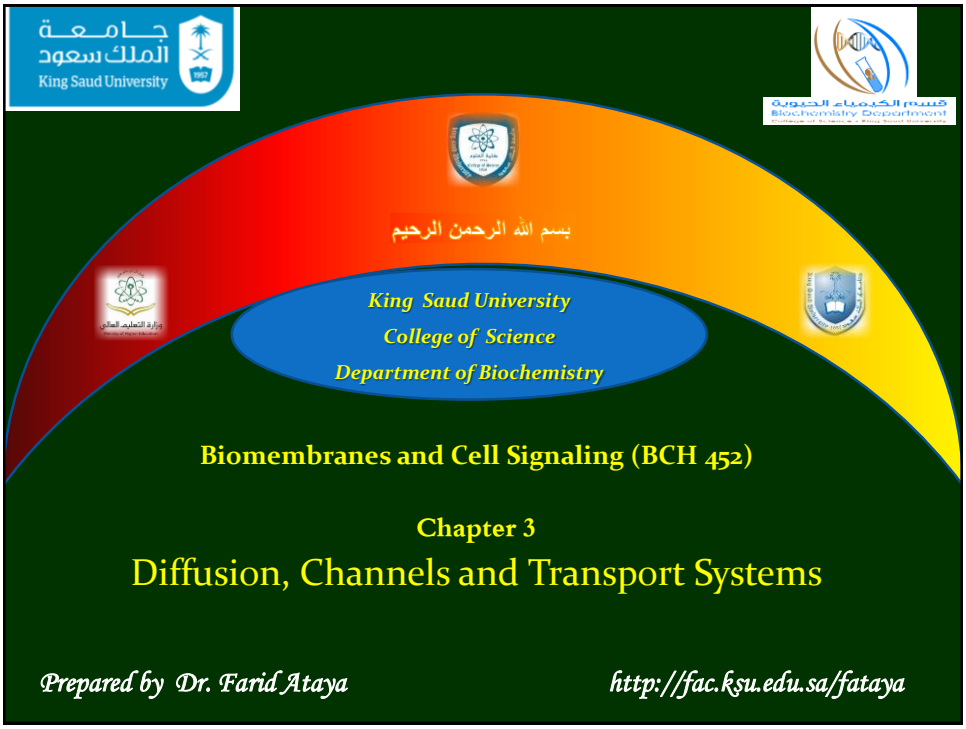


Topics to be covered	Lect No.
Role of cell surface carbohydrates in recognise ion, as receptor of antigens, hormones, toxins, viruses and bacteria. Their role in histocompatibility and cell-cell adhesion.	7
Diffusion. Diffusion across biomembranes. Ficks law. Structural types of channels (pores): α-type, β-barrel, pore forming toxins, ionophores. Functional types of channels (pores): • voltage-gated channels e.g. sodium channels, • ligand-gated channels e.g. acetylcholine receptor (nicotinic-acetylcholine channel), • c-AMP regulated.	8
Gap junctions and nuclear pores. Transport systems: • Energetics of transport systems, G calculation in each type. • Passive Transport (facilitated diffusion).	9

Topics to be covered	No. Lect
Kinetic properties. Passive transport: • Glucose transporters (GLUT 1 to5), • $C1^-$, HCO_3 exchanger (anion exchanger protein) in erythrocyte membrane	9
Kinetic properties. Active transport: Types of active transport: Primary ATPases (Primary active transporters): P transporters (e.g. Na^+, K^+, ATPase)	10
First assessment Exam	
ATP binding cassettes (ABC transports) • (e.g. cystic fibrosis transmembrane conductance regulator-chloride transport). Multidrug resistance protein transporter. V transporters, F transporters. • Secondary active transporters (e.g. Na^+ -dependent transport of glucose and amino acids). To be covered under intestinal brush border	11
Transport of large molecules (Macromolecules) Types: Exocytosis, Endocytosis-pinocytosis and phagocytosis Types of pinocytosis: • Absorptive pinocytosis, characteristics and examples. • Fluid phase pinocytosis, characteristics and examples	12

The role of cell surface carbohydrates: Glycoproteins

- Membrane glycoproteins are proteins that contain 1-30% carbohydrate in their structure.
- They are found attached to biomembranes inside and outside the cells:
  - Inside cells: they are found in specific organelles such as Golgi complexes, secretory granules, and lysosomes.
  - Outside the cell on the outer face of the plasma membrane.
    - Notice, there are many soluble glycoproteins in the cytoplasm, blood and in the extracellular matrix.
  - The oligosaccharide portions of glycoproteins are rich in information, forming highly specific sites for recognition and high-affinity binding by other proteins.

Functions of membrane glycoproteins

- Gylcoproteins have many biological functions:
- 1- Immunological protection and antigenic determinants
- 2- Mediators for cell-cell recognition and interaction
- 3- Blood clotting
- 4- Host-pathogen interaction

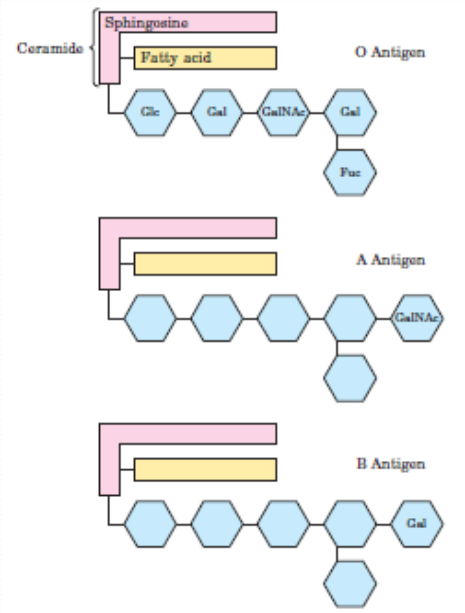
Linkage between sugar and protein part in glycoproteins

- Carbohydrates link through the *anomeric* carbon to:
  - The amide nitrogen in the side chain of *asparagine* (N-glycosidic bond) or
  - The hydroxyl oxygen of *serine or threonine* (O-glycosidic bond).

Do you remember the meaning of anomeric carbon?

The addition of sugar moiety determines the blood group

- Sugars attached to glycoproteins and glycolipids on the surfaces of red blood cells determine the blood group termed A, B, and O.
- The A and B antigens differ from the O antigen by the addition of one extra monosaccharide *N*-acetylgalactosamine (for A) or galactose (for B) through an α -1,3 linkage to a galactose moiety of the O antigen.,
- The addition of *N*-acetylgalactosamine or galactose is mediated by specific enzyme called glycosyltransferases which add the extra monosaccharide to the O antigen.
- Each person inherits the gene for one glycosyltransferase of this type from each parent.
  - The type A transferase specifically adds *N*-acetylgalactosamine,
  - The type B transferase adds galactose.
  - The O phenotype lack that enzyme due to mutation that leads to premature termination of translation and, hence, it produces inactive glycosyltransferase.



