis of the Resting Membrane Potential. Note that sodium ions are much more concentrated in the extracellular fluid (ECF) than in the intracellular fluid (ICF), while potassium ions are more concentrated in the ICF. Large anions unable to penetrate the plasma membrane give the cytoplasm a negative charge relative to the ECF.
If we suddenly increased the concentration of Cl^- ions in the ICF, would the membrane potential become higher or lower than the RMP?

Local Potentials

We now consider the disturbances in membrane potential that occur when a neuron is stimulated. Typically (but with exceptions), the response of a neuron begins at a dendrite, spreads through the soma, travels down the axon, and ends at the synaptic knobs. We consider the process in that order.

Neurons can be stimulated by chemicals, light, heat, or mechanical distortion of the plasma membrane. We'll take as our example a neuron being chemically stimulated on its dendrite (fig. 12.10). The chemical—perhaps a pain signal from a damaged tissue or odor molecule in a breath of air—binds to receptors on the neuron. These receptors are ligand-regulated sodium gates that open and allow Na^+ to rush into the cell. The inflow of Na^+ neutralizes some of the internal negative charge, so the voltage across the membrane drifts toward zero. Any such case in which membrane voltage shifts to a less negative value is called **depolarization.** The incoming sodium ions diffuse for short distances along the inside of the plasma membrane and produce a current that travels from the point of stimulation toward the cell's trigger zone. Such a short-range change in voltage is called a **local potential.**

There are four characteristics that distinguish local potentials from the action potentials we will study shortly (table 12.2). You will appreciate these distinctions more fully after you have studied action potentials.

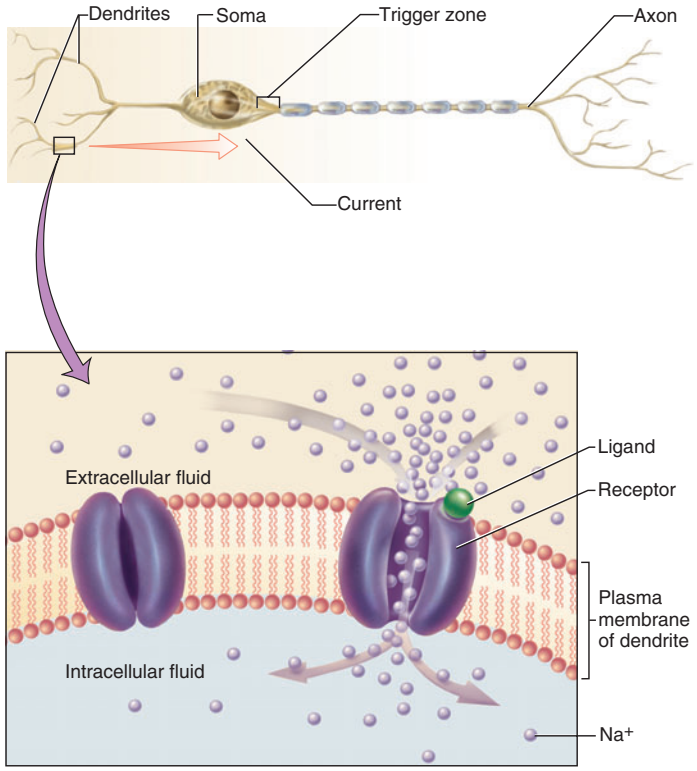


Figure 12.10 Excitation of a Neuron by a Chemical Stimulus. When the chemical (ligand) binds to a receptor on the neuron, the receptor acts as a ligand-regulated ion gate through which Na^+ diffuses into the cell. This depolarizes the plasma membrane.

Table 12.2 Comparison of Local Potentials and Action Potentials

Local Potential	Action Potential
Produced by ligand-regulated gates on the dendrites and soma	Produced by voltage-regulated gates on the trigger zone and axon
May be a positive (depolarizing) or negative (hyperpolarizing) voltage change	Always begins with depolarization
Graded; proportional to stimulus strength	All-or-none; either does not occur at all or exhibits same peak voltage regardless of stimulus strength
Reversible; returns to RMP if stimulation ceases before threshold is reached	Irreversible; goes to completion once it begins
Local; has effects for only a short distance from point of origin	Self-propagating; has effects a great distance from point of origin
Decremental; signal grows weaker with distance	Nondecremental; signal maintains same strength regardless of distance

1. Local potentials are **graded,** meaning that they vary in magnitude (voltage) according to the strength of the stimulus. A more intense or prolonged stimulus opens more ion gates than a weaker stimulus. Thus, more Na^+ enters the cell and the voltage changes more than it does with a weaker stimulus.
2. Local potentials are **decremental,** meaning they get weaker as they spread from the point of stimulation. The decline in strength occurs because as Na^+ spreads out under the plasma membrane and depolarizes it, K^+ flows out and reverses the effect of the Na^+ inflow. Therefore, the voltage shift caused by Na^+ diminishes rapidly with distance. This prevents local potentials from having any long-distance effects.
3. Local potentials are **reversible,** meaning that if stimulation ceases, K^+ diffusion out of the cell quickly returns the membrane voltage to its resting potential.

4. Local potentials can be either **excitatory** or **inhibitory.** So far, we have considered only excitatory local potentials, which depolarize a cell and make a neuron more likely to produce an action potential. Acetylcholine usually has this effect. Other neurotransmitters, such as glycine, cause an opposite effect—they **hyperpolarize** a cell, or make the membrane more negative. The neuron is then less sensitive and less likely to produce an action potential. A balance between excitatory and inhibitory potentials is very important to information processing in the nervous system, and we explore this more fully later in the chapter.

Action Potentials

An **action potential** is a more dramatic change produced by voltage-regulated ion gates in the plasma membrane. Action potentials occur only where there is a high enough density of voltage-regulated gates. Most of the soma has only 50 to 75 gates per square micrometer (μm^2) and cannot generate action potentials. The trigger zone, however, has 350 to 500 gates per μm^2. If an excitatory local potential spreads all the way to the trigger zone and is still strong enough when it arrives, it can open these gates and generate an action potential.

The action potential is a rapid up-and-down shift in membrane voltage. Figure 12.11*a* shows an action potential numbered to correspond to the following description. Figure 12.12 correlates these voltage changes with events in the plasma membrane.

1. When sodium ions arrive at the axon hillock, they depolarize the membrane at that point. This appears as a steadily rising local potential.
2. For anything more to happen, this local potential must rise to a critical voltage called the **threshold** (typically about −55 mV). This is the minimum needed to open voltage-regulated gates.
3. The neuron now "fires," or produces an action potential. At threshold, voltage-regulated Na^+ gates open quickly, while K^+ gates open more slowly. The initial effect on membrane potential is therefore due to Na^+. Initially, only a few Na^+ gates open but as Na^+ enters the cell, it further depolarizes the membrane. This stimulates still more voltage-regulated Na^+ gates to open and admit even more Na^+. Thus, a positive feedback cycle is created that makes the membrane voltage rise rapidly.
4. As the rising membrane potential passes 0 mV, Na^+ gates are *inactivated* and begin closing. By the time they all close and Na^+ inflow ceases, the voltage peaks at approximately +35 mV. (The peak is as low as 0 mV in some neurons and as high as 50 mV in others.) The membrane is now positive on the inside and negative on the outside—its polarity is reversed compared to the RMP.
5. By the time the voltage peaks, the slow K^+ gates are fully open. Potassium ions, repelled by the positive intracellular fluid, exit the cell. Their outflow **repolarizes** the membrane—that is, it shifts the voltage back into the negative numbers. The action potential consists of the up-and-down voltage shifts

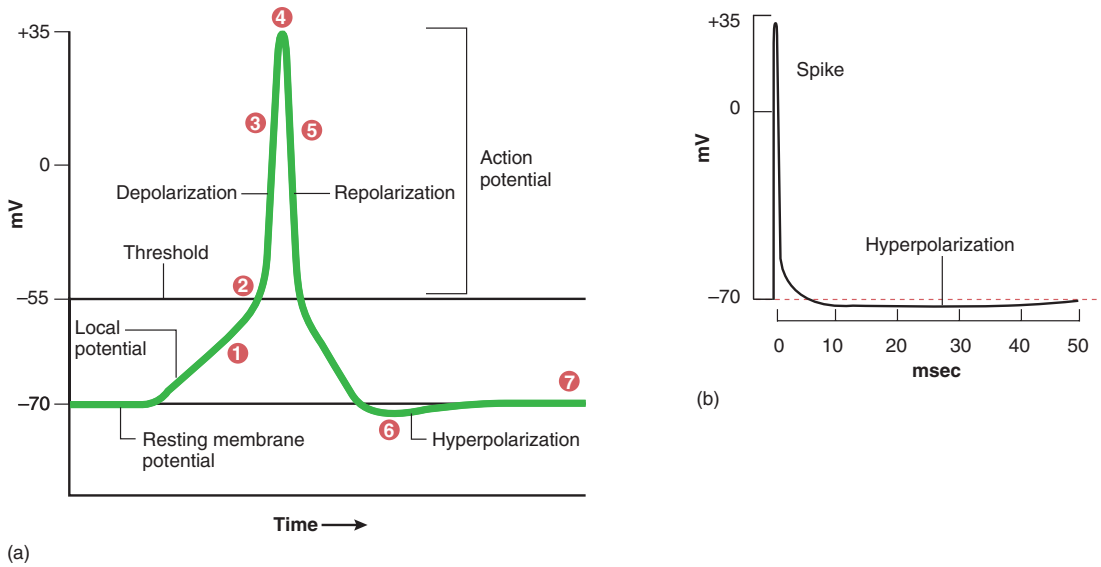


Figure 12.11 An Action Potential. (*a*) Diagrammed with a distorted timescale to make details of the action potential visible. Numbers correspond to stages discussed in the text. (*b*) On an accurate timescale, the local potential is so brief it is imperceptible, the action potential appears as a spike, and the hyperpolarization is very prolonged.

that occur from the time the threshold is reached to the time the voltage returns to the RMP.

6. Potassium gates stay open longer than Na^+ gates, so the amount of potassium that leaves the cell is greater than the amount of sodium that entered. Therefore, the membrane voltage drops to 1 or 2 mV more negative than the original RMP, producing a negative overshoot called *hyperpolarization.*
7. As you can see, Na^+ and K^+ switch places across the membrane during an action potential. During hyperpolarization, ion diffusion through the membrane and (in the CNS) the removal of extracellular K^+ by the astrocytes gradually restores the original resting membrane potential.

At the risk of being misleading, figure 12.12 is drawn as if most of the Na^+ and K^+ had traded places. In reality, only about one ion in a million crosses the membrane to produce an action potential, and an action potential affects ion distribution only in a thin layer close to the membrane. If the illustration tried to represent these points accurately, the difference would be so slight you could not see it, indeed the changes in ion concentrations inside and outside the cell are so slight they cannot be measured in the laboratory unless a neuron has been stimulated for a long time. Even after thousands of action potentials, the cytosol still has a higher concentration of K^+ and a lower concentration of Na^+ than the ECF does.

Figure 12.11*a* also is deliberately distorted. In order to demonstrate the different phases of the local potential and action potential, the magnitudes of the local potential and hyperpolarization are exaggerated, the local potential is stretched out to make it seem longer, and the duration of hyperpolarization is shrunken so the graph does not run off the page. When these events are plotted on a more realistic timescale, they look like figure 12.11*b*. The local potential is so brief it is unnoticeable, and hyperpolarization is very long but only slightly more negative than the RMP. An action potential is often called a *spike;* it is easy to see why from this figure.

Earlier we saw that local potentials are graded, decremental, and reversible. We can now examine how action potentials compare on these points.

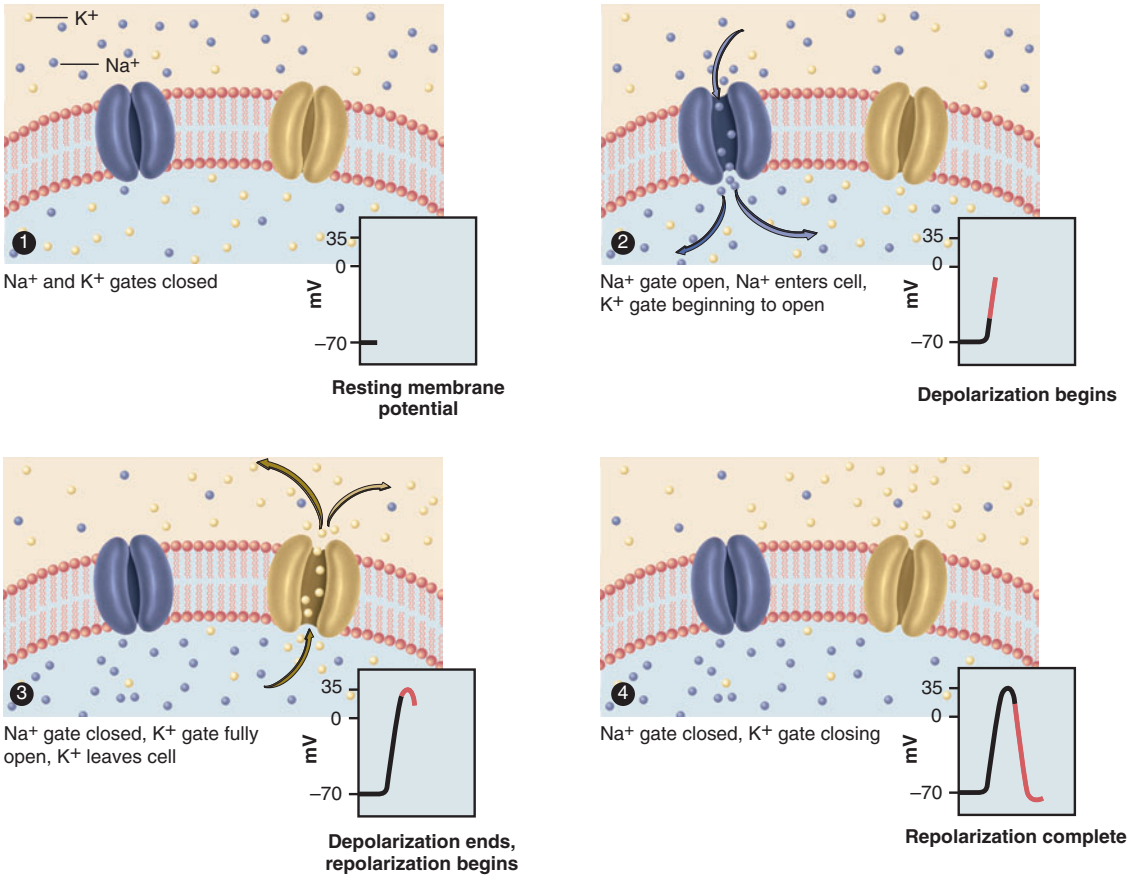


Figure 12.12 Actions of the Sodium and Potassium Gates During an Action Potential.

