Biological Membrane & Transport

Table of contents

Membrane (boundary)

- Flexible
- Self-sealing
- Selectively permeable
- Two-dimensional

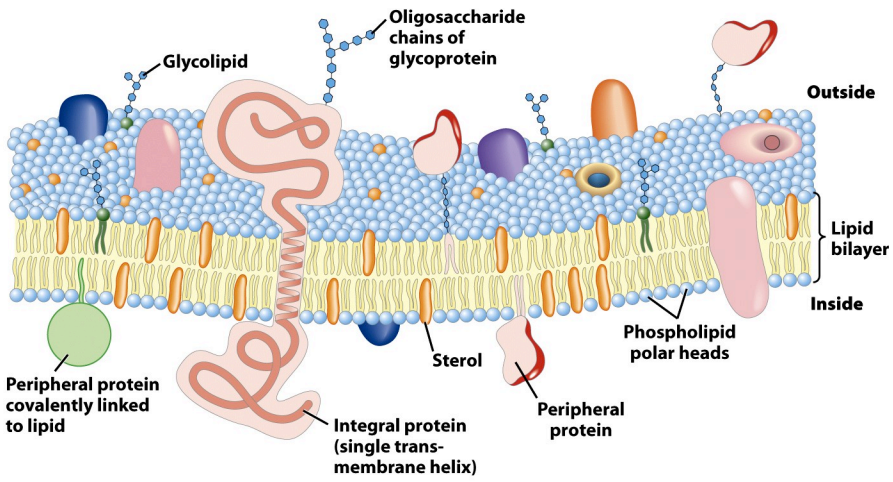

Figure 11-3
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Membrane components:
proteins, polar lipids and carbohydrates

Ratio of protein/lipids: depends on type & role of membrane

TABLE 11–1 Major Components of Plasma Membranes in Various Organisms

	Components (% by weight)				
	Protein	Phospholipid	Sterol	Sterol type	Other lipids
Human myelin sheath	30	30	19	Cholesterol	Galactolipids, plasmalogens
Mouse liver	45	27	25	Cholesterol	—
Maize leaf	47	26	7	Sitosterol	Galactolipids
Yeast	52	7	4	Ergosterol	Triacylglycerols, steryl esters
Paramecium (ciliated protist)	56	40	4	Stigmasterol	—
E. coli	75	25	0	—	—

Note: Values do not add up to 100% in every case, because there are components other than protein, phospholipids, and sterol; plants, for example, have high levels of glycolipids.

Table 11-1
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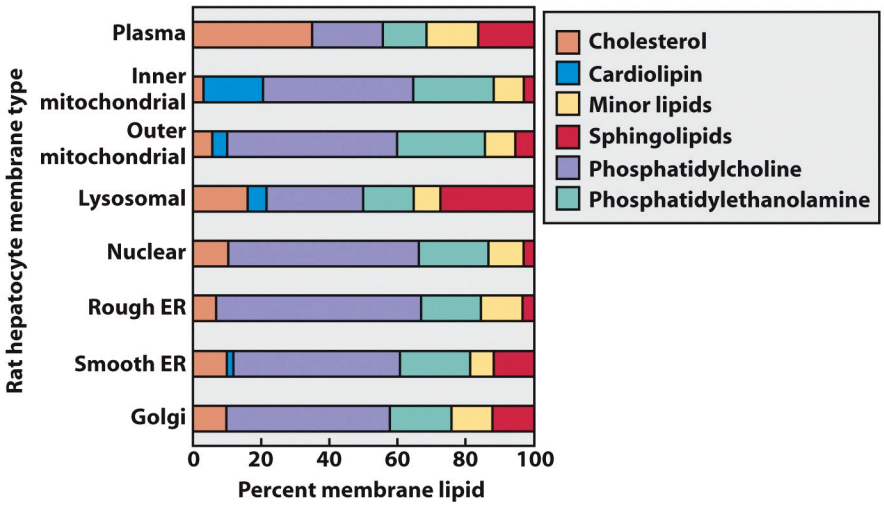

Figure 11-2
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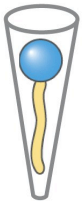
Supramolecular Architecture of Membranes