Sugars determining blood groups.
Abbreviations:
Fuc, fucose;
Gal, galactose;
GalNAc, *N*-acetylgalactosamine;
GlcNAc, *N*-acetylglucosamine.

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- **Type A**
  - has lots of sugar bound but there is a different sugar at non-reducing end
  - people have antibodies against B sugars
  - donors (receive blood from): A or O

- **Type B**
  - has lots of sugar bound but there is a different sugar at non-reducing end
  - people have antibodies against A sugars
  - donor (receive blood from): B or O

- **Type AB**
  - mix of both types of sugars as A and B
  - people have no antibodies towards A or B
  -donors (receive blood from): A, B or AB or O

- **Type O**
  - Lack of sugars specific for A and B (lack of terminal *N*-acetylgalactosamine; or terminal galactose)
  i.e. missing sugar at non-reducing end
  - people have antibodies towards both A or B
  - donors (receive blood from): O only
  - Universal donor : give blood to all groups (A, B, AB and O)

Transport across the membrane

Why transport is important?

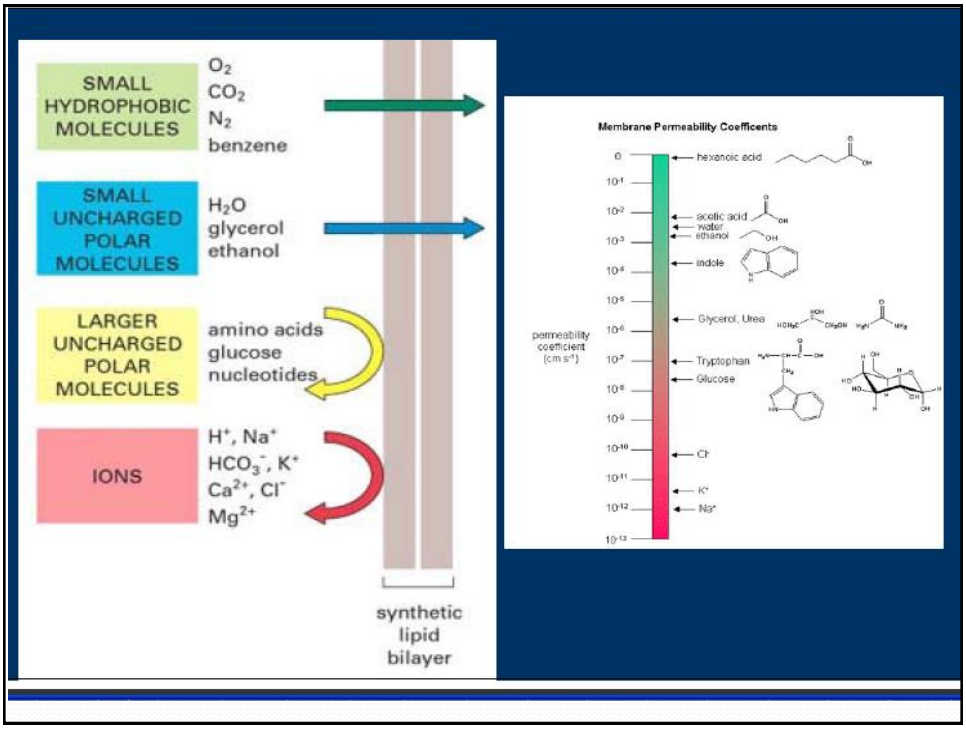
- Every living cell must acquire from its surroundings the raw materials for biosynthesis and for energy production, and must release to its environment the byproducts of metabolism. So, the transport across biological membranes are important.

Biological membrane is a supramolecular characterized by their selective permeability.

The selective nature of membrane comes from both the discriminating nature of phospholipids and the specific transporter proteins.

Lipid bilayer is:

- *Permeable* to small nonpolar molecules such as CO_2 and O_2.
- *Impermeable* to ions and polar molecules such as glucose, sucrose. Na^+. Cl^-.
  - Polar molecules and water enters to the cell through special transport proteins that make the cell permeable to them.



Three ways of Transport

1. Passive Transport: Diffusion across the membrane down the concentration gradient.

a- Osmosis: Passive transport of water

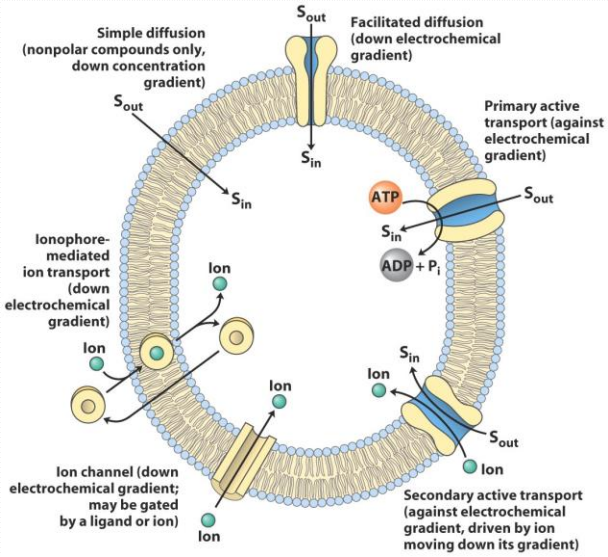
b- Facilitated Diffusion: Specific protein helps in transport of water and other nutrients

2. Active Transport: Pumping of solutes against the concentration gradient.

Co transport: membrane protein helps in transport of one solute to another

3. Exocytosis and Endocytosis: Transport of large molecules.

Types of Membrane Transport



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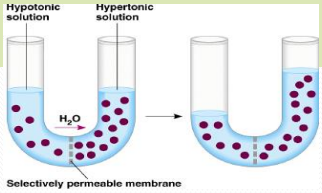
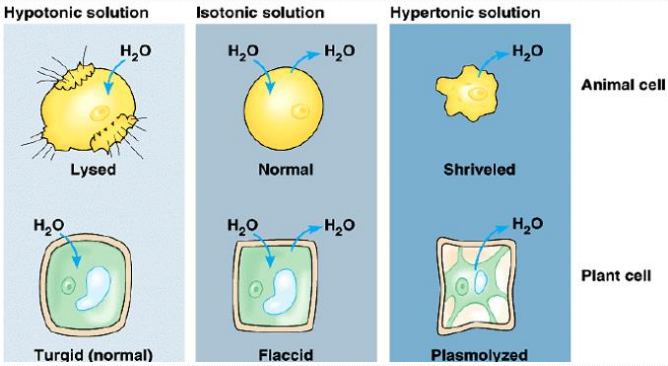
Passive Transport of water: a- Osmosis