- Action potentials follow an **all-or-none law.** If a stimulus depolarizes the neuron to threshold, the neuron fires at its maximum voltage (such as +35 mV); if threshold is not reached, the neuron does not fire at all. Above threshold, stronger stimuli do not produce stronger action potentials. Thus, action potentials are not graded (proportional to stimulus strength).
- Action potentials are **nondecremental.** For reasons to be examined shortly, they do not get weaker with distance. An action potential at the end of a nerve fiber will be just as strong as an action potential in the trigger zone up to a meter away.
- Action potentials are **irreversible.** If a neuron reaches threshold, the action potential goes to completion; it cannot be stopped once it begins.

In some respects, we can compare the firing of a neuron to the firing of a gun. As the trigger is squeezed, a gun either fires with maximum force or does not fire at all (analogous to the all-or-none law). You cannot fire a fast bullet by squeezing the trigger hard or a slow bullet by squeezing it gently—once the trigger is pulled to its "threshold," the bullet always leaves the muzzle at the same velocity. And, like an action potential, the firing of a gun is irreversible once the threshold is reached. Table 12.2 further contrasts a local potential with an action potential, including some characteristics of action potentials explained in the next section.

The Refractory Period

During an action potential and for a few milliseconds after, it is difficult or impossible to stimulate that region of a neuron to fire again. This period of resistance to restimulation is called the **refractory period.** It is divided into two phases—an *absolute refractory period* in which no stimulus of any strength will trigger a new action potential, and then a *relative refractory period* in which it is possible to trigger a new action potential, but only with an unusually strong stimulus (fig. 12.13).

The absolute refractory period lasts from the start of the action potential until the membrane returns to the resting potential—that is, for as long as the Na^+ gates are open and subsequently inactivated. The relative refractory period lasts until hyperpolarization ends. During this period, K^+ gates are still open. A new stimulus tends to admit Na^+ and depolarize the membrane, but K^+ diffuses out through the open gates as Na^+ comes in, and thus opposes the effect of the stimulus. It requires an especially strong stimulus to override the K^+ outflow and depolarize the cell enough to set off a new action potential. By the end of hyperpolarization, K^+ gates are closed and the cell is as responsive as ever.

The refractory period refers only to a small patch of membrane where an action potential has already begun, not to the entire neuron. Other parts of the neuron can still be stimulated while a small area of it is refractory, and even this area quickly recovers once the nerve signal has passed on.

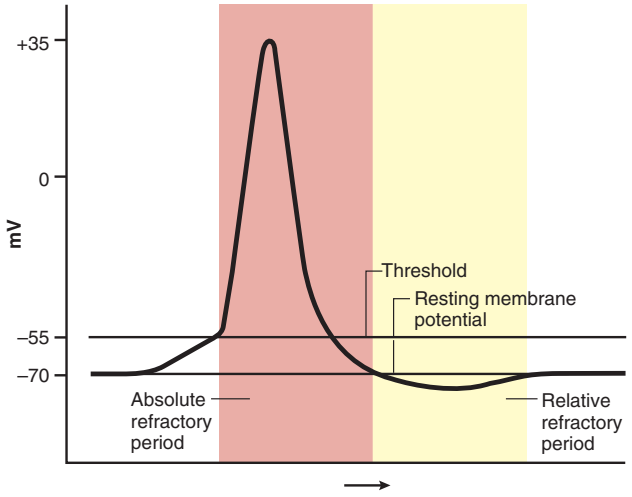


Figure 12.13 **The Absolute and Relative Refractory Periods in Relation to the Action Potential.**

Signal Conduction in Nerve Fibers

If a neuron is to communicate with another cell, a signal has to travel to the end of the axon. We now see how this is achieved.

Unmyelinated Fibers

Unmyelinated fibers present a relatively simple case of signal conduction, easy to understand based on what we have already covered (fig. 12.14). An unmyelinated fiber has voltage-regulated Na^+ gates along its entire length. When an action potential occurs at the trigger zone, Na^+ enters the axon and diffuses to adjacent regions just beneath the plasma membrane. The resulting depolarization excites voltage-regulated gates immediately distal to the action potential. Sodium and potassium gates open and close just as they did at the trigger zone, and a new action potential is produced. By repetition, this excites the membrane immediately distal to that. This chain reaction continues until the traveling signal reaches the end of the axon.

Note that an action potential itself does not travel along an axon; rather, it stimulates the production of a new action potential in the membrane just ahead of it. Thus, we can distinguish an *action potential* from a *nerve signal.* The nerve signal is a traveling wave of excitation produced by self-propagating action potentials. It is a little like a line of falling dominoes. No one domino travels to the end of the line, but each domino pushes over the next one and there is a transmission of energy from the first

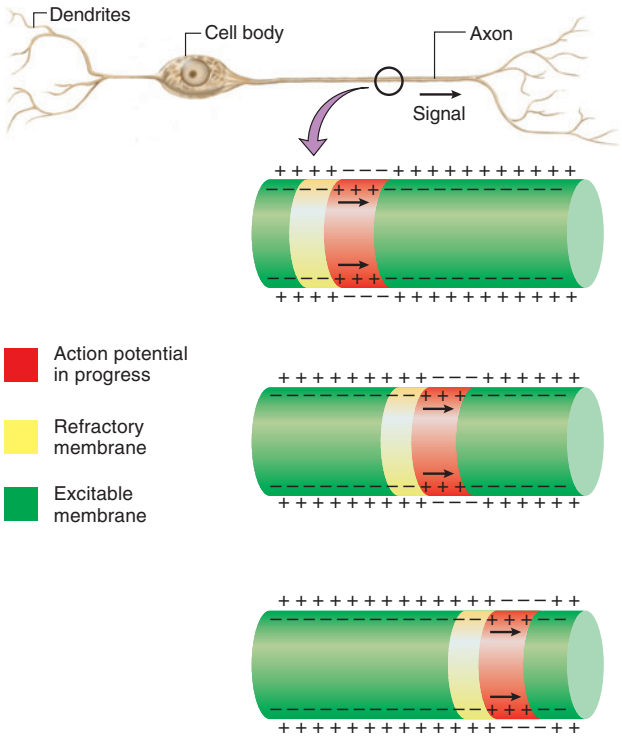


Figure 12.14 Conduction of a Nerve Signal in an Unmyelinated Fiber. Note that the membrane polarity is reversed in the region of the action potential (*red*). A region of membrane in its refractory period (*yellow*) trails the action potential and prevents the nerve signal from going backward toward the soma. The other membrane areas (*green*) are fully polarized and ready to respond.

domino to the last. Similarly, no one action potential travels to the end of an axon; a nerve signal is a chain reaction of action potentials.

If one action potential can stimulate the production of a new one next to it, you might think that the signal could also start traveling backward and return to the soma. This does not occur, however, because the membrane behind the nerve signal is still in its refractory period and cannot be restimulated. Only the membrane ahead is sensitive to stimulation. The refractory period thus ensures that nerve signals are conducted in the proper direction, from the soma to the synaptic knobs.

A traveling nerve signal is an electrical current, but it is not the same as a current traveling through a wire. A current in a wire travels millions of meters per second and is decremental—it gets weaker with distance. A nerve signal is much slower (not more than 2 m/sec in unmyelinated fibers), but it is *nondecremental.* Even in the longest axons, the last action potential generated in a synaptic knob has the same voltage as the first one generated in the trigger zone. To clarify this concept we can compare the nerve signal to a burning fuse. When a fuse is lit, the heat ignites powder immediately in front of this point, and this event repeats itself in a self-propagating fashion until the end of the fuse is reached. At the end, the fuse burns just as hotly as it did at the beginning. In a fuse, the combustible powder is the source of potential energy that keeps the process going in a nondecremental fashion. In an axon, the potential energy comes from the ion gradient across the plasma membrane. Thus, the signal does not grow weaker with distance; it is self-propagating, like the burning of a fuse.

Myelinated Fibers

Matters are somewhat different in myelinated fibers, because voltage-regulated ion gates are scarce in the myelin-covered internodes—fewer than 25 per μm^2 in these regions compared with 2,000 to 12,000 per μm^2 at the nodes of Ranvier. There would be little point in having ion gates in the internodes—myelin insulates the fiber from the ECF at these points, and sodium ions from the ECF could not flow into the cell even if more gates were present.

The only way a nerve signal can travel along an internode is for Na^+ that enters at the previous node to diffuse down the fiber under the axolemma (fig. 12.15*a*). This is a very fast process, but the nerve fiber resists their flow (just as a wire resists a current) and the signal becomes weaker the farther it goes. Therefore, this aspect of conduction is decremental. The signal cannot travel much farther than 1 mm before it becomes too weak to open any voltage-regulated gates. But fortunately, there is another node of Ranvier every millimeter or less along the axon, where the axolemma is exposed to ECF and there is an abundance of voltage-regulated gates. When the diffusing ions reach this point, the signal is just strong enough to open these gates and create a new action potential. This action potential has the same strength as the one at the previous node, so each node of Ranvier boosts the signal back to its original strength (+35 mV). This mode of signal conduction is called **saltatory**[25] **conduction**—the propagation of a nerve signal that seems to jump from node to node (fig. 12.15*b*).

In the internodes, saltatory conduction is therefore based on a process that is very fast (diffusion of ions along the fiber) but decremental. In the nodes, conduction is slower but nondecremental. Since most of the axon is covered with myelin, conduction occurs mainly by the fast longitudinal diffusion process. This is why myelinated fibers transmit signals much faster (up to 120 m/sec) than unmyelinated ones (up to 2 m/sec) and why the signal is just as strong at the end of the fiber as it was at the beginning.

[25]from *saltare* = to leap, to dance

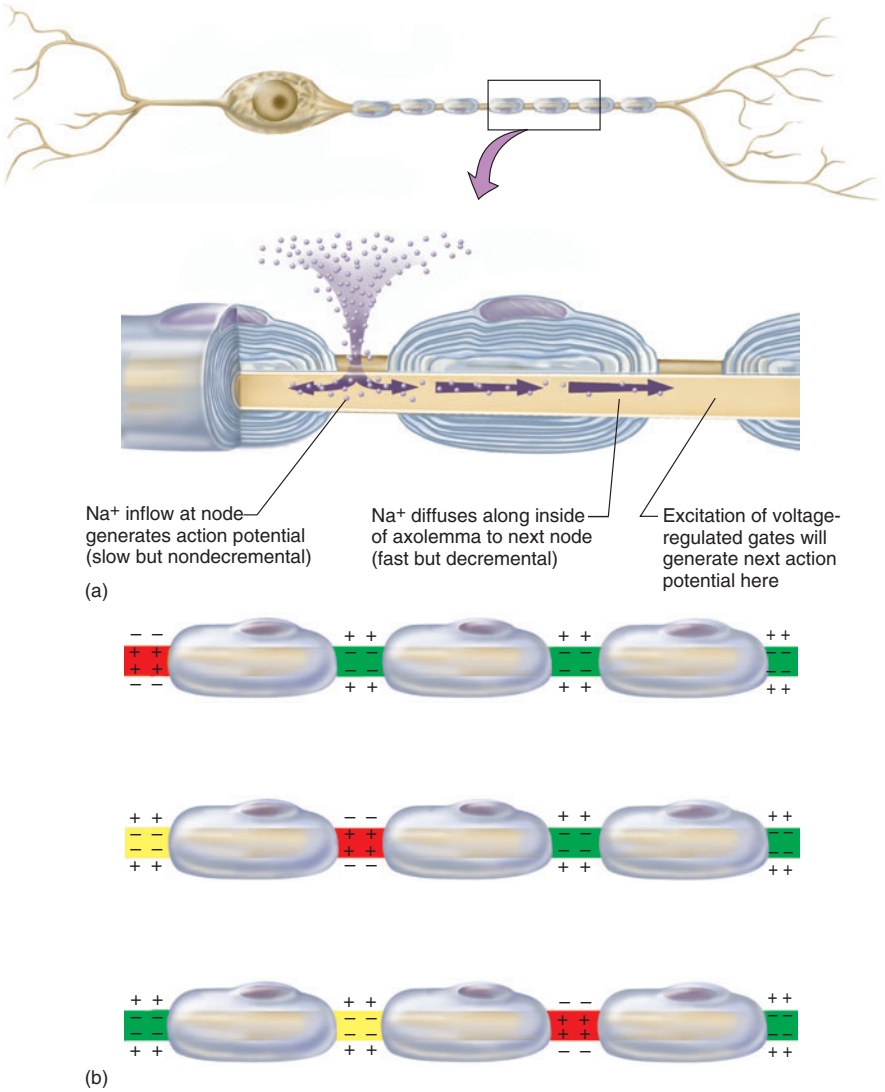


Figure 12.15 Saltatory Conduction of a Nerve Signal in a Myelinated Fiber. (*a*) Ions can be exchanged with the ECF only at the nodes of Ranvier. In the internodes, the nerve signal travels by the rapid diffusion of ions along the inside of the plasma membrane. (*b*) Action potentials (*red*) occur only at the nodes, and the nerve signal therefore appears to jump from node to node. *Yellow* areas indicate refractory (recovering) membrane.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