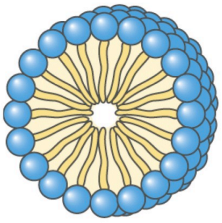
Common properties:

- **Impermeable**
- **5 to 8 nm thick**
- **Trilaminar**
- **Asymmetric (structural & functional)**
- **Fluid**
- **Able to undergo fusion**

Lipid aggregates: depending on the size of head & tail



Individual units are wedge-shaped (cross section of head greater than that of side chain)



Micelle

Figure 11-4a
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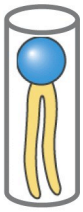
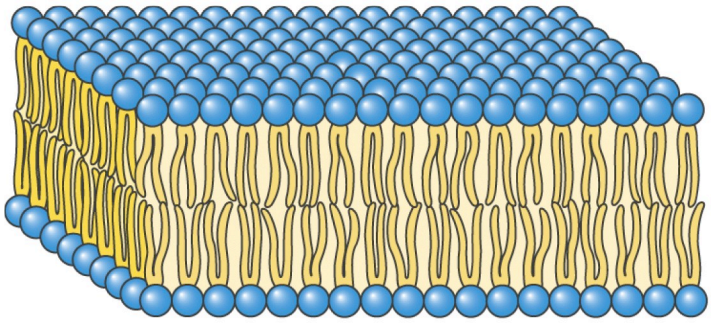


Individual units are cylindrical (cross section of head equals that of side chain)



Bilayer

Figure 11-4b
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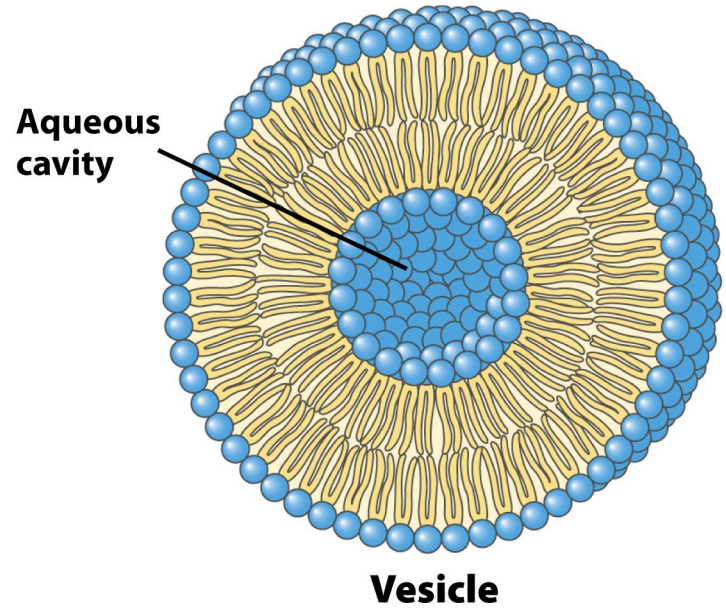

Figure 11-4c
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Asymmetric Distribution of Phospholipids on Membrane

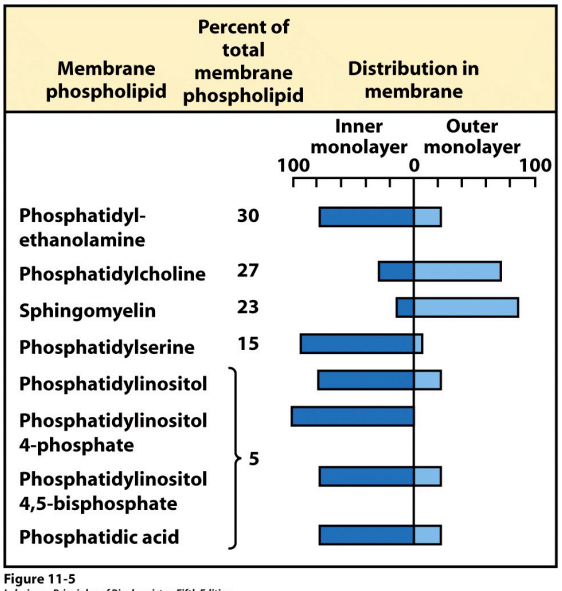

Figure 11-5
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Membrane Motion

Conformational motion

Paracrystalline, transition temperature
Sterols moderate extremes of fluidity & solidity