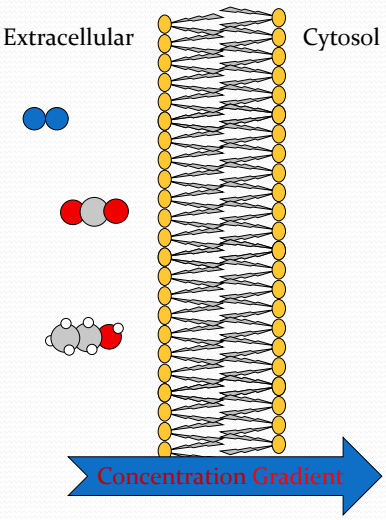
If a cell is put in water, the transport of water is determined according to its concentration in both sides of the cell membrane. Water moves from less concentration (hypotonic solution) to higher concentration (hypertonic solution).

Osmosis is the movement of a solvent (e.g. water) across a semipermeable membrane toward a higher concentration of solute (e.g. salts and ions).



Passive Transport: Simple diffusion

- The movement of solute from higher concentration to lower concentration without needing energy.
- <150 Da, uncharged species, going down their concentration gradient
  - O_2
  - CO_2
  - Alcohol
  - Anaesthetics
  - Pesticides



When two aqueous compartments containing unequal concentrations of a soluble compound (C1 & C2) are separated by a permeable divider (membrane), the solute moves by **simple diffusion** from the region of higher concentration, through the membrane, to the region of lower concentration, until the two compartments have equal solute concentrations (C1=C2).

When ions of opposite charge are separated by a permeable membrane, there is a transmembrane electrical gradient, a **membrane potential, *V*m** (expressed in volts or millivolts). The net movement of electrically charged solutes is dictated by a combination of both the electrical potential (*V*m) and the chemical concentration difference across the membrane; net ion movement continues until this electrochemical potential reaches zero.

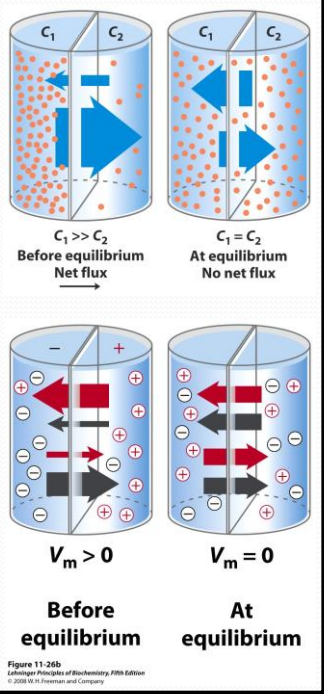


Figure 11-26b
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Diffusion is passive and occurs only down a concentration gradient.
It can be calculated by Fick's Law:

Fick's First Law measures the amount of substance that will flow through a unit area during a unit time interval.

$$J = \frac{dN}{dt} = -DA\frac{dC}{dx}$$

- D, diffusion coefficient
- A, area
- dC, concentration difference (C1-C2)
- dx, thickness of hydrophobic phase

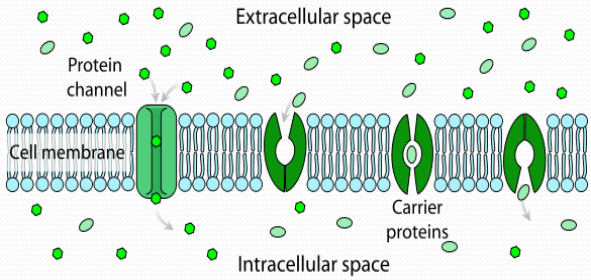
Negative sign indicates direction
Diffusion also depends on the solubility.

Passive Transport: b- Facilitated diffusion

- Specific ions and polar molecules can cross the lipid bilayer by passing through **transport proteins** *(also known as permeases)* that span the membrane.
  - Example: channel proteins and carrier proteins
- ***a- Channel proteins***
- *Channel proteins,* are membrane transport proteins having a hydrophilic channel that facilitate the passage of certain molecules by acting as a tunnel in the membrane.
  - For example, **aquaporins are** channel proteins that greatly facilitate the passage of water to the cell through the membrane**.**

Passive Transport: b- Facilitated diffusion (cont.)

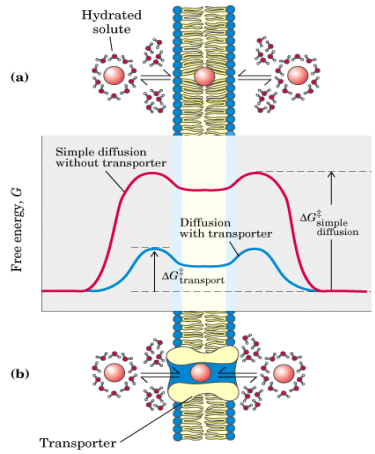
- ***b- Carrier proteins,*** they are proteins that bind to molecules and change their shape to shuttle molecules across the membrane.
- Each transport protein is specific to the substances that it will translocate.
  - Example, the glucose transport protein in the liver will carry glucose into the cell but will not transport fructose, its structural isomer.



Passive Transport:
b- Facilitated diffusion (cont.)

To pass through a lipid bilayer, the polar or charged solute must give up its interactions with the water molecules in its hydration shell. (i.e. leave water before passing through the membrane), then diffuse about 3 nm (30 Å) through a solvent (lipid).

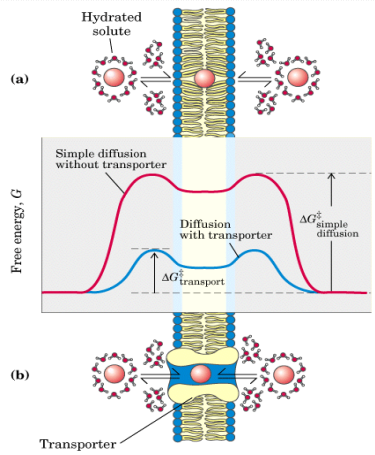
After passing the water will gain water just when it leaves the membrane and inters the cytoplasm. The energy used to strip away the hydration shell and to move the polar compound through lipid is regained as the compound leaves the membrane on the other side and is rehydrated.



Passive Transport:
b- Facilitated diffusion (cont.)