11. What causes K^+ to diffuse out of a resting cell? What attracts it into the cell?
12. What happens to Na^+ when a neuron is stimulated on its dendrite? Why does the movement of Na^+ raise the voltage on the plasma membrane?
13. What does it mean to say a local potential is graded, decremental, and reversible?
14. How does the plasma membrane at the trigger zone differ from that on the soma? How does it resemble the membrane at a node of Ranvier?
15. What makes an action potential rise to +35 mV? What makes it drop again after this peak?
16. List four ways in which an action potential is different from a local potential.
17. Explain why myelinated fibers transmit signals much faster than unmyelinated fibers.

Synapses

Objectives

When you have completed this section, you should be able to

- explain how messages are transmitted from one neuron to another;
- explain how stimulation of a postsynaptic cell is stopped; and
- give examples of neurotransmitters and describe their actions.

A nerve signal soon reaches the end of an axon and can go no farther. In most cases, it triggers the release of a neurotransmitter that stimulates a new wave of electrical activity in the next cell across the synapse. The most thoroughly studied type of synapse is the neuromuscular junction described in chapter 11, but here we consider synapses between two neurons. The first neuron in the signal path is the **presynaptic neuron,** which releases the neurotransmitter. The second is the **postsynaptic neuron,** which responds to it.

The presynaptic neuron may synapse with a dendrite, the soma, or the axon of a postsynaptic neuron and form an *axodendritic, axosomatic,* or *axoaxonic synapse,* respectively. A neuron can have an enormous number of synapses (fig. 12.16). For example, a spinal motor neuron is covered with about 10,000 synaptic knobs from other neurons—8,000 ending on its dendrites and another 2,000 on the soma. In part of the brain called the cerebellum, one neuron can have as many as 100,000 synapses.

The Discovery of Neurotransmitters

As the neuron doctrine became generally accepted, it raised the question of how neurons communicate with each other. In the early twentieth century, biologists assumed that synaptic communication was electrical—a logical hypothesis given that neurons seemed to touch each other and signals were transmitted so quickly from one to the next. Closer histological examination, however, revealed a 20- to 40-nm gap between neurons—the **synaptic cleft**—casting doubt on the possibility of electrical conduction.

In 1921, the German pharmacologist Otto Loewi (1873–1961) conclusively demonstrated that neurons communicate by releasing chemicals. The *vagus nerves* supply the heart, among other organs, and slow it down. Loewi opened two frogs and flooded the hearts with saline to keep them moist. He stimulated the vagus nerve of one frog, and its heart rate dropped as expected. He then removed some of the saline from that heart and squirted it onto the heart of the second frog. The solution alone reduced that frog's heart rate. Evidently it contained something released by the vagus nerve of the first frog. Loewi called it *Vagusstoffe* ("vagus substance") and it was later renamed acetylcholine—the first known neurotransmitter.

Think About It

As described, does the previous experiment conclusively prove that the second frog's heart slowed as a result of something released by the vagus nerves? If you were Loewi, what control experiment would you do to rule out alternative explanations?

Following Loewi's work, the idea of electrical communication between cells fell into disrepute. Now, however, we realize that some neurons, neuroglia, and cardiac and single-unit smooth muscle (see chapter 11) do indeed have **electrical synapses,** where adjacent cells are joined by gap junctions and ions can diffuse directly from one cell into the next. These junctions have the advantage of quick transmission because there is no delay for the release and binding of neurotransmitter. Their disadvantage, however, is that they cannot integrate information and make decisions. The ability to do that is a property of **chemical synapses,** in which neurons communicate by neurotransmitters.

Structure of a Chemical Synapse

The synaptic knob (fig. 12.17) was described in chapter 11. It contains synaptic vesicles, many of which are "docked" at release sites on the plasma membrane, ready to release their neurotransmitter on demand. A reserve pool of synaptic vesicles is located a little farther away from the membrane, clustered near the release sites and tethered to the cytoskeleton by protein microfilaments.

The postsynaptic neuron does not show such conspicuous specializations. At this end, the neuron has no synaptic vesicles and cannot release neurotransmitters. Its membrane does, however, contain proteins that function as receptors and ligand-regulated ion gates.

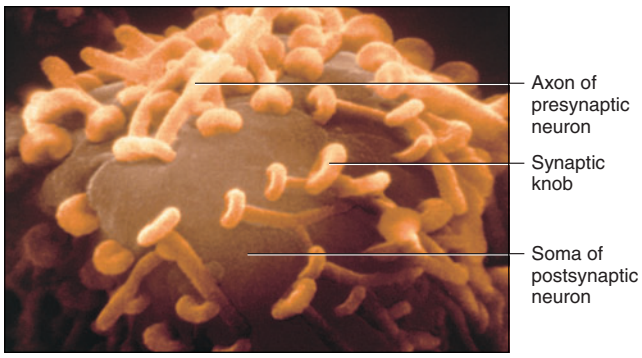


Figure 12.16 Synaptic Knobs on the Soma of a Neuron in a Marine Slug, *Aplysia* (SEM).
Are these synapses axodendritic, axosomatic, or axoaxonic?

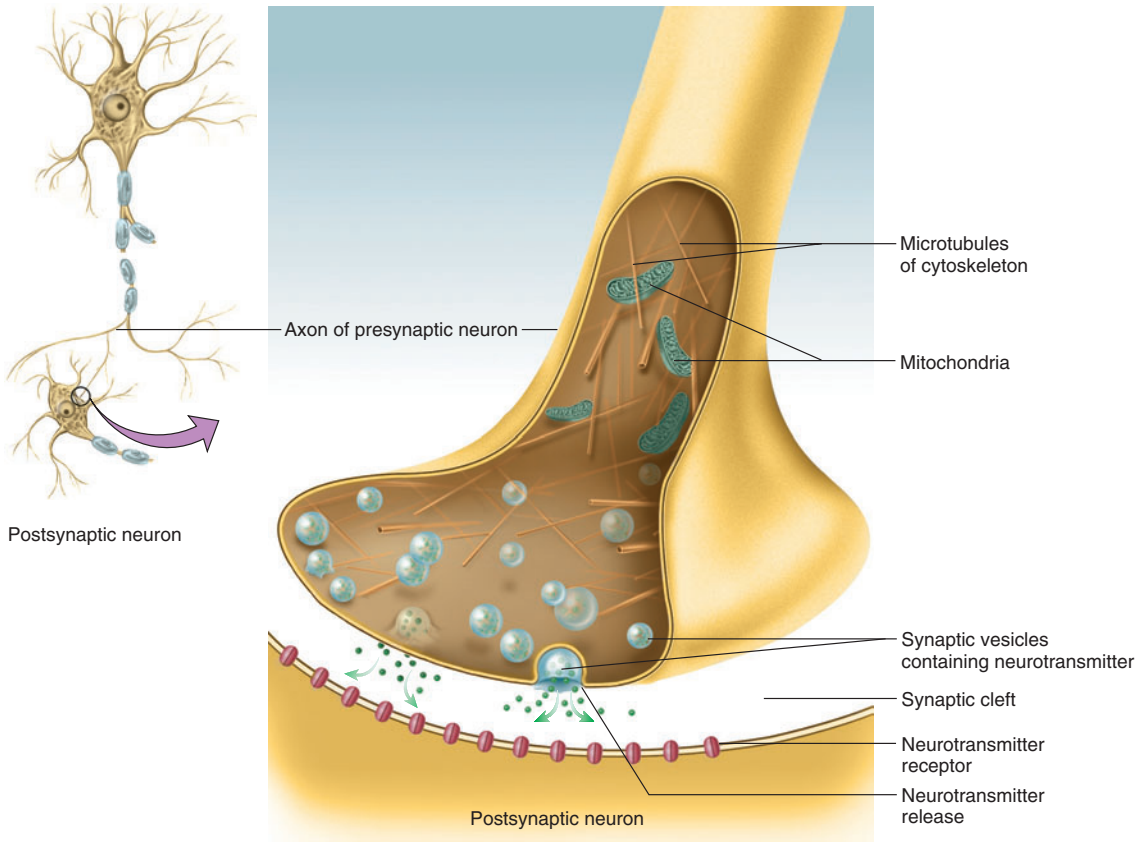


Figure 12.17 **Structure of a Chemical Synapse.**

Neurotransmitters and Related Messengers

More than 100 confirmed or suspected neurotransmitters have been identified since Loewi discovered acetylcholine. Neurotransmitters fall into three major categories according to chemical composition (fig. 12.18). Some of the best-known ones are listed in table 12.3. Parts of the brain referred to in this table will become familiar to you as you study chapter 14, and you may wish to refer back to this table then to enhance your understanding of brain function.

1. **Acetylcholine** is in a class by itself. It is formed from acetic acid (acetate) and choline.
2. **Monoamines (biogenic amines)** are synthesized from amino acids by removal of the −COOH group. They retain the $-NH_2$ (amino group), hence their name. The major monoamines are epinephrine, norepinephrine, dopamine, histamine, and serotonin (5-hydroxytryptamine, or 5-HT). The first three of these are in a subclass of monoamines called **catecholamines** (CAT-eh-COAL-uh-meens).
3. **Amino acid** neurotransmitters include glycine, glutamate, aspartate, and γ-aminobutyric acid (GABA).
4. **Neuropeptides** are chains of 2 to 40 amino acids. Some examples are β-endorphin and substance P. Neuropeptides typically act at lower concentrations and have longer lasting effects than other neurotransmitters, and they are stored in *secretory granules (dense-core vesicles)* that are about 100 nm in diameter, twice as large as typical synaptic vesicles. Some neuropeptides also function as hormones or as **neuromodulators,** whose action is discussed later in this chapter. Some neuropeptides are produced not only by neurons but also by the digestive tract; thus they are known as *gut-brain peptides.* Some of these cause cravings for specific nutrients such as fat or sugar and may be associated with certain eating disorders.

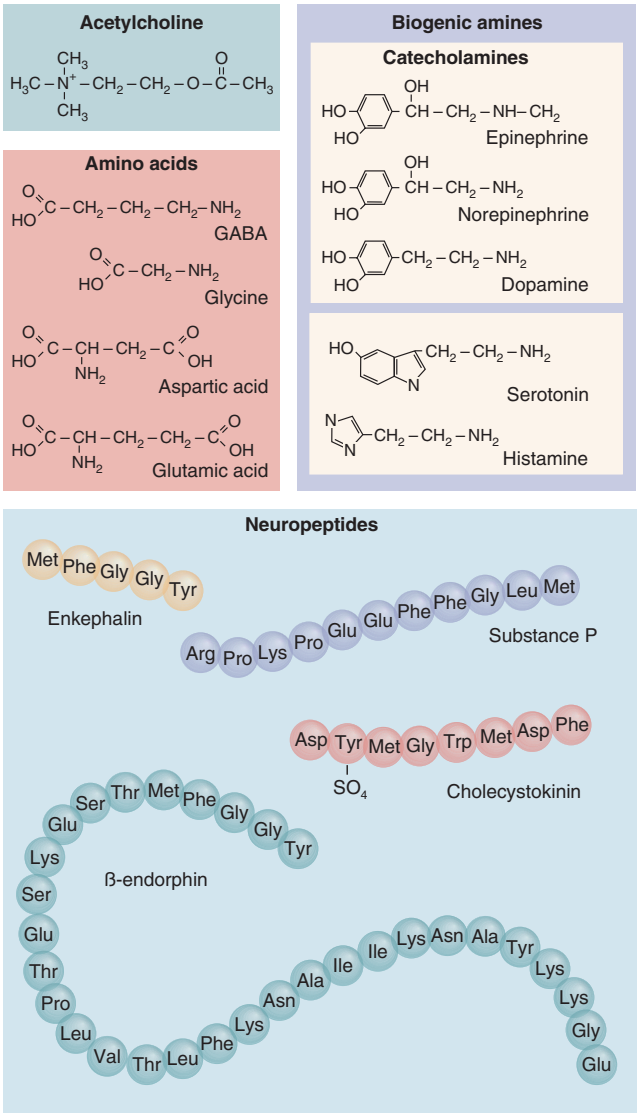


Figure 12.18 **Classification of Some Neurotransmitters.**

Think About It

Neuropeptides can be synthesized only in the soma and must be transported to the synaptic knobs. Why is their synthesis limited to the soma?