Lateral diffusion

High degree of regularity in one dimension &
Great mobility in the other

Flip-flop diffusion

Transbilayer diffusion
flippases

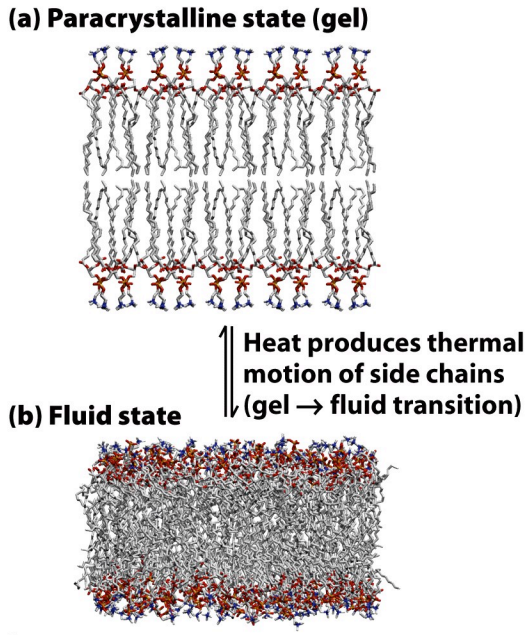

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TABLE 11–2 Fatty Acid Composition of *E. coli* Cells Cultured at Different Temperatures

	Percentage of total fatty acids*			
	10 °C	20 °C	30 °C	40 °C
Myristic acid (14:0)	4	4	4	8
Palmitic acid (16:0)	18	25	29	48
Palmitoleic acid (16:1)	26	24	23	9
Oleic acid (18:1)	38	34	30	12
Hydroxymyristic acid	13	10	10	8
Ratio of unsaturated to saturated†	2.9	2.0	1.6	0.38

Source: Data from Marr, A.G. & Ingraham, J.L. (1962) Effect of temperature on the composition of fatty acids in *Escherichia coli*. *J. Bacteriol.* **84**, 1260.

*The exact fatty acid composition depends not only on growth temperature but on growth stage and growth medium composition.

†Ratios calculated as the total percentage of 16:1 plus 18:1 divided by the total percentage of 14:0 plus 16:0. Hydroxymyristic acid was omitted from this calculation.

Table 11-2
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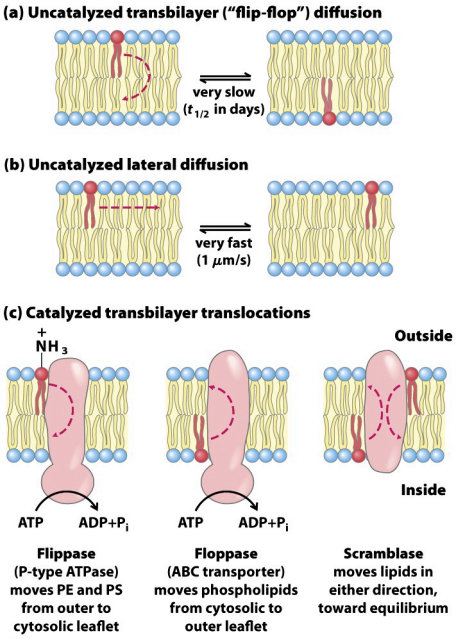

Figure 11-16
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Uncatalyzed transbilayer ("flip-flop") diffusion

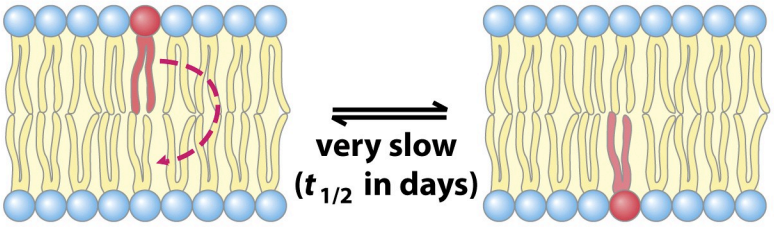

Figure 11-16a
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Uncatalyzed lateral diffusion