The intermediate stage of transmembrane passage is a high-energy state comparable to the transition state in an enzyme-catalyzed chemical reaction. The energy of activation ($\Delta G^{\ddagger}$) for translocation of a polar solute across the bilayer is so large.

Membrane proteins lower the activation energy for transport of polar compounds and ions using **facilitated diffusion,** or **passive transport pathway** that depend on specific membrane proteins.
These proteins are called **transporters** or **permeases. They are** not enzymes since their "substrates" are not converted into products but they move only from one compartment to another, without changing their chemical structure.



- In certain inherited diseases, specific transport systems may be defective or absent.
- Cystinuria is a human disease characterized by the absence of a protein that transports cysteine and other amino acids across the membranes of kidney cells.
- An individual with cystinuria develops painful kidney stones as amino acids accumulate and crystallize in the kidneys.

- **Energetics of transport systems, G calculation in each type**

- Free energy of transporting materials across the membrane depends on concentration gradient across the membrane. Where C1 and C2 are the two concentration gradient.

$$\Delta G_t = RT \ln \frac{C_2}{C_1}$$

  - Solutes move spontaneously (Gt < 0) ***from*** compartment of ***higher*** concentration ***to*** compartment of ***lower*** concentration
  - **G = 0** when **C1 = C2 (equilibrium)**
  - Diffusion "down" the concentration gradient (from region of greater concentration to region of lower concentration, toward equilibrium of equal concentrations) is a manifestation of the **2nd law of thermodynamics** - molecules tend spontaneously to assume the distribution of greatest ***randomness*** until system is maximally randomized.

- A transport process must be active when G is positive, whereas it can be passive when G is negative.
  - For example, consider the transport of an uncharged molecule from $C_1 = 10^{-3}$ M to $C_2 = 10^{-1}$ M. At 25°C (298 K),

$$\begin{aligned}\Delta G &= 2.303RT \log_{10}(10^{-1}/10^{-3}) \\ &= 2.303 \times 1.99 \times 298 \times 2 \\ &= +2.7 \text{ kcal mol}^{-1} (+11.3 \text{ kJ mol}^{-1})\end{aligned}$$

- G is + 2.7 kcal mol^{-1} (+11.3 kJ mol-1), indicating that this transport process requires an input of free energy.
- It could be driven, for example, by the hydrolysis of ATP, which yields -12 kcal mol^{-1} (-50.2 kJ mol^{-1}) under typical cellular conditions.
- If G is negative, the transport process can occur spontaneously without free-energy input

$$\Delta G_t = RT \ln \frac{C_2}{C_1} + ZF\Delta\Psi$$

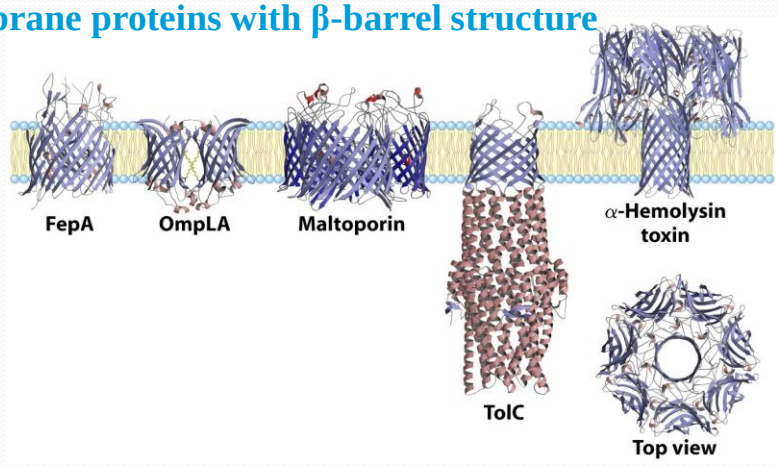
- where ***Z*** = **charge** on the ion, ***F*** = the **Faraday cor**$\Delta\Psi$ **t** (96.5 **kJ**/(V•mol) and = the **membrane potential** (the charge gradient across the membrane, in *volts,* or *millivolts*, etc.)
- **If Y is negative, going from outside to inside, the** Δ **the transport of cations into the cell is favored over anions. The opposite would be true if Y were positive**

$\Delta($

Structural types of membrane channels

- α-type, β-barrel, pore forming toxins, ionophores

Membrane proteins with β-barrel structure



- **FIGURE 11–13 Membrane proteins with -barrel structure.** Five examples are shown, viewed in the plane of the membrane; The first four are from the *E. coli* outer membrane. FepA (PDB ID 1FEP), involved in iron uptake, has 22 membrane-spanning strands. OmpLA (derived from PDB ID 1QD5), a phospholipase, is a 12-stranded barrel that exists as a dimer in the membrane. Maltoporin derived from PDB ID 1MAL), a maltose transporter, is a trimer, each monomer constructed of 16 strands. TolC (PDB ID 1EK9), another transporter, has three separate subunits, each contributing four strands in this 12-stranded barrel. The *Staphylococcus aureus* -hemolysin toxin (PDB ID 7AHL; top view below) is composed of seven identical subunits, each contributing one hairpin-shaped pair of strands to the 14-stranded barrel.

26

Ionophores

Ionophores help the charged ions to cross the membrane passively.

Ionophores are lipid-soluble small molecules that enter the cell membrane and change its permeability.

They make the ions move inward and outward of the cell membrane, so the ion concentrations will become equal in both sides.

There are two types of ionophores,

1- Pore-forming ionophres. Those which make a hole in the cell membrane which permits the ions to move upon gradient of concentration: Gramicidin and Tyrotricin.

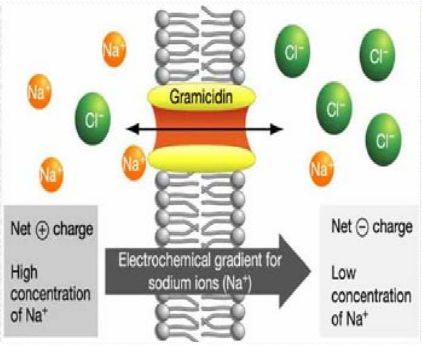
2- Ion carries ionopheres. They bind specific ions and mask their charge to allow them to diffuse passively through the lipid bilayer. Ex.Valinomycin and synthetic molecules such as crown ethers and cryptates.

Ionophores

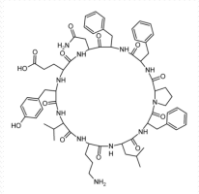
1- Pore-forming ionophres

A characteristic property of all the ionophores is their ability to adopt a cyclic ring formation by concentrating all the oxygen functions at the centre of the structure where they are available for complexing mono-or divalent cations.