The more we learn about neurotransmitters, hormones, and other chemical messengers, the harder it is to distinguish them from each other or even to rigorously define "neurotransmitter." Traditionally, neurotransmitters have been conceived as small organic compounds that function at the synapse as follows: (1) they are synthesized by the presynaptic neuron, (2) they are released in response to stimulation, (3) they bind to specific receptors on the postsynaptic cell, and (4) they alter the physiology of that cell. Neuropeptides are an exception to the small size of neurotransmitters, and neurons have additional means of communication, such as the gas nitric oxide, that fall outside the scope of this traditional concept.

We will see, especially in chapter 15, that a given neurotransmitter does not have the same effect everywhere in the body. There are multiple receptor types in the body for a particular neurotransmitter—over 14 receptor types for serotonin, for example—and it is the receptor that governs what effect a neurotransmitter has on its target cell.

Synaptic Transmission

Neurotransmitters are quite diverse in their action. Some are excitatory, some are inhibitory, and for some the effect depends on what kind of receptor the postsynaptic cell has. Some neurotransmitters open ligand-regulated ion gates while others act through second-messenger systems. Bearing this diversity in mind, we will here examine three kinds of synapses with different modes of action: an *excitatory cholinergic synapse,* an *inhibitory GABA-ergic synapse,* and an *excitatory adrenergic synapse.*

An Excitatory Cholinergic Synapse

A **cholinergic**[26] (CO-lin-UR-jic) synapse employs acetylcholine (ACh) as its neurotransmitter. ACh excites some postsynaptic cells (such as skeletal muscle; chapter 11) and inhibits others, but here we will consider an excitatory action. The steps in transmission at such a synapse are as follows (fig. 12.19):

1. The arrival of a nerve signal at the synaptic knob opens voltage-regulated calcium gates.
2. Ca^{2+} enters the synaptic knob and triggers exocytosis of the synaptic vesicles, releasing ACh.
3. Empty vesicles drop back into the cytoplasm to be refilled with ACh, while synaptic vesicles in the reserve pool move forward to the active sites and release their ACh—a bit like a line of Revolutionary War soldiers firing their muskets and falling back to reload as another line moves to the fore.
4. Meanwhile, ACh diffuses across the synaptic cleft and binds to ligand-regulated gates on the postsynaptic neuron. These gates open, allowing Na^+ to enter the cell and K^+ to leave. Although illustrated separately, Na^+ and K^+ pass in opposite directions through the same gates.

[26] *cholin* = acetylcholine + *erg* = work, action

Table 12.3 Neurotransmitters and Neuropeptides

Name	Locations and Actions
Acetylcholine (Ach)	Neuromuscular junctions, most synapses of autonomic nervous system, retina, and many parts of the brain; excites skeletal muscles, inhibits cardiac muscle, and has excitatory or inhibitory effects on smooth muscle and glands depending on location
Excitatory Amino Acids	
Glutamate (glutamic acid)	Cerebral cortex and brainstem; retina; accounts for about 75% of all excitatory synaptic transmission in the brain; involved in learning and memory
Aspartate (aspartic acid)	Spinal cord; effects similar to those of glutamate
Inhibitory Amino Acids	
Glycine	Inhibitory neurons of the brain, spinal cord, and retina; most common inhibitory neurotransmitter in the spinal cord
GABA (γ-aminobutyric acid)	Thalamus, hypothalamus, cerebellum, occipital lobes of cerebrum, and retina; most common inhibitory neurotransmitter in the brain
Monoamines (biogenic amines)	
Catecholamines	
Norepinephrine	Sympathetic nervous system, cerebral cortex, hypothalamus, brainstem, cerebellum, and spinal cord; involved in dreaming, waking, and mood; excites cardiac muscle; can excite or inhibit smooth muscle and glands depending on location
Epinephrine	Hypothalamus, thalamus, spinal cord, and adrenal medulla; effects similar to those of norepinephrine
Dopamine	Hypothalamus, limbic system, cerebral cortex, and retina; highly concentrated in substantia nigra of midbrain; involved in elevation of mood and control of skeletal muscles
Other Monoamines	
Serotonin	Hypothalamus, limbic system, cerebellum, retina, and spinal cord; also secreted by blood platelets and intestinal cells; involved in sleepiness, alertness, thermoregulation, and mood
Histamine	Hypothalamus; also a potent vasodilator released by mast cells of connective tissue
Neuropeptides	
Substance P	Basal nuclei, midbrain, hypothalamus, cerebral cortex, small intestine, and pain-receptor neurons; mediates pain transmission
Enkephalins	Hypothalamus, limbic system, pituitary, pain pathways of spinal cord, and nerve endings of digestive tract; act as analgesics (pain-relievers) by inhibiting substance P; inhibit intestinal motility; secretion increases sharply in women in labor
β-endorphin	Digestive tract, spinal cord, and many parts of the brain; also secreted as a hormone by the pituitary; suppresses pain; reduces perception of fatigue and produces "runner's high" in athletes
Cholecystokinin (CCK)	Cerebral cortex and small intestine; suppresses appetite

5. As Na^+ enters the cell, it spreads out along the inside of the plasma membrane and depolarizes it, producing a local potential called the **postsynaptic potential.** Like other local potentials, if this is strong and persistent enough (that is, if enough Na^+ makes it to the axon hillock), it opens voltage-regulated ion gates in the trigger zone and causes the postsynaptic neuron to fire.

An Inhibitory GABA-ergic Synapse

A **GABA-ergic** synapse employs γ-aminobutyric acid (GABA) as its neurotransmitter. Amino acid neurotransmitters work by the same mechanism as ACh—binding to ion gates and causing immediate changes in membrane potential. The release of GABA and binding to its receptor are similar to the preceding case. The GABA receptor, however, is a chloride channel. It responds by opening

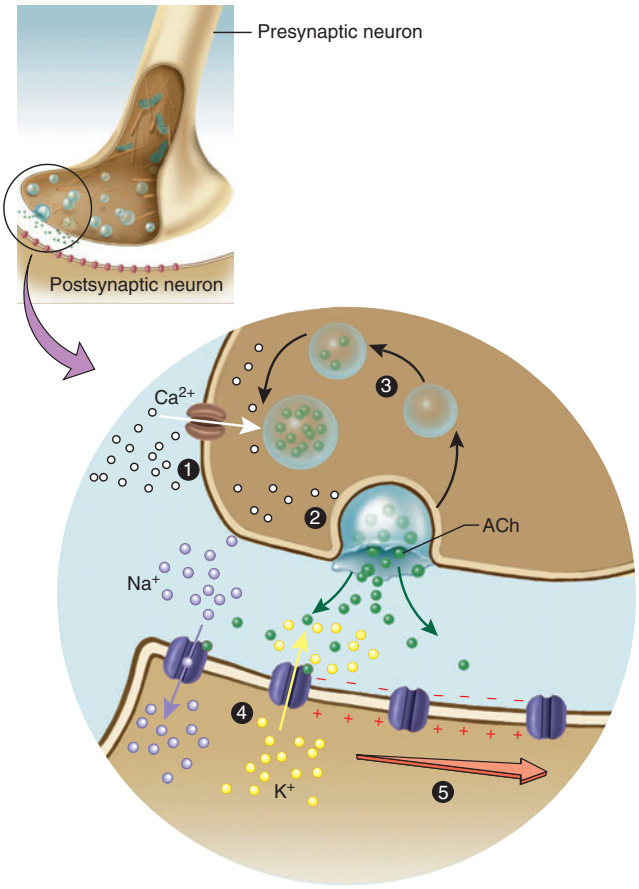


Figure 12.19 Transmission at a Cholinergic Synapse. Acetylcholine directly opens ion gates in the plasma membrane of the postsynaptic neuron. Numbered steps correspond to the description in the text.

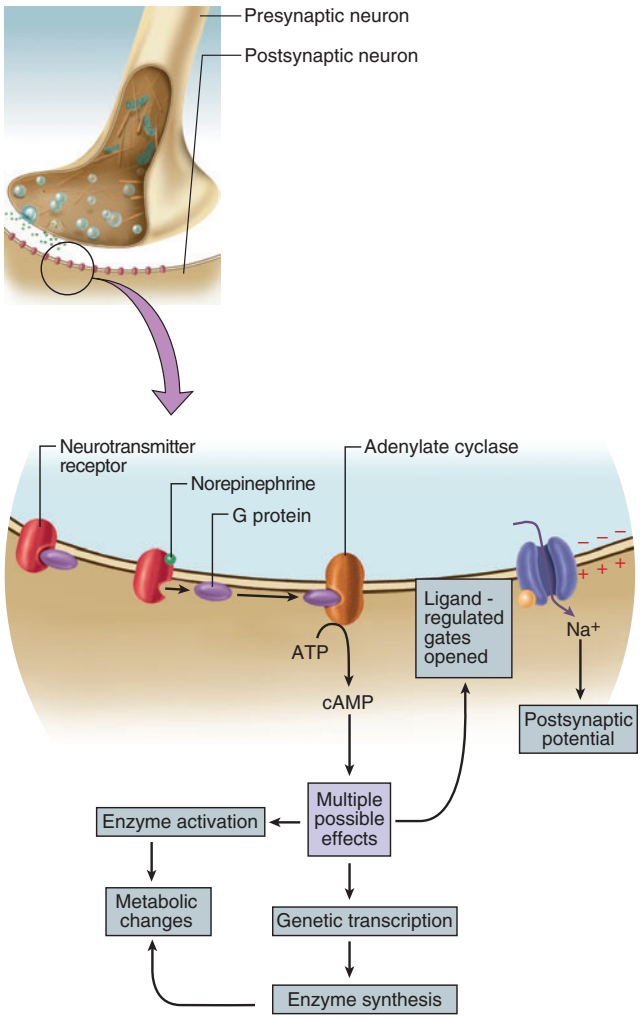


Figure 12.20 Transmission at an Adrenergic Synapse. The norepinephrine receptor is not an ion channel. It activates a second-messenger system with a variety of possible effects in the postsynaptic cell.

and admitting Cl^- to the cell, making the inside of the cell even more negative than the resting membrane potential, and thus making the neuron less likely to fire.

An Excitatory Adrenergic Synapse

An **adrenergic synapse** employs the neurotransmitter norepinephrine (NE), also called noradrenaline. NE, other monoamines, and neuropeptides act through second-messenger systems such as cyclic AMP (cAMP). The receptor is not an ion gate but an integral protein associated with a G protein. The binding of NE activates the G protein, which activates adenylate cyclase, which converts ATP to cAMP (fig. 12.20). The cAMP can have multiple effects such as stimulating the synthesis of new enzymes, activating preexisting enzymes, or opening ligand-regulated gates and producing a postsynaptic potential.

As complex as synaptic events may seem, they typically require only 0.5 msec or so—an interval called **synaptic delay.** This is the time from the arrival of a signal at the axon terminal of a presynaptic cell to the beginning of an action potential in the postsynaptic cell.

Cessation of the Signal

It is important not only to stimulate a postsynaptic cell but also to turn off the stimulus in due time. Here we examine some ways this is done.

A neurotransmitter molecule binds to its receptor for only 1 msec or so, then dissociates from it. If the presynaptic

cell continues to release neurotransmitter, one molecule is quickly replaced by another and the postsynaptic cell is restimulated. This immediately suggests a way of stopping synaptic transmission—stop adding new neurotransmitter and get rid of that which is already there. The first step is achieved simply by the cessation of signals in the presynaptic nerve fiber. The second can be achieved in the following ways:

- **Diffusion.** Neurotransmitter diffuses away from the synapse into the nearby ECF, where astrocytes may absorb it and return it to the neurons.
- **Reuptake.** The synaptic knob reabsorbs amino acids and monoamines by endocytosis and then breaks them down with an enzyme called **monoamine oxidase (MAO).** Some antidepressant drugs work by inhibiting MAO (see insight 15.2 at the end of chapter 15).
- **Degradation in the synaptic cleft.** The enzyme acetylcholinesterase (AChE), located within the synaptic cleft and on the postsynaptic membrane, breaks acetylcholine down into acetate and choline. These breakdown products have no stimulatory effect on the postsynaptic cell. The synaptic knob reabsorbs the choline and uses it to synthesize more ACh.

Neuromodulators

Neuromodulators are hormones, neuropeptides, and other messengers that modify synaptic transmission. They may stimulate a neuron to raise or lower the number of receptors in the postsynaptic membrane, thus adjusting its sensitivity to a neurotransmitter, or they may alter the rate of neurotransmitter synthesis, release, reuptake, or breakdown. One example—a rather recent and surprising discovery—is nitric oxide (NO), a lightweight gas that is released by postsynaptic neurons in some areas of the brain concerned with learning and memory. NO diffuses into the presynaptic neuron and stimulates it to release more neurotransmitter—like one neuron's way of telling the other, "Give me more." Thus, there is at least some chemical communication that goes backward across a synapse.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

18. Concisely describe five steps that occur between the arrival of an action potential at the synaptic knob and the beginning of a new action potential in the postsynaptic neuron.
19. Contrast the actions of acetylcholine, GABA, and norepinephrine at their respective synapses.
20. Describe three mechanisms that stop synaptic transmission.
21. What is the function of neuromodulators?