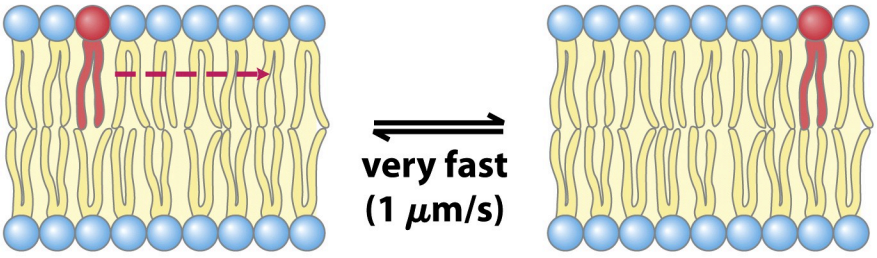

Figure 11-16b
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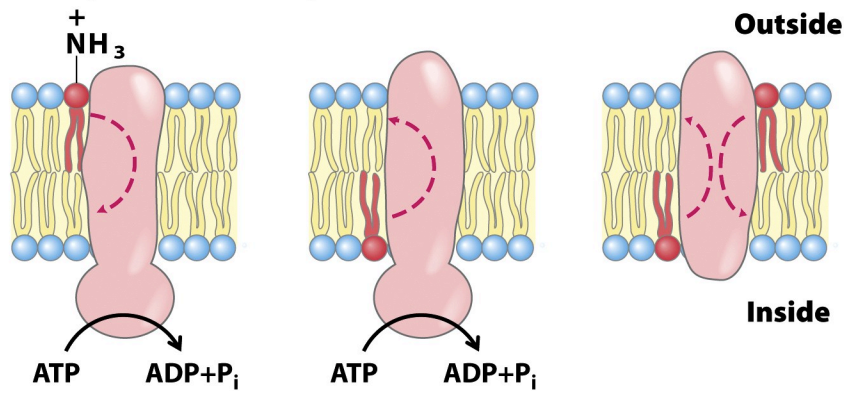

Figure 11-16c
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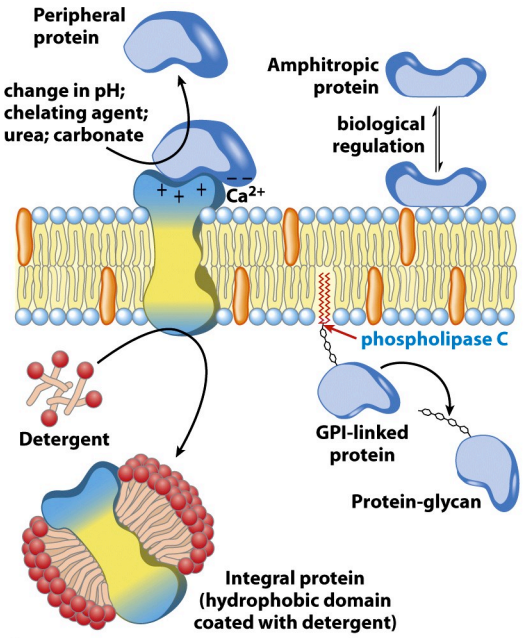
Membrane proteins

Integral (intrinsic) proteins:

Firmly associated, removable only by agents that interfere with hydrophobic interactions such as detergents, organic solvents or denaturants.