- Following complexing the branched alkyl groups are spread over the molecular surface, rendering the compound highly lipid soluble.
- As a result the complex can facilitate the transport of cations through cell membranes of the target organisms (protozoa and gram-positive bacteria).
- This facilitated transport of K^+, Na^+, Ca^{2+} or Mg^{2+} across the cell membrane results in an increase in intracellular calcium to toxic levels which case increased intracellular pressure that destroy cellular structures, a collapse in the trans-membrane electrochemical potentials and eventually bursting the cell.



Pore-forming ionophore ex. Gramicidin

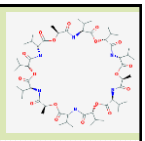


Two molecules of gramicidin make a channel in the bacterial cell membrane, N-terminals meet in the middle of the membrane and C-terminals are outside it.

- Each gramicidin molecule is in the form of a left-handed helix, which results in the polar groups lining the interior of the channel. This facilitates the transfer of polar ions through the channel.
- A single gramicidin channel can allow the transport of up to 10^7 K^+ ions per second.
- In general, gramicidin channels are ideally selective for monovalent cations.
- Divalent cations like Ca^{2+} block the channel by binding near the mouth of the channel. So it is basically impermeable to divalent cations.
- The channel is permeable to most monovalent cations, which move through the channel in single file.
- The channel is filled with about six water molecules, almost all of which must be displaced when an ion is transported. Thus, ions moving through the gramicidin pore carry along a single file of water molecules

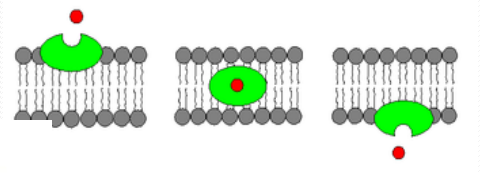
Ionophores

2- Ion carries ionopheres



Ions may also move across membranes via carries that bind specific ions and mask their charge to allow them to diffuse passively through the lipid bilayer.

Valinomycin an antibiotic acts as Ionophore . It carries 10^5 K^+ per second across membranes.



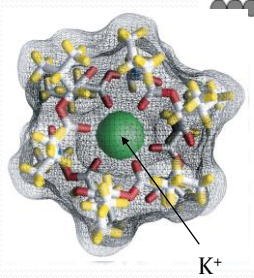
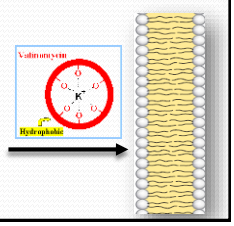


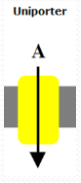
FIGURE 11-45 Valinomycin, a peptide ionophore that binds K^+. In this image, the surface contours are shown as a transparent mesh, through which a stick structure of the peptide and a K^+ atom (green) are visible. The oxygen atoms (red) that bind K^+ are part of a central hydrophilic cavity. Hydrophobic amino acid side chains (yellow) coat the outside of the molecule. Because the exterior of the K^+-valinomycin complex is hydrophobic, the complex readily diffuses through membranes, carrying K^+ down its concentration gradient. The resulting dissipation of the transmembrane ion gradient kills microbial cells, making valinomycin a potent antibiotic.



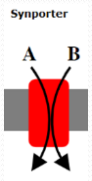
The Major facilitator superfamily

There are three major facilitator protein

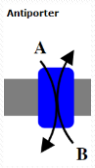
1- *Uniport* carrier proteins are type of passive protein transporters that work by binding to ONLY ONE molecule of substrate at a time and transporting it with its concentration gradient.
Uniporter channels open in response to a stimulus and allow the free flow of specific molecules.



2- *Symport* (cotransporter). Two molecules travel together, one as a passenger, the other as a driver. The driver diffuses down its electrochemical gradient, but it cannot do so unless it has the passenger. It is a type of passive transport. i.e. ATP is not directly involved, but it sets up the electrochemical gradient used to propel the driver.



3- *Antiport*. The driver and passenger travel in opposite directions. It is involved in secondary active transport of two or more different molecules or ions across a phospholipid membrane.
Ex. Ca^{2+}-Na^{+} antiport takes place in cardiac muscle, Na^{+} -H^{+} antiport, Ca^{2+}-H^{+} antiport, sucrose-H^{+} antiport in mitochondria, in plant chloroplast and vacuoles.



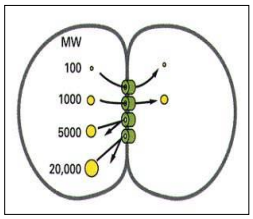
Functional types of channels (pores)

- voltage-gated channels e.g. sodium channels,
- ligand-gated channels e.g. acetylcholine receptor (nicotinic-acetylcholine channel),
- c-AMP regulated.

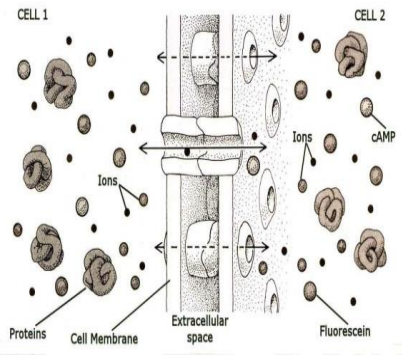
Gap junctions

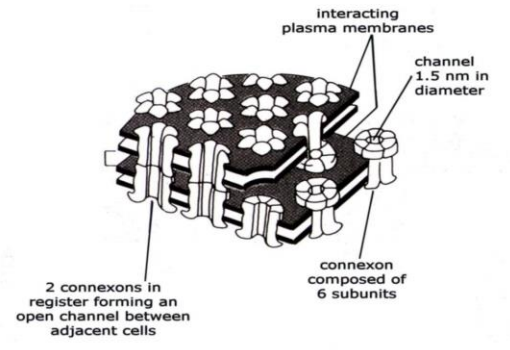
• Protein channels link the cytosols of cells.
• It is composed of six units of protein called connexon forming cylinder with a central open pore.
• Each unit is called connexin.
• The pore form hydrophilic channel between the cytoplasm of two adjacent cells. The plasma membranes come within 2-4 nm of each other.

•This pore :
-enables the passage of small molecules and ions (Na^+, K^+)
-excludes large molecules
-allows chemical messengers to cross from one cell to another
-coordinates activities between cells.



Gap Junction





•Connexon allows ions and small metabolites (amino acids, sugars, hormones) to flow from cell-to-cell and thus coordinate cell activity.

Glucose Transport

- Glucose is transported to the cell passively by many transporters.
- Many types of glucose transporters are identified.
- They are tissue specific and differ in sensitivity to glucose concentration.
- Often they are specific for glucose but some of them can act as transporters for fructose or deoxyglucose.
- Some of them uniport other symport.