Neural Integration

Objectives

When you have completed this section, you should be able to

- explain how a neuron "decides" whether or not to produce action potentials;
- explain how the nervous system translates complex information into a simple code;
- explain how neurons work together in groups to process information and produce effective output; and
- describe how memory works at a cellular and molecular level.

Synaptic delay slows the transmission of nerve signals; the more synapses there are in a neural pathway, the longer it takes information to get from its origin to its destination. You might wonder, therefore, why we have synapses—why a nervous pathway is not, indeed, a continuous "wire" as biologists believed before the neuron doctrine was accepted. The presence of synapses is not due to limitations on the length of a neuron—after all, one nerve fiber can reach from your toes to your brainstem; imagine how long some nerve fibers may be in a giraffe or a whale! We also have seen that cells can communicate through gap junctions much more quickly than they can through chemical synapses. So why have chemical synapses at all?

What we value most about our nervous system is its ability to process information, store it, and make decisions—and chemical synapses are the decision-making devices of the system. The more synapses a neuron has, the greater its information-processing capability. At this moment, you are using certain *pyramidal cells* of the cerebral cortex (see fig. 12.5) to read and comprehend this passage. Each pyramidal cell has about 40,000 synaptic contacts with other neurons. The cerebral cortex alone (the main information-processing tissue of your brain) is estimated to have 100 trillion (10^{14}) synapses. To get some impression of this number, imagine trying to count them. Even if you could count two synapses per second, day and night without stopping, and you were immortal, it would take you 1.6 million years. The ability of your neurons to process information, store and recall it, and make decisions is called **neural integration.**

Postsynaptic Potentials

Neural integration is based on the postsynaptic potentials produced by neurotransmitters. Remember that a typical neuron has a resting membrane potential (RMP) of about −70 mV and a threshold of about −55 mV. A neuron has to be depolarized to this threshold in order to produce action potentials. Any voltage change in that direction makes a neuron more likely to fire and is therefore called an **excitatory postsynaptic potential (EPSP)** (fig. 12.21*a*). EPSPs usually result from Na^+ flowing into the cell and

canceling some of the negative charge on the inside of the membrane.

In other cases, a neurotransmitter hyperpolarizes the postsynaptic cell and makes it more negative than the RMP. Since this makes the postsynaptic cell less likely to fire, it is called an **inhibitory postsynaptic potential (IPSP)** (fig. 12.21*b*). Some IPSPs are produced by a neurotransmitter opening ligand-regulated chloride gates, causing Cl^- to flow into the cell and make the cytosol more negative. A less common way is to open selective K^+ gates, increasing the diffusion of K^+ out of the cell.

It should be stressed that because of ion leakage through their membranes, all neurons fire at a certain background rate even when they are not being stimulated. EPSPs and IPSPs do not determine whether or not a neuron fires, but only change the rate of firing by stimulating or inhibiting the production of more action potentials.

Glutamate and aspartate are excitatory neurotransmitters that produce EPSPs. Glycine and GABA produce IPSPs and are therefore inhibitory. Acetylcholine (ACh) and norepinephrine are excitatory to some cells and inhibitory to others, depending on the type of receptors present on the target cells. For example, ACh excites skeletal muscle but inhibits cardiac muscle because the two types of muscle have different types of ACh receptors. This is discussed more fully in chapter 15.

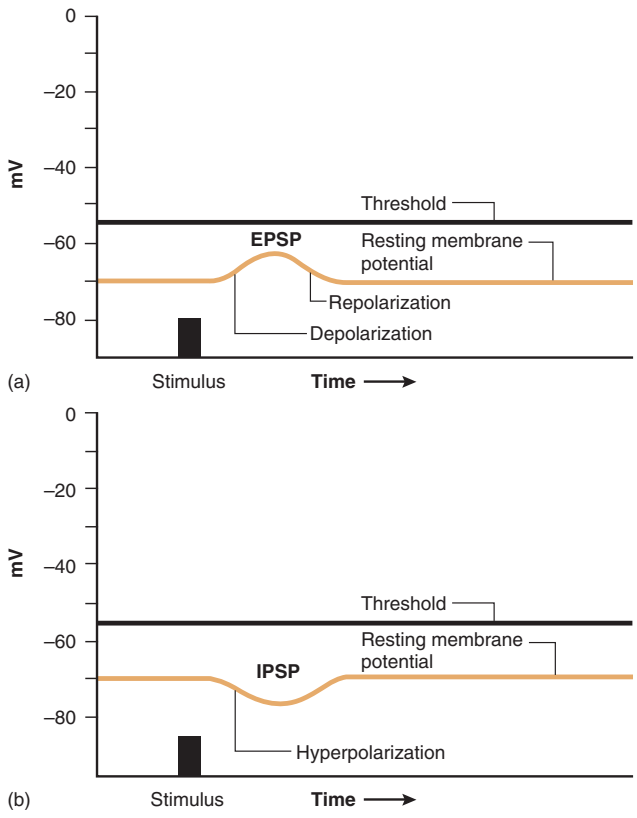


Figure 12.21 Postsynaptic Potentials. (*a*) An excitatory postsynaptic potential (EPSP). (*b*) An inhibitory postsynaptic potential (IPSP). The sizes of these postsynaptic potentials are greatly exaggerated here for clarity; compare figure 12.23.

Why is a single EPSP insufficient to make a neuron fire?

Summation, Facilitation, and Inhibition

A neuron may receive input from thousands of presynaptic neurons simultaneously. Some incoming nerve fibers may produce EPSPs while others produce IPSPs. Whether or not the neuron fires depends on whether the *net* input is excitatory or inhibitory. If the EPSPs override the IPSPs, threshold may be reached and the neuron will fire; if the IPSPs prevail, the neuron will not fire. **Summation** is the process of adding up postsynaptic potentials and responding to their net effect. It occurs in the trigger zone.

Suppose, for example, you are working in the kitchen and accidentally touch a hot cooking pot. EPSPs in your motor neurons might cause you to jerk your hand back quickly and avoid being burned. Yet a moment later, you might nonchalantly pick up a cup of tea that is even hotter than the pot. Since you are expecting the teacup to be hot, you do not jerk your hand away. You have learned that it will not injure you, so at some level of the nervous system, IPSPs prevail and inhibit the motor response.

It is fundamentally a balance between EPSPs and IPSPs that enables the nervous system to make decisions. A postsynaptic neuron is like a little cellular democracy acting on the "majority vote" of hundreds of presynaptic cells. In the teacup example, some presynaptic neurons are sending messages that signify "hot! danger!" in the form of EPSPs that may activate a hand-withdrawal reflex, while at the same time, others are producing IPSPs that signify "safe" and suppress the withdrawal reflex. Whether the postsynaptic neurons cause you to jerk your hand back depends on whether the EPSPs override the IPSPs or vice versa.

One action potential in a synaptic knob does not produce enough activity to make a postsynaptic cell fire. An EPSP may be produced, but it decays before reaching threshold. A typical EPSP has a voltage of 0.5 mV and lasts only 15 to 20 msec. If a neuron has an RMP of −70 mV and a threshold of −55 mV, it needs about 30 EPSPs to reach threshold and fire. There are two ways in which EPSPs can add up to do this, and both may occur simultaneously.

1. **Temporal summation** (fig. 12.22*a*). This occurs when a single synapse generates EPSPs at such short time intervals that each is generated before the previous one decays. This allows the EPSPs to add up over time to a threshold voltage that triggers an action potential (fig. 12.23). Temporal summation

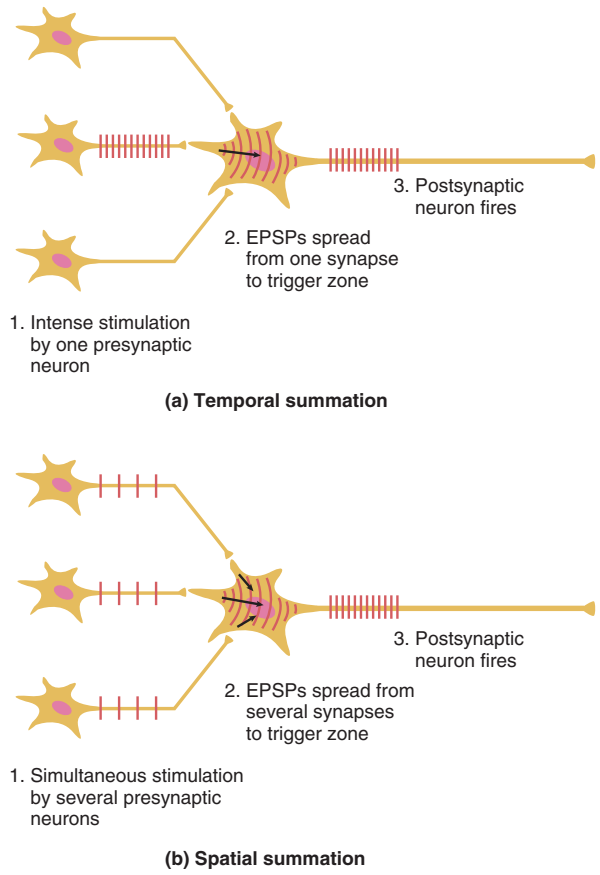


Figure 12.22 Temporal and Spatial Summation. (*a*) In temporal summation, a single presynaptic neuron stimulates the postsynaptic neuron so intensely that its EPSPs add up to threshold and make it fire. (*b*) In spatial summation, multiple inputs to the postsynaptic cell each produce a moderate amount of stimulation, but collectively they produce enough EPSPs to add up to threshold at the trigger zone and make the cell fire.

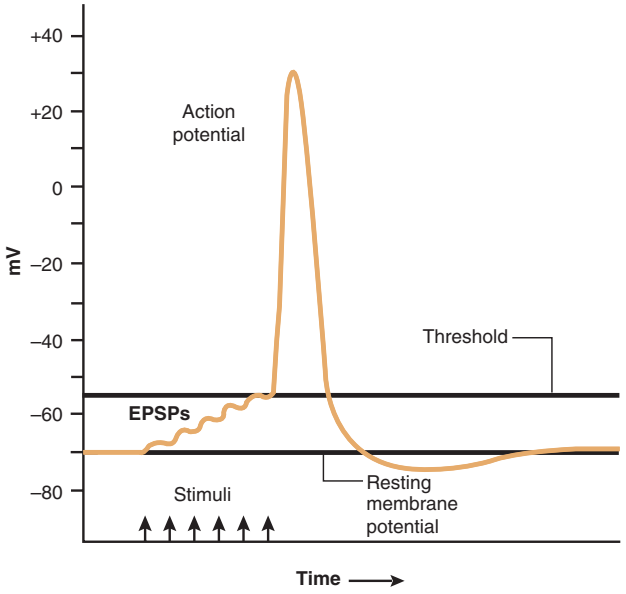


Figure 12.23 Summation of EPSPs. If enough EPSPs arrive at the trigger zone faster than they decay, they can build on each other to bring the neuron to threshold and trigger an action potential.

can occur if even one presynaptic neuron intensely stimulates the postsynaptic neuron.

2. **Spatial summation** (fig. 12.22*b*). This occurs when EPSPs from several different synapses add up to threshold at the axon hillock. Any one synapse may admit only a moderate amount of Na^+ into the cell, but several synapses acting together admit enough Na^+ to reach a threshold. The presynaptic neurons cooperate to induce the postsynaptic neuron to fire.

Facilitation is a process in which one neuron enhances the effect of another one. In spatial summation, for example, one neuron acting alone may be unable to induce a postsynaptic neuron to fire. But when they cooperate, their combined "effort" does induce firing in the postsynaptic cell. They each enhance one another's effect, or *facilitate* each other.

Presynaptic inhibition is the opposite of facilitation, a mechanism in which one presynaptic neuron suppresses another one. This mechanism is used to reduce or halt unwanted synaptic transmission. In figure 12.24, we see three neurons which we will call neuron *S* for the stimulator, neuron *I* for the inhibitor, and neuron *R* for the responder. Neuron I forms an axoaxonic synapse with S (that is, I synapses with the axon of S). When presynaptic inhibition is not occurring, neuron S releases its neurotransmitter and triggers a response in R. But when there is a need to block transmission across this pathway, neuron I releases the inhibitory neurotransmitter GABA. GABA prevents the voltage-regulated calcium gates of neuron S from opening. Consequently, neuron S releases less neurotransmitter or none, and fails to stimulate neuron R.

Neural Coding

The nervous system must interpret and pass along both quantitative and qualitative information about its environment—whether a light is dim or bright, red or green; whether a taste is mild or intense, salty or sour; whether a sound is loud or soft, high-pitched or low. Considering the complexity of information to be communicated about conditions in and around the body, it is a marvel that it can be done in the form of something as simple as action potentials—particularly since all the action potentials of a given neuron are identical. Yet when we considered the genetic code in chapter 4, we saw that complex messages can indeed be expressed in simple

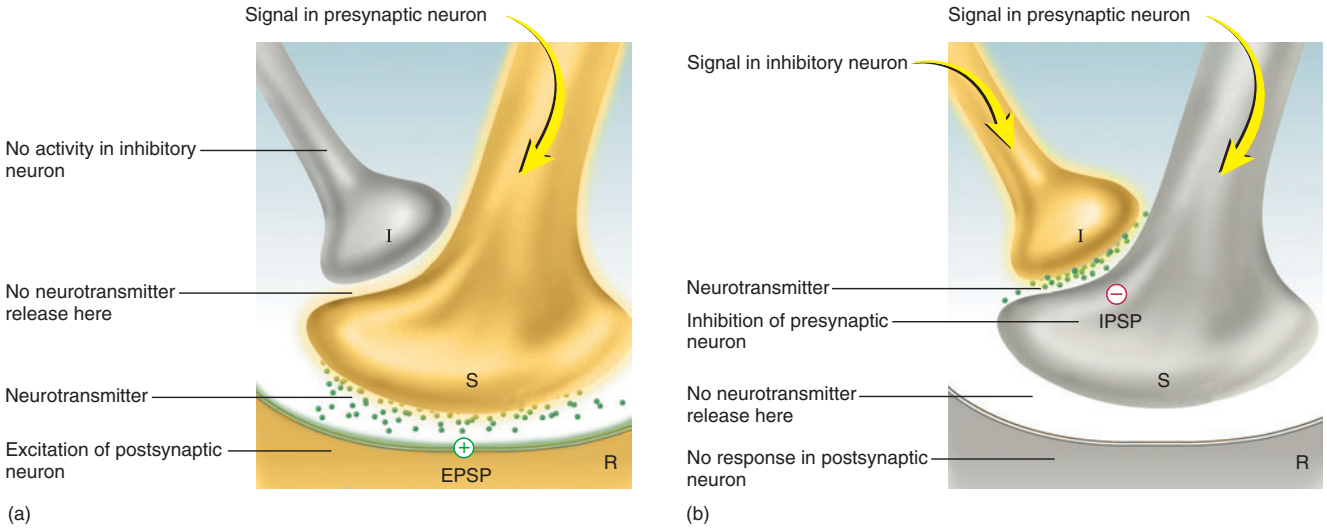


Figure 12.24 Presynaptic Inhibition. (*a*) In the absence of inhibition, neuron *S* releases neurotransmitter and stimulates neuron *R*. (*b*) In presynaptic inhibition, neuron *I* suppresses the release of neurotransmitter by *S*, and *S* cannot stimulate *R*.

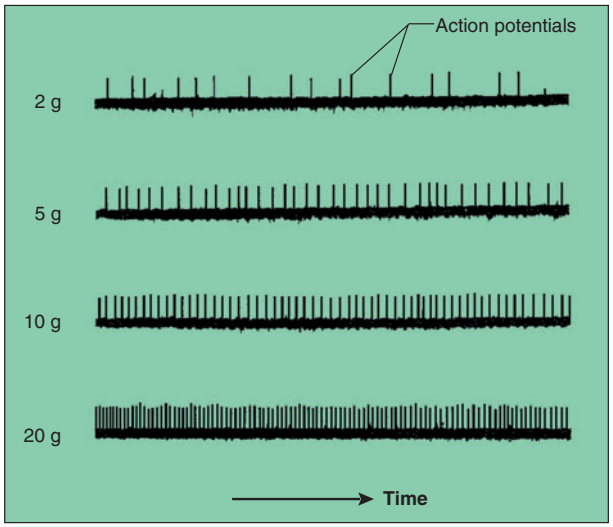


Figure 12.25 An Example of Neural Coding. This figure is based on recordings made from a sensory fiber of the frog sciatic nerve as the gastrocnemius muscle was stretched by suspending weights from it. As the stimulus strength (weight) and stretch increase, the firing frequency of the neuron increases. Firing frequency is a coded message that informs the CNS of stimulus intensity.
In what other way is the CNS informed of stimulus intensity?

codes. The way in which the nervous system converts information to a meaningful pattern of action potentials is called **neural coding** (or *sensory coding* when it occurs in the sense organs).

Qualitative information is encoded in terms of which neurons are firing. Red light and green light, for example, excite different fibers in the optic nerve; a high-pitched sound and a low-pitched sound excite different fibers in the auditory nerve; a sweet substance and a sour one excite different taste cells. The brain interprets input from different fibers in terms of these stimulus qualities.

Quantitative information—information about the intensity of a stimulus—is encoded in two ways. One depends on the fact that different neurons have different thresholds of excitation. A weak stimulus excites neurons with the lowest thresholds, while a strong stimulus excites less sensitive high-threshold neurons. Bringing additional neurons into play as the stimulus becomes stronger is called **recruitment.** It enables the nervous system to judge stimulus strength by which neurons, and how many of them, are firing.

Another way of encoding stimulus strength depends on the fact that the more strongly a neuron is stimulated, the more frequently it fires. A weak stimulus may cause a neuron to generate 6 action potentials per second, and a strong stimulus, 600 per second. Thus, the central nervous system can judge stimulus strength from the firing frequency of afferent neurons (fig. 12.25).

There is a limit to how often a neuron can fire, set by its absolute refractory period. Think of an electronic camera flash by analogy. If you take a photograph and your flash unit takes 15 seconds to recharge, then you cannot take more than four photographs per minute. Similarly, if a nerve fiber takes 1 msec to repolarize after it has fired, then it cannot fire more than 1,000 times per second. Refractory periods may be as short as 0.5 msec, which sets a theoretical limit to firing frequency of 2,000 action potentials per second. The highest frequencies actually observed, however, are between 500 and 1,000 per second.

Think About it

How is neuronal recruitment related to the process of multiple motor unit summation described in chapter 11?

Neuronal Pools and Circuits

So far, we have dealt with interactions involving only two or three neurons at a time. Actually, neurons function in larger ensembles called **neuronal pools,** each of which consists of thousands to millions of interneurons concerned with a particular body function—one to control the rhythm of your breathing, one to move your limbs rhythmically as you walk, one to regulate your sense of hunger, and another to interpret smells, for example. At this point, we explore a few ways in which neuronal pools collectively process information.

Information arrives at a neuronal pool through one or more input neurons, which branch repeatedly and synapse with numerous interneurons in the pool. Some input neurons form multiple synapses with a single postsynaptic cell. They can produce EPSPs at all points of contact with that cell and, through spatial summation, make it fire more easily than if they synapsed with it at only one point. Within the **discharge zone** of an input neuron, an input neuron acting alone can make the postsynaptic cells fire (fig. 12.26). But in a broader **facilitated zone,** it synapses with still other neurons in the pool, with fewer synapses on each of them. It can stimulate those neurons to fire only with the assistance of other input neurons; that is, it facilitates the other input neurons. Along with other inputs, it "has a vote" on what the postsynaptic cells in the facilitated zone will do, but it cannot alone determine what they do. Such arrangements, repeated thousands of times throughout the central nervous system, give neuronal pools great flexibility in integrating input from several sources and "deciding" on an appropriate output.

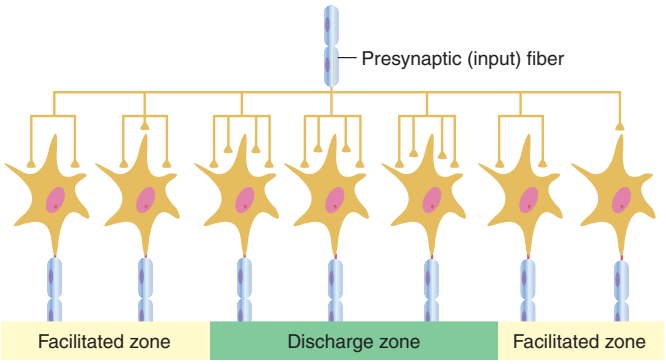


Figure 12.26 Facilitated and Discharge Zones in a Neuronal Pool. In a facilitated zone, the input neuron has few synaptic contacts with each output neuron. The input neuron makes it easier for those neurons to respond to stimulation from other sources, but it cannot, by itself, make them fire. In the discharge zone, the input neuron has extensive connections with each output neuron and is capable, by itself, of making the output neurons fire.

The functioning of a radio can be understood from a circuit diagram showing its components and their connections. Similarly, the functions of a neuronal pool are partly determined by its **neuronal circuit**—the pathways among its neurons. Just as a wide variety of electronic devices are constructed from a relatively limited number of circuit types, a wide variety of neuronal functions result from the operation of four principal kinds of neuronal circuits (fig. 12.27):

1. In a **diverging circuit,** one nerve fiber branches and synapses with several postsynaptic cells. Each of those may synapse with several more, so input from just one neuron may produce output through dozens of neurons. Such a circuit allows one motor neuron of the brain, for example, to ultimately stimulate thousands of muscle fibers.
2. A **converging circuit** is the opposite of a diverging circuit—input from many different nerve fibers is funneled to one neuron or neuronal pool. Such an arrangement allows input from your eyes, inner ears, and stretch receptors in your neck to be channeled to an area of the brain concerned with the sense of balance. Also through neuronal convergence, a respiratory center in your brainstem receives input from other parts of your brain, from receptors for blood chemistry in your arteries, and from stretch receptors in your lungs. The respiratory center can then produce an output that takes all of these factors into account and sets an appropriate pattern of breathing.
3. In a **reverberating circuit,** neurons stimulate each other in a linear sequence such as A → B → C → D, but neuron *C* sends an axon collateral back to *A.* As a result, every time *C* fires it not only stimulates output neuron *D,* but also restimulates *A* and starts the process over. Such a circuit produces a prolonged or repetitive effect that lasts until one or more neurons in the circuit fail to fire, or until an inhibitory signal from another source stops one of them from firing. A reverberating circuit sends repetitious signals to your diaphragm and intercostal muscles, for example, to make you inhale. When the circuit stops firing, you exhale, the next time it fires, you inhale again. Reverberating circuits may also be involved in short-term memory, as discussed in the next section, and they may play a role in the uncontrolled "storms" of neuronal activity that occur in epilepsy.
4. In a **parallel after-discharge circuit,** an input neuron diverges to stimulate several chains of

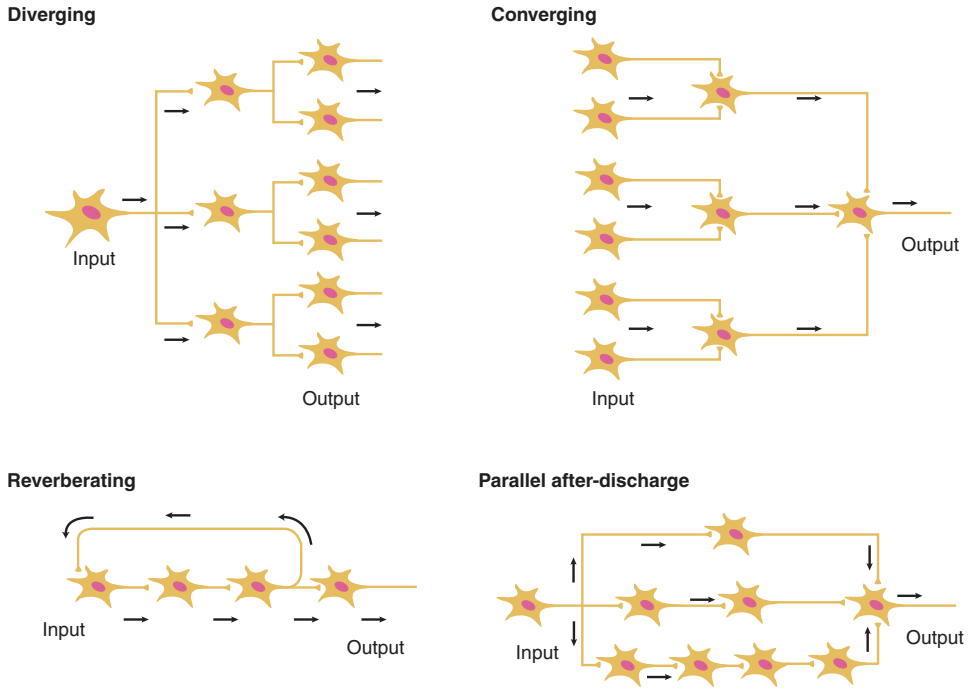


Figure 12.27 Four Types of Neuronal Circuits. *Arrows* indicate the direction of the nerve signal.
Which of these four circuits is likely to fire the longest after a stimulus ceases? Why?

neurons. Each chain has a different number of synapses, but eventually they all reconverge on a single output neuron. Since each pathway differs in total synaptic delay, their signals arrive at the output neuron at different times, and the output neuron may go on firing for some time after input has ceased. Unlike a reverberating circuit, this type has no feedback loop. Once all the neurons in the circuit have fired, the output ceases. Continued firing after the stimulus stops is called *after-discharge.* It explains why you can stare at a lamp, then close your eyes and continue to see an image of it for a while. Such a circuit is also important to withdrawal reflexes, in which a brief pain produces a longer-lasting output to the limb muscles and causes you to draw back your hand or foot from danger.

Memory and Synaptic Plasticity

You may have wondered as you studied this chapter, How am I going to remember all of this? It seems fitting that we end this chapter with the subject of how memory works, for you now have the information necessary to understand its cellular and chemical basis.