TABLE 11–3 Glucose Transporters in Humans

Transporter	Tissues where Expressed	K_t (mM)	Role
GLUT1	Ubiquitous	3	Basal glucose uptake
GLUT2	Liver, pancreatic islets, intestine	17	In liver and kidney, removal of excess glucose from blood; in pancreas, regulation of insulin release
GLUT3	Brain (neuronal), testis (sperm)	1.4	Basal glucose uptake
GLUT4	Muscle, fat, heart	5	Activity increased by insulin
GLUT5	Intestine (primarily), testis, kidney	6‡	Primarily fructose transport
GLUT6	Spleen, leukocytes, brain	>5	Possibly no transporter function
GLUT7	Small intestine, colon	0.3	—
GLUT8	Testis	~2	—
GLUT9	Liver, kidney	0.6	—
GLUT10	Heart, lung, brain, liver, muscle, pancreas, kidney	0.3§	—
GLUT11	Heart, skeletal muscle, kidney	0.16	—
GLUT12	Skeletal muscle, heart, prostate, small intestine	—	—

*K_t for glucose, except as noted, from Augustin, R. (2010) The protein family of glucose transport facilitators: it's not only about glucose after all. *IUBMB Life* 62, 315–333.

†Dash indicates role uncertain.

‡K_m for fructose.

§K_m for 2-deoxyglucose.

Table 11-3
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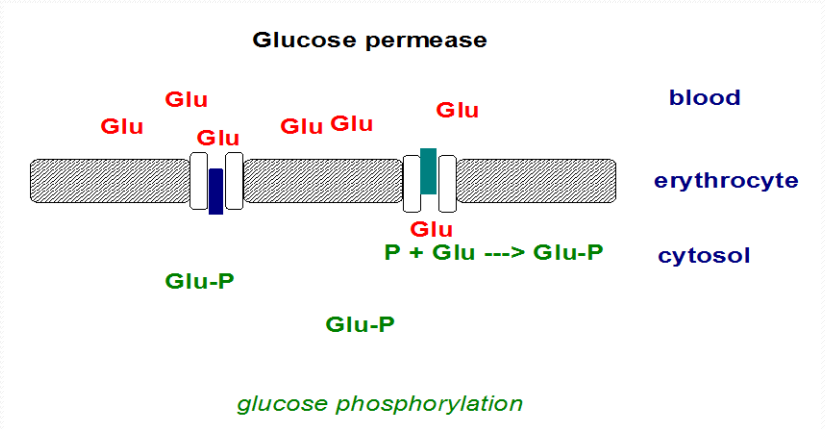
Transport of glucose

- A family of **glucose transporters** in various tissues (GluT1, GluT2, etc.) facilitate glucose movement DOWN its concentration gradient.
- Erythrocytes depend on constant supply of glucose from blood plasma, where the glucose concentration is maintained at about 5 mM, to use as energy source (fuel) via glycolysis .
- GluT1 increases rate of glucose diffusion across membrane by facilitated diffusion at a rate about 50,000 times greater than the uncatalyzed diffusion rate.
- The transported molecule (glucose) moves down its concentration gradient. Once inside the cell, the molecule is transformed into another, impermeant species, thus lowering the inside concentration and maintaining the concentration gradient.

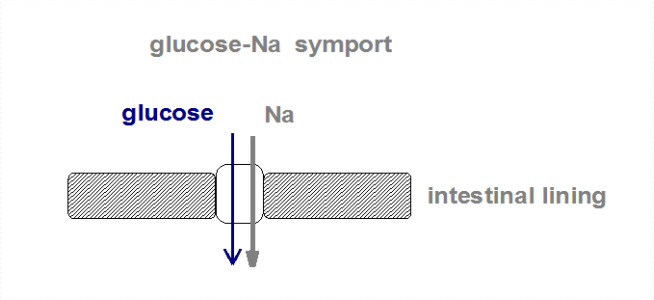
Glucose transport as uniport



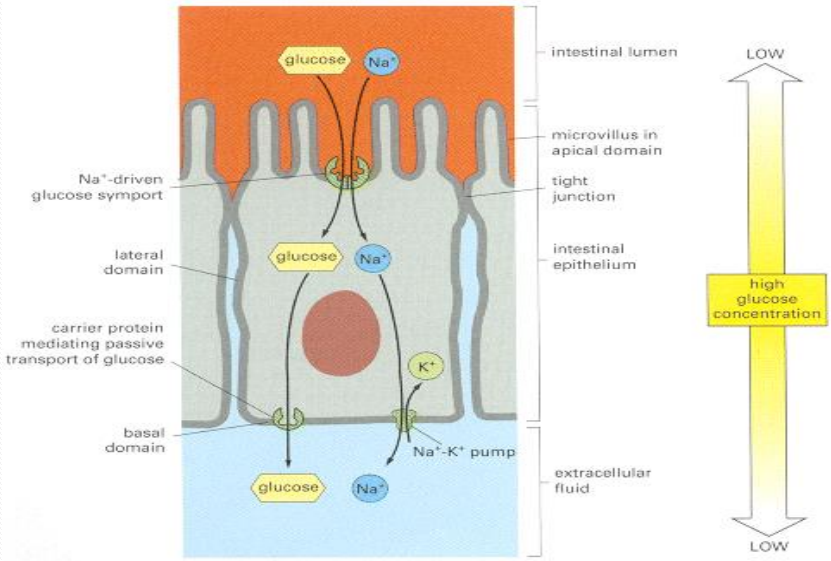
Glucose/Na symport in intestine

The Na^+/glucose transporter.

- This transmembrane protein allows sodium ions and glucose to enter the cell together. The sodium ions flow **down** their concentration gradient while the glucose molecules are pumped **up** theirs. Later the sodium is pumped back out of the cell by the Na^+/K^+ ATPase.



Glucose transport from intestinal lumen



Active transport

Definition

- Active Transport uses ATP to pump molecules AGAINST/UP the concentration gradient.
- Transport occurs from a low concentration of solute to high concentration of solute. Requires cellular energy.