The things we learn and remember are not stored in individual "memory cells" in the brain. We do not have a neuron assigned to remember our phone number and another assigned to remember our mother's birthday, for example. Instead, the physical basis of a memory is a *pathway* through the brain called a **memory trace (engram[27]),** in which new synapses have formed or existing synapses have been modified to make transmission easier. In other words, synapses are not fixed for life; in response to experience, they can be added, taken away, or modified to make transmission easier or harder. This ability of synapses to change is called **synaptic plasticity.**

Think about when you learned as a child to tie your shoes. The procedure was very slow, confusing, and laborious at first, but eventually it became so easy you could do it with little thought—like a motor program playing out in your brain without requiring your conscious attention. It became easier to do because the synapses in a certain pathway were modified to allow signals to travel more easily across them than across "untrained" synapses. The process of making transmission easier is called **synaptic potentiation** (one form of synaptic plasticity).

Neuroscientists still argue about how to classify the various forms of memory, but three kinds often recognized are *immediate memory, short-term memory,* and *long-term memory.* We also know of different modes of synaptic

[27] *en* = inner + *gram* = mark, trace, record

potentiation that last from just a few seconds to a lifetime, and we can correlate these at least tentatively with different forms of memory.

Immediate Memory

Immediate memory is the ability to hold something in mind for just a few seconds. By remembering what just happened, we get a feeling for the flow of events and a sense of the present. Immediate memory might be based on reverberating circuits. Our impression of what just happened can thus "re-echo" in our minds for a few seconds as we experience the present moment and plan the next one.

Short-Term Memory

Short-term memory (STM) lasts from a few seconds to a few hours and is limited to a few bits of information such as the digits of a telephone number. Information stored in STM may be quickly forgotten if we stop mentally reciting it, we are distracted, or we have to remember something new. **Working memory** is a form of STM that allows us to hold an idea in mind long enough to carry out an action such as calling a telephone number we just looked up, working out the steps of a mathematics problem, or searching for a lost set of keys while remembering where we have already looked. These short-term memory tasks may be carried out by reverberating circuits of neurons.

Somewhat longer-lasting memories, however, probably involve a synaptic effect called **facilitation** (different from the facilitation of one neuron by another that we studied earlier in the chapter). This form of facilitation is induced by *tetanic stimulation,* the rapid arrival of repetitive signals at a synapse. Each signal causes a certain amount of Ca^{2+} to enter the synaptic knob. If signals arrive so close together that the neuron cannot pump out all the Ca^{2+} admitted by one action potential before the next action potential occurs, then more and more Ca^{2+} will accumulate in the knob. Since Ca^{2+} is what triggers the release of neurotransmitter, each signal will trigger the release of more neurotransmitter than the one before. With more neurotransmitter, the EPSPs in the postsynaptic cell will become stronger and stronger, and that cell will be more likely to fire. Thus, tetanic stimulation facilitates the synapse and makes it easier for the postsynaptic cell to fire.

Memories lasting for a few hours, such as remembering what someone said to you earlier in the day or remembering an upcoming appointment, may involve **posttetanic potentiation.** In this process, the Ca^{2+} level in the synaptic knob stays elevated for so long that another signal, coming along well after the tetanic stimulation has ceased, releases an exceptionally large burst of neurotransmitter. That is, if a synapse has been heavily used in the recent past, a new stimulus can excite the postsynaptic cell more easily. Thus your memory may need only a slight jog to recall something from several hours earlier.

Long-Term Memory

Long-term memory (LTM) lasts up to a lifetime and is less limited than STM in the amount of information it can store. LTM allows you to memorize the lines of a play, the words of a favorite song, or textbook information for an exam. On a still longer timescale, it enables you to remember your name, the route to your home, and your childhood experiences.

There are two forms of long-term memory—declarative and procedural. **Declarative memory** is the retention of events and facts that you can put into words—numbers, names, dates, and so forth. **Procedural memory** is the retention of motor skills—how to tie your shoes, play a musical instrument, or type on a keyboard. These forms of memory involve different regions of the brain but are probably similar at the cellular level.

Some LTM involves the physical remodeling of synapses or the formation of new ones through the growth and branching of axons and dendrites. In the pyramidal cells of the brain, the dendrites are studded with knoblike *dendritic spines* that increase the area of synaptic contact. Studies on fish and other experimental animals have shown that social and sensory deprivation causes these spines to decline in number, while a richly stimulatory environment causes them to proliferate—an intriguing clue to the importance of a stimulating environment to infant and child development. In some cases of LTM, a new synapse grows beside the original one, giving the presynaptic cell twice as much input into the postsynaptic cell.

LTM can also be grounded in molecular changes called **long-term potentiation.** This involves *NMDA*[28] *receptors,* which occur on the synaptic knobs of the pyramidal cells and bind the neurotransmitter glutamate. NMDA receptors are usually blocked by magnesium ions (Mg^{2+}), but when they bind glutamate *and* are simultaneously subjected to tetanic stimulation, they expel the Mg^{2+} and open to admit Ca^{2+} into the dendrite. When Ca^{2+} enters the dendrite, it acts as a second messenger that leads to a variety of effects:

- The neuron produces an increased number of NMDA receptors, which makes it more sensitive to glutamate in the future.
- It synthesizes proteins concerned with physically remodeling a synapse.
- It releases nitric oxide, which diffuses back to the presynaptic neuron and triggers a chain reaction of events there that ultimately increases glutamate release.

You can see that in all of these ways, long-term potentiation can increase transmission across "experienced" synapses. Remodeling a synapse or increasing the number of neurotransmitter receptors has longer-lasting effects than facilitation or posttetanic potentiation.

[28]N-methyl-D-aspartate, a chemical similar to glutamate

Before You Go On

Answer the following questions to test your understanding of the preceding section:

22. Contrast the two types of summation at a synapse.
23. Describe how the nervous system communicates quantitative and qualitative information about stimuli.
24. List the four types of neuronal circuits and describe their similarities and differences. Discuss the unity of form and function in these four types—that is, explain why each type would not perform as it does if its neurons were connected differently.
25. How does long-term potentiation enhance the transmission of nerve signals along certain pathways?

Insight 12.4 Clinical Application

Alzheimer and Parkinson Diseases

Alzheimer and Parkinson diseases are degenerative disorders of the brain associated with neurotransmitter deficiencies.

Alzheimer[29] *disease (AD)* may begin before the age of 50 with symptoms so slight and ambiguous that early diagnosis is difficult. One of its first symptoms is memory loss, especially for recent events. A person with AD may ask the same questions repeatedly, show a reduced attention span, and become disoriented and lost in previously familiar places. Family members often feel helpless and confused as they watch their loved one's personality gradually deteriorate beyond recognition. The AD patient may become moody, confused, paranoid, combative, or hallucinatory—he or she may ask irrational questions such as, Why is the room full of snakes? The patient may eventually lose even the ability to read, write, talk, walk, and eat. Death ensues from pneumonia or other complications of confinement and immobility.

AD affects about 11% of the U.S. population over the age of 65; the incidence rises to 47% by age 85. It accounts for nearly half of all nursing home admissions and is a leading cause of death among the elderly. AD claims about 100,000 lives per year in the United States.

Diagnosis of AD is confirmed on autopsy. There is atrophy of some of the gyri (folds) of the cerebral cortex and the hippocampus, an important center of memory. Nerve cells exhibit *neurofibrillary tangles*—dense masses of broken and twisted cytoskeleton (fig. 12.28). These were first observed by Alois Alzheimer in 1907 in the brain of a patient who had died of senile dementia. The more severe the disease symptoms, the more neurofibrillary tangles are seen at autopsy. In the intercellular spaces, there are *senile plaques* consisting of aggregations of cells, altered nerve fibers, and a core of *β-amyloid protein*—the breakdown product of a glycoprotein of plasma membranes. β-amyloid protein is rarely seen in elderly people without AD.

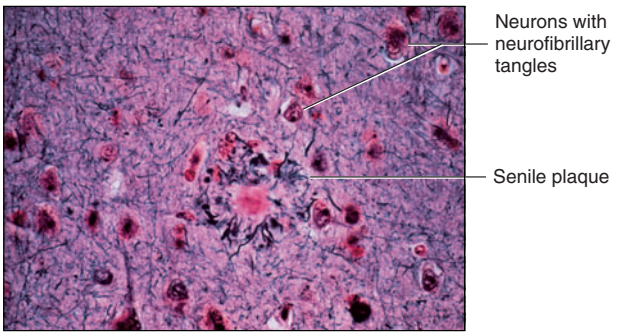


Figure 12.28 Cerebral Tissue from a Person with Alzheimer Disease. Neurofibrillary tangles appear within the neurons, and a senile plaque is evident in the extracellular matrix.

AD is marked by the degeneration of cholinergic neurons and a deficiency of ACh. Treatment with ACh precursors is ineffective, but therapy with cholinesterase inhibitors to slow down the degradation of existing ACh has been of some value. AD patients show a deficiency of nerve growth factor (NGF; see insight 12.3) in some regions of the brain. NGF stimulates ACh synthesis; it helps to retard brain degeneration in humans and other animals and improves memory in some AD patients. Intense biomedical research efforts are currently geared toward identifying the cause of AD and developing treatment strategies. Researchers have identified three genes on chromosomes 1, 14, and 21 for various forms of early- and late-onset AD.

Parkinson[30] *disease (PD),* also called *paralysis agitans* or *parkinsonism,* is a progressive loss of motor function beginning in a person's 50s or 60s. It is due to degeneration of dopamine-releasing neurons in a portion of the brain called the *substantia nigra.* A gene has recently been identified for a hereditary form of PD, but most cases are nonhereditary and of little-known cause; some authorities suspect environmental neurotoxins.

Dopamine (DA) is an inhibitory neurotransmitter that normally prevents excessive activity in motor centers of the brain called the *basal nuclei.* Degeneration of the dopamine-releasing neurons leads to an excessive ratio of ACh to DA, leading to hyperactivity of the basal nuclei. As a result, a person with PD suffers involuntary muscle contractions. These take such forms as shaking of the hands (tremor) and compulsive "pill-rolling" motions of the thumb and fingers. In addition, the facial muscles may become rigid and produce a staring, expressionless face with a slightly open mouth. The patient's range of motion diminishes. He or she takes smaller steps and develops a slow, shuffling gait with a forward-bent posture and a tendency to fall forward. Speech becomes slurred and handwriting becomes cramped and eventually illegible. Tasks such as buttoning clothes and preparing food become increasingly laborious.

Patients cannot be expected to recover from PD, but its effects can be alleviated with drugs and physical therapy. Treatment with dopamine is ineffective because it cannot cross the blood-brain barrier, but its precursor, levodopa (l-DOPA), does cross the barrier and has been used to treat PD since the 1960s. l-DOPA affords some relief from symptoms, but it does not slow progression of the disease and it has undesirable side effects on the liver and heart. It is effective for only 5 to 10 years of treatment. A newer drug, Deprenyl, is a monoamine oxidase (MAO) inhibitor that retards neuronal degeneration and delays the development of symptoms. Modest improvement has been obtained by implanting other dopamine-producing tissues into the brains of PD patients—namely, adrenal medulla and fetal brain tissue. Even though the latter tissue has not come from elective abortions, this approach has triggered ethical controversy.

A surgical technique called *pallidotomy* has been used since the 1940s to alleviate severe tremors. It involves the destruction of a small portion of cerebral tissue in an area called the *globus pallidus.* Pallidotomy fell out of favor in the late 1960s when l-DOPA came into common use. By the early 1990s, however, the limitations of l-DOPA had become apparent, while MRI- and CT-guided methods had improved surgical precision and reduced the risks. Pallidotomy has thus made a comeback. Other surgical treatments for parkinsonism target brain areas called the *subthalamic nucleus* and the *ventral intermediate nucleus* of the thalamus, and involve either the destruction of tiny areas of tissue or the implantation of a stimulating electrode.

[29]Alois Alzheimer (1864–1915), German neurologist
[30]James Parkinson (1755–1824), British physician

Chapter Review

Review of Key Concepts

Overview of the Nervous System (p. 444)

1. The nervous and endocrine systems are the body's two main systems of internal communication and physiological coordination. Study of the nervous system, or *neuroscience,* includes *neurophysiology, neuroanatomy,* and clinical *neurology.*
2. The nervous system receives information from *receptors, integrates* information, and issues commands to *effectors.*
3. The nervous system is divided into the *central nervous system (CNS)* and *peripheral nervous system (PNS).* The PNS has *sensory* and *motor* divisions, and each of these has *somatic* and *visceral* subdivisions.
4. The visceral motor division is also called the *autonomic nervous system,* which has *sympathetic* and *parasympathetic* divisions.

Nerve Cells (Neurons) (p. 445)

1. Neurons have the properties of excitability, conductivity, and secretion.
2. A neuron has a *soma* where its nucleus and most other organelles are located; usually multiple *dendrites* that receive signals and conduct them to the soma; and one *axon (nerve fiber)* that carries nerve signals away from the soma.
3. The axon branches at the distal end into a *terminal arborization,* and each branch ends in a *synaptic knob.* The synaptic knob contains *synaptic vesicles,* which contain neurotransmitters.
4. Neurons are described as multipolar, bipolar, or unipolar depending on the number of dendrites present, or anaxonic if they have no axon.
5. Neurons move material along the axon by *axonal transport,* which can be *fast* or *slow, anterograde* (away from the soma) or *retrograde* (toward the soma).