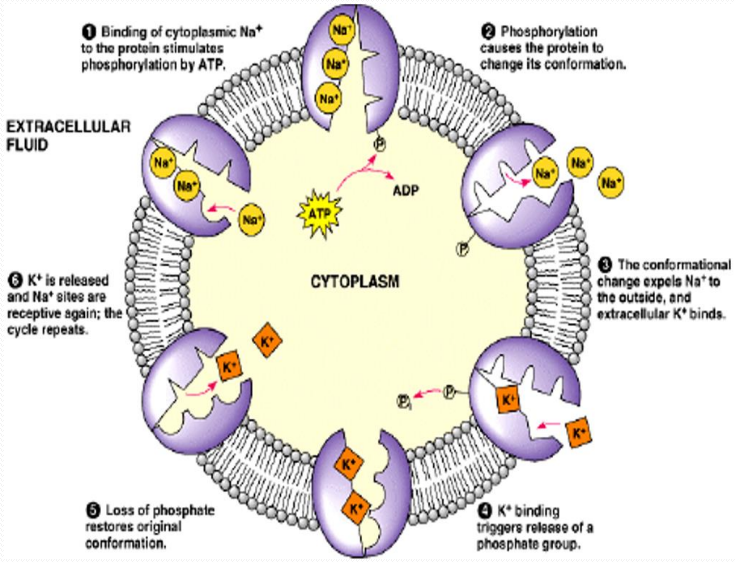
Types of Active Transport

- Endocytosis, cell membrane/sodium-potassium pump & exocytosis

Functions

- Transports molecules through the cell membrane against the concentration gradient so more of the substance is inside the cell (i.e. a nutrient) or outside the cell (i.e. a waste) than normal. Disrupts equilibrium established by diffusion.

Active transport



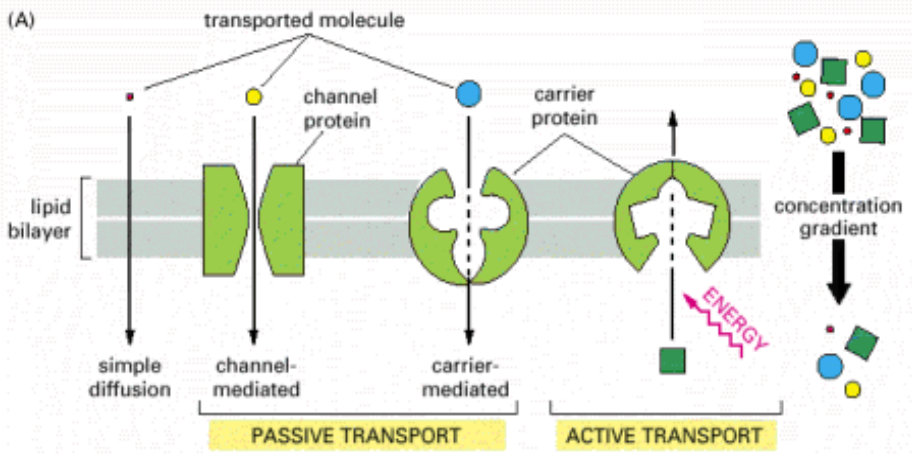
Active Transport

- Special transport proteins, **electrogenic pumps,** generate the voltage gradient across a membrane.
- The sodium-potassium pump in animals restores the electrochemical gradient not only by the active transport of Na^+ and K^+, setting up a concentration gradient, but because it pumps two K^+ inside for every three Na^+ that it moves out, setting up a voltage across the membrane.
- The sodium-potassium pump is the major electrogenic pump of animal cells.

Active vs. passive transport

Active Transport	Passive Transport
Definition Active Transport uses ATP to pump molecules AGAINST/UP the concentration gradient. Transport occurs from a low concentration of solute to high concentration of solute. Requires cellular energy.	Movement of molecules DOWN the concentration gradient. It goes from high to low concentration, in order to maintain equilibrium in the cells. Does not require cellular energy.
Types of Transport Endocytosis, cell membrane/sodium-potassium pump & exocytosis	Diffusion, facilitated diffusion, and osmosis.
Functions Transports molecules through the cell membrane against the concentration gradient so more of the substance is inside the cell (i.e. a nutrient) or outside the cell (i.e. a waste) than normal. Disrupts equilibrium established by diffusion.	Maintains dynamic equilibrium of water, gases, nutrients, wastes, etc. between cells and extracellular fluid; allows for small nutrients and gases to enter/exit. No NET diffusion/osmosis after equilibrium is established.
Types of Particles Transported proteins, ions, large cells, complex sugars.	Anything soluble (meaning able to dissolve) in lipids, small monosaccharides, water, oxygen, carbon dioxide, sex hormones, etc.
Examples phagocytosis, pinocytosis, sodium/potassium pump, secretion of a substance into the bloodstream (process is opposite of phagocytosis & pinocytosis)	diffusion, osmosis, and facilitated diffusion.
Importance In eukaryotic cells, amino acids, sugars and lipids need to enter the cell by protein pumps, which require active transport. These items either cannot diffuse or diffuse too slowly for survival.	It maintains equilibrium in the cell. Wastes (carbon dioxide, water, etc.) diffuse out and are excreted; nutrients and oxygen diffuse in to be used by the cell.

Comparison of different transport mechanism



Kinetic properties of Passive transport

- Glucose transporters (GLUT 1 to5),
- $C1^-$, HCO_3 exchanger (anion exchanger protein) in erythrocyte membrane

Kinetic properties of active transport

Primary ATPases (Primary active transporters):

- P transporters (e.g. Na^+, K^+, ATPase)
- ATP binding cassettes (ABC transports)
- (e.g. cystic fibrosis transmembrane conductance regulator-chloride transport). Multidrug resistance protein transporter. V transporters, F transporters.

Secondary active transporters (e.g. Na^+ -dependent transport of glucose and amino acids).

- To be covered under intestinal brush border

Two Types of Active Transport

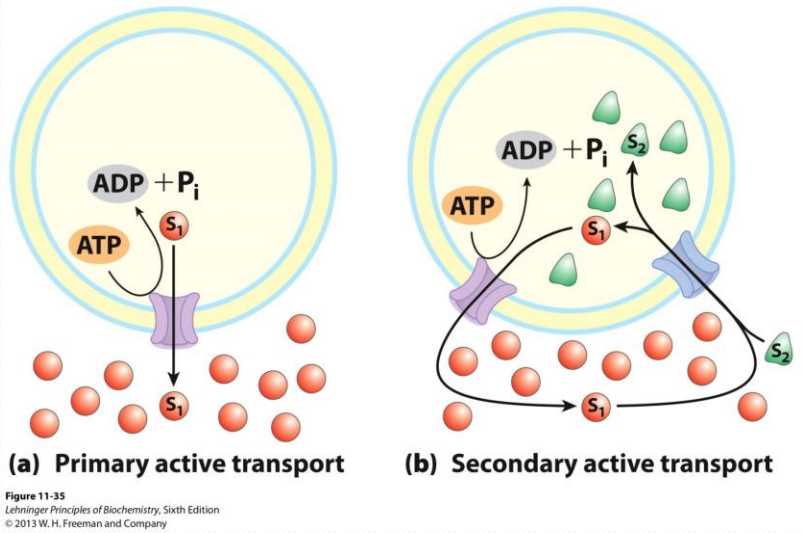


Figure 11-35
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Transport of large molecules (Macromolecules)

- There are three types of transport of large molecules:
  1- Exocytosis,
- 2- Endocytosis-pinocytosis and phagocytosis
- Types of pinocytosis:
- Absorptive pinocytosis, characteristics and examples.
- Fluid phase pinocytosis, characteristics and examples

Exocytosis

- Most cells release macromolecules to the exterior by exocytosis.
- This process is also involved in membrane remodeling, when the components synthesized in the Golgi apparatus are carried in vesicles to the plasma membrane.
- The signal for exocytosis is often a hormone which, when it binds to a cell-surface receptor, induces a local and transient change in Ca^{2+} concentration. Ca^{2+} triggers exocytosis.

Endocytosis

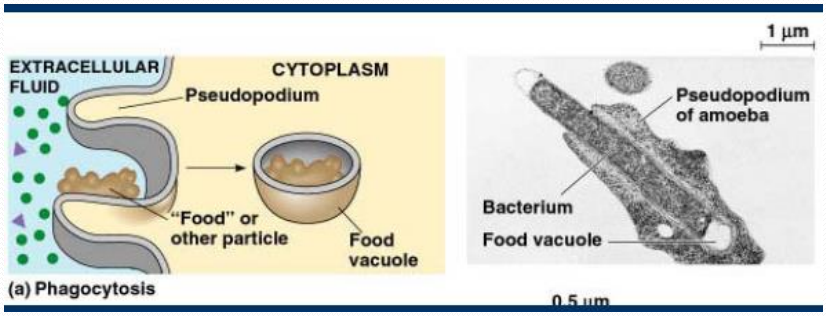
Endocytosis is the process by which cell takes in macromolecules and particulate matter by forming new vesicles from the plasma membrane.

There are 3 types of endocytosis:

a- phagocytosis = cellular eating
b- pinocytosis = cellular drinking
c- receptor-mediated endocytosis

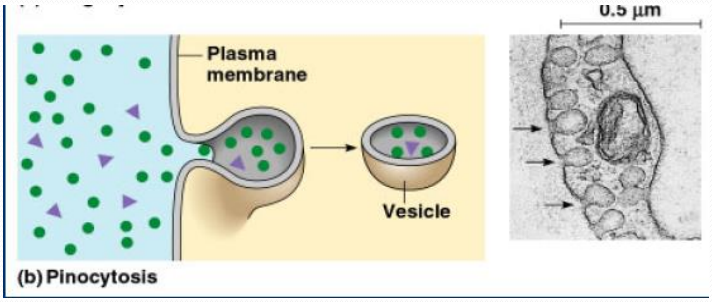
a- Phagocytosis

- It occurs only in specialized cells such as macrophages and granulocytes.
- Phagocytosis involves the ingestion of large particles such as viruses, bacteria, cells, or debris.



b- Pinocytosis

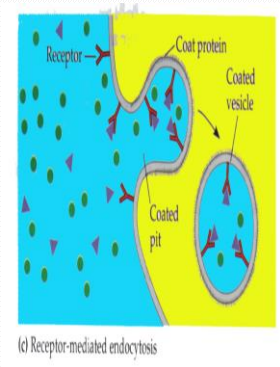
- Pinocytosis is a property of all cells and leads to the cellular uptake of fluid and fluid contents.



c- Receptor mediated endocytosis

- It is primarily responsible for the uptake of macromolecules for which there are a finite number of binding sites on the plasma membrane.

These high-affinity receptors permit the selective concentration of ligands from the medium, minimize the uptake of fluid or soluble unbound macromolecules, and markedly increase the rate at which specific molecules enter the cell.



c- Receptor mediated endocytosis (cont.)

- Human cells use this process to take in cholesterol for use in the synthesis of membranes and as a precursor for the synthesis of steroids.
- Cholesterol travels in the blood in low-density lipoproteins (LDL), complexes of protein and lipid.
- These lipoproteins act as ligands to bind to LDL receptors and enter the cell by endocytosis.
- In an inherited disease called familial hypercholesterolemia, the LDL receptors are defective, leading to an accumulation of LDL and cholesterol in the blood.
- This contributes to early atherosclerosis.

Comparison of simple endocytosis and receptor mediated endocytosis

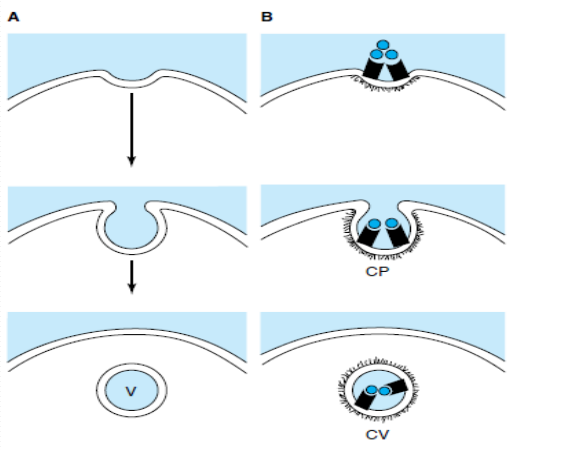


TABLE 15–3 SOME TYPICAL SIGNAL SEQUENCES

Function of Signal	Example of Signal Sequence
Import into ER	$^{+}H_3N$-Met-Met-Ser-Phe-Val-Ser-Leu-Leu-Leu-Val-Gly-Ile-Leu-Phe-Trp-Ala-Thr-Glu-Ala-Glu-Gln-Leu-Thr-Lys-Cys-Glu-Val-Phe-Gln-
Retention in lumen of ER	-Lys-Asp-Glu-Leu-COO^{-}
Import into mitochondria	$^{+}H_3N$-Met-Leu-Ser-Leu-Arg-Gln-Ser-Ile-Arg-Phe-Phe-Lys-Pro-Ala-Thr-Arg-Thr-Leu-Cys-Ser-Ser-Arg-Tyr-Leu-Leu-
Import into nucleus	-Pro-Pro-Lys-Lys-Lys-Arg-Lys-Val-
Export from nucleus	-Met-Glu-Glu-Leu-Ser-Gln-Ala-Leu-Ala-Ser-Ser-Phe-
Import into peroxisomes	-Ser-Lys-Leu-

Positively charged amino acids are shown in *red* and negatively charged amino acids in *blue*. Important hydrophobic amino acids are shown in *green*. $^{+}H_3N$ indicates the N-terminus of a protein; COO^{-} indicates the C-terminus.