Supportive Cells (Neuroglia) (p. 449)

1. Supportive cells called *neuroglia* greatly outnumber neurons. There are six kinds of neuroglia: oligodendrocytes, astrocytes, ependymal cells, and microglia in the CNS, and Schwann cells and satellite cells in the PNS.
2. *Oligodendrocytes* produce the myelin sheath around CNS nerve fibers.
3. *Astrocytes* play a wide variety of protective, nutritional, homeostatic, and communicative roles for the neurons, and form scar tissue when CNS tissue is damaged.
4. *Ependymal cells* line the inner cavities of the CNS and secrete and circulate cerebrospinal fluid.
5. *Microglia* are macrophages that destroy microorganisms, foreign matter, and dead tissue in the CNS.
6. *Schwann cells* cover nerve fibers in the PNS and produce myelin around many of them.
7. *Satellite cells* surround somas of the PNS neurons and have an uncertain function.
8. *Myelin* is a multilayered coating of oligodendrocyte or Schwann cell membrane around a nerve fiber, with periodic gaps called *nodes of Ranvier* between the glial cells.
9. Signal transmission is relatively slow in small nerve fibers, unmyelinated fibers, and at nodes of Ranvier. It is much faster in large nerve fibers and myelinated segments *(internodes)* of a fiber.
10. Damaged nerve fibers in the PNS can regenerate if the soma is unharmed. Repair requires a *regeneration tube* composed of *neurilemma* and *endoneurium,* which are present only in the PNS.

Electrophysiology of Neurons (p. 455)

1. An *electrical potential* is a difference in electrical charge between two points. When a cell has a charge difference between the two sides of the plasma membrane, it is *polarized.* The charge difference is called the *resting membrane potential (RMP).* For a resting neuron, it is typically −70 mV (negative on the intracellular side).
2. A *current* is a flow of charge particles—especially, in living cells, Na^+ and K^+. Resting cells have more K^+ inside than outside the cell, and more Na^+ outside than inside. A current occurs when gates in the plasma membrane open and allow these ions to diffuse across the membrane, down their concentration gradients.
3. When a neuron is stimulated on the dendrites or soma, Na^+ gates open and allow Na^+ to enter the cell. This slightly depolarizes the membrane, creating a *local potential.* Short-distance diffusion of Na^+ inside the cell allows local potentials to spread to nearby areas of membrane.
4. Local potentials are *graded, decremental, reversible,* and can be *excitatory* or *inhibitory.*
5. The trigger zone and unmyelinated regions of a nerve fiber have voltage-regulated Na^+ and K^+ gates that open in response to changes in membrane potential and allow these ions through.
6. If a local potential reaches *threshold,* voltage-regulated gates open. The inward movement of Na^+ followed by the outward movement of K^+ creates a quick voltage change called an *action potential.* The cell *depolarizes* as the membrane potential becomes less negative, and *repolarizes* as it returns toward the RMP.
7. Unlike local potentials, action potentials follow an *all-or-none law* and are *nondecremental* and *irreversible.* Following an action potential, a patch of cell membrane has a *refractory period* in which it cannot respond to another stimulus.
8. One action potential triggers another in the plasma membrane just distal to it. By repetition of this process, a chain of action potentials, or *nerve signal,* travels the entire length of an unmyelinated axon. The refractory period of the recently active membrane prevents this signal from traveling backward toward the soma.
9. In myelinated fibers, only the nodes of Ranvier have voltage-regulated

gates. In the internodes, the signal travels rapidly by Na^+ diffusing along the intracellular side of the membrane. At each node, new action potentials occur, slowing the signal somewhat, but restoring signal strength. Myelinated nerve fibers are said to show *saltatory conduction* because the signal seems to jump from node to node.

Synapses (p. 463)

1. At the distal end of a nerve fiber is a *synapse* where it meets the next cell (usually another neuron or a muscle or gland cell).
2. The *presynaptic* neuron must release chemical signals called *neurotransmitters* to cross the synaptic cleft and stimulate the next *(postsynaptic)* cell.
3. Neurotransmitters include acetylcholine (ACh), monoamines such as norepinephrine (NE) and serotonin, amino acids such as glutamate and GABA, and neuropeptides such as β-endorphin and substance P. A single neurotransmitter can affect different cells differently, because of the variety of receptors for it that various cells possess.
4. Some synapses are excitatory, as when ACh triggers the opening of Na^+-K^+ gates and depolarizes the postsynaptic cell, or when NE triggers the synthesis of the second messenger cAMP.
5. Some synapses are inhibitory, as when GABA opens a Cl^- gate and the inflow of Cl^- hyperpolarizes the postsynaptic cell.
6. Synaptic transmission ceases when the neurotransmitter diffuses away from the synaptic cleft, is reabsorbed by the presynaptic cell, or is degraded by an enzyme in the cleft such as acetylcholinesterase (AChE).
7. Hormones, neuropeptides, nitric oxide (NO), and other chemicals can act as *neuromodulators,* which alter synaptic function by altering neurotransmitter synthesis, release, reuptake, or breakdown.

Neural Integration (p. 468)

1. Synapses slow down communication in the nervous system, but their role in *neural integration* (information processing and decision making) overrides this drawback.
2. Neural integration is based on the relative effects of small depolarizations called *excitatory postsynaptic potentials (EPSPs)* and small hyperpolarizations called *inhibitory postsynaptic potentials (IPSPs)* in the postsynaptic membrane. EPSPs make it easier for the postsynaptic neuron to fire, and IPSPs make it harder.
3. Some combinations of neurotransmitter and receptor produce EPSPs and some produce IPSPs. The postsynaptic neuron can fire only if EPSPs override IPSPs enough for the membrane voltage to reach threshold.
4. One neuron receives input from thousands of others, some producing EPSPs and some producing IPSPs. *Summation,* the adding up of these potentials, occurs in the trigger zone. Two types of summation are temporal (based on how frequently a presynaptic neuron is stimulating the postsynaptic one) or spatial (based on how many presynaptic neurons are simultaneously stimulating the postsynaptic one).
5. One presynaptic neuron can *facilitate* another, making it easier for the second to stimulate a postsynaptic cell, or it can produce *presynaptic inhibition,* making it harder for the second one to stimulate the postsynaptic cell.
6. Neurons encode qualitative and quantitative information by means of *neural coding.* Stimulus type (qualitative information) is represented by which nerve cells are firing. Stimulus intensity (quantitative information) is represented both by which nerve cells are firing and by their firing frequency.
7. The refractory period sets an upper limit on how frequently a neuron can fire.
8. Neurons work in groups called neuronal pools.
9. A presynaptic neuron can, by itself, cause postsynaptic neurons in its *discharge zone* to fire. In its *facilitated zone,* it can only get a postsynaptic cell to fire by collaborating with other presynaptic neurons (facilitating each other).
10. Signals can travel *diverging, converging, reverberating,* or *parallel after-discharge circuits* of neurons.
11. Memories are formed by neural pathways of modified synapses. The ability of synapses to change with experience is called *synaptic plasticity,* and changes that make synaptic transmission easier are called *synaptic potentiation.*
12. Immediate memory may be based on reverberating circuits. Short-term memory (STM) may employ these circuits as well as *synaptic facilitation,* which is thought to involve an accumulation of Ca^{2+} in the synaptic knob.
13. *Long-term memory* (LTM) involves the remodeling of synapses, or modification of existing synapses so that they release more neurotransmitter or have more receptors for a neurotransmitter. The two forms of LTM are *declarative* and *procedural memory.*

Selected Vocabulary

central nervous system 444
peripheral nervous system 444
afferent neuron 446
interneuron 446
efferent neuron 446
soma 446
dendrite 446
axon 448
synapse 448
synaptic vesicle 448
oligodendrocyte 450
astrocyte 450
ependymal cell 450
microglia 451
Schwann cell 451
myelin sheath 451
node of Ranvier 453
resting membrane potential 455
depolarization 456
local potential 456
hyperpolarize 458
action potential 458
repolarize 458
excitatory postsynaptic potential 468
inhibitory postsynaptic potential 469
synaptic potentiation 473

Testing Your Recall

1. The integrative functions of the nervous system are performed mainly by
   a. afferent neurons.
   b. efferent neurons.
   c. neuroglia.
   d. sensory neurons.
   e. interneurons.
2. The highest density of voltage-regulated ion gates is found on the _____ of a neuron.
   a. dendrites
   b. soma
   c. nodes of Ranvier
   d. internodes
   e. synaptic knobs
3. The soma of a mature neuron lacks
   a. a nucleus.
   b. endoplasmic reticulum.
   c. lipofuscin.
   d. centrioles.
   e. ribosomes.
4. The glial cells that destroy microorganisms in the CNS are
   a. microglia.
   b. satellite cells.
   c. ependymal cells.
   d. oligodendrocytes.
   e. astrocytes.
5. Posttetanic potentiation of a synapse increases the amount of _____ in the synaptic knob.
   a. neurotransmitter
   b. neurotransmitter receptors
   c. calcium
   d. sodium
   e. NMDA
6. An IPSP is _____ of the postsynaptic neuron.
   a. a refractory period
   b. an action potential
   c. a depolarization
   d. a repolarization
   e. a hyperpolarization
7. Saltatory conduction occurs only
   a. at chemical synapses.
   b. in the initial segment of an axon.
   c. in both the initial segment and axon hillock.
   d. in myelinated nerve fibers.
   e. in unmyelinated nerve fibers.
8. Some neurotransmitters can have either excitatory or inhibitory effects depending on the type of
   a. receptors on the postsynaptic neuron.
   b. synaptic vesicles in the axon.
   c. synaptic potentiation that occurs.
   d. postsynaptic potentials on the synaptic knob.
   e. neuromodulator involved.
9. Differences in the volume of a sound are likely to be encoded by differences in _____ in nerve fibers from the inner ear.
   a. neurotransmitters
   b. signal conduction velocity
   c. types of postsynaptic potentials
   d. firing frequency
   e. voltage of the action potentials
10. Motor effects that depend on repetitive output from a neuronal pool are most likely to use
    a. parallel after-discharge circuits.
    b. reverberating circuits.
    c. facilitated circuits.
    d. diverging circuits.
    e. converging circuits.
11. Neurons that convey information to the CNS are called sensory, or _____, neurons.
12. To perform their role, neurons must have the properties of excitability, secretion, and _____.
13. The _____ is a period of time in which a neuron is producing an action potential and cannot respond to another stimulus of any strength.
14. Neurons receive incoming signals by way of specialized processes called _____.
15. In the central nervous system, cells called _____ perform one of the same functions that Schwann cells do in the peripheral nervous system.
16. A myelinated nerve fiber can produce action potentials only in specialized regions called _____.
17. The trigger zone of a neuron consists of its _____ and _____.
18. The neurotransmitter secreted at an adrenergic synapse is _____.
19. A presynaptic nerve fiber cannot cause other neurons in its _____ to fire, but it can make them more sensitive to stimulation from other presynaptic fibers.
20. _____ are substances released along with a neurotransmitter that modify the neurotransmitter's effect.

Answers in Appendix B

True or False

Determine which five of the following statements are false, and briefly explain why.

1. A neuron never has more than one axon.
2. Oligodendrocytes perform the same function in the brain as Schwann cells do in the peripheral nerves.
3. A resting neuron has a higher concentration of K^+ in its cytoplasm than in the extracellular fluid surrounding it.
4. During an action potential, a neuron is repolarized by the outflow of sodium ions.
5. Excitatory postsynaptic potentials lower the threshold of a neuron and thus make it easier to stimulate.
6. The absolute refractory period sets an upper limit on how often a neuron can fire.
7. A given neurotransmitter has the same effect no matter where in the body it is secreted.
8. Nerve signals travel more rapidly through the nodes of Ranvier than through the internodes.

9. The synaptic contacts in the nervous system are fixed by the time of birth and cannot be changed thereafter.
10. Mature neurons are incapable of mitosis.

Answers in Appendix B

Testing Your Comprehension

1. Schizophrenia is sometimes treated with drugs such as chlorpromazine that inhibit dopamine receptors. A side effect is that patients begin to develop muscle tremors, speech impairment, and other disorders similar to Parkinson disease. Explain.
2. Hyperkalemia is an excess of potassium in the extracellular fluid. What effect would this have on the resting membrane potentials of the nervous system and on neuronal excitability?
3. Suppose the Na^+-K^+ pumps of nerve cells were to slow down because of some metabolic disorder. How would this affect the resting membrane potentials of neurons? Would it make neurons more excitable than normal, or make them more difficult to stimulate? Explain.
4. The unity of form and function is an important concept in understanding synapses. Give two structural reasons why nerve signals cannot travel backward across a chemical synapse. What might be the consequences if signals did travel freely in both directions?
5. The local anesthetics tetracaine and procaine (Novocain) prevent voltage-regulated Na^+ gates from opening. Explain why this would block the conduction of pain signals in a sensory nerve.

Answers at the Online Learning Center

Answers to Figure Legend Questions

12.9 It would become lower (more negative).
12.16 They are axosomatic.
12.21 One EPSP is a voltage change of only 0.5 mV or so. It requires a change of about 15 mV to bring a neuron to threshold.
12.25 The CNS interprets a stimulus as more intense if it receives signals from high-threshold sensory neurons than if it receives signals only from low-threshold neurons.
12.27 A reverberating circuit, because a neuron early in the circuit is continually restimulated