Peripheral (extrinsic) proteins

Associated through electrostatic interactions & hydrogen bonding with the hydrophilic domains of integral proteins and with the polar head groups of membrane lipids, readily removable by mild treatments



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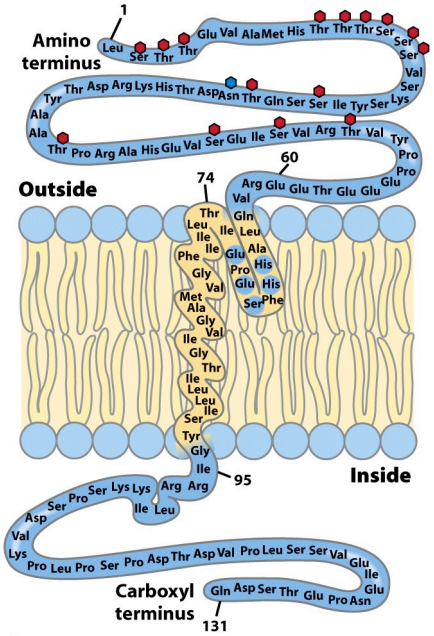

Figure 11-7
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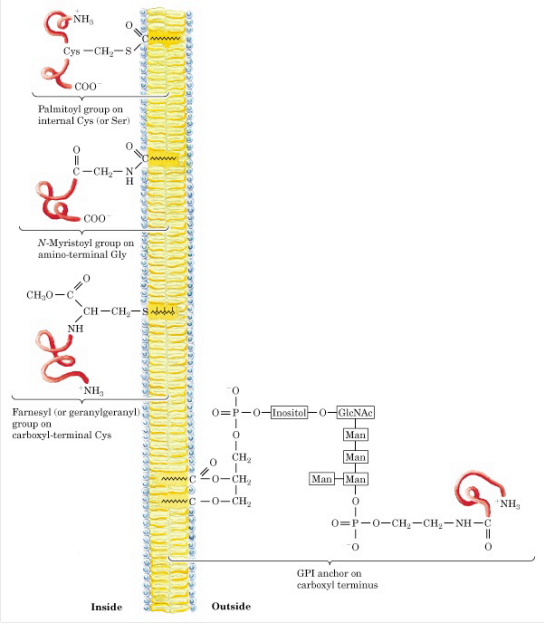
Peripheral proteins anchored by covalently attached lipids

Lipids with long-chain fatty acids, isoprenoids, or glycosylated derivatives of phosphatidylinositol (GPI)

Proteins with GPI anchors are exclusively on the outer face (extracellular), whereas other types of lipid-linked proteins are found exclusively on the inner face (cytosolic)



Integral proteins

Integral proteins are held in the membrane by hydrophobic interactions with lipids, i.e., firmly fixed by interaction between membrane lipids and hydrophobic domain of proteins.

According to the spatial relationship of protein domains to the lipid bilayer, plasma membrane proteins fall into six categories.

Types I & II have only one transmembrane helix, the amino terminal domain is outside the cell in type I proteins and inside in type II.

Type III proteins have multiple transmembrane helices in a single polypeptide.

Type IV proteins have several transmembrane domains from different polypeptide chains to form a channel through the membrane

Type V proteins are held to the bilayer primarily by covalently linked lipid

Type VI proteins have both transmembrane helices and lipid (GPI) anchors.

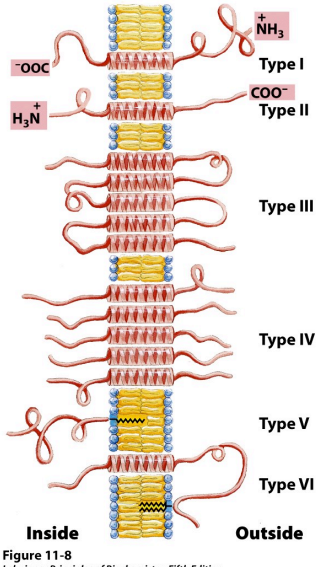


Figure 11-8
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Topology of an integral protein

Table 5–1

Properties and Conventions Associated with the Standard Amino Acids

Amino acid	Abbreviated names		M_r	pK_0 values: pK_1 (—COOH)	pK_2 ($—NH_3^+$)	pK_R (R group)	pI	Hydropathy index*	Occurrence in proteins (%)†
Nonpolar, aliphatic R groups									
Glycine	Gly	G	75	2.34	9.60		5.97	−0.4	7.2
Alanine	Ala	A	89	2.34	9.69		6.01	1.8	7.8
Valine	Val	V	117	2.32	9.62		5.97	4.2	6.6
Leucine	Leu	L	131	2.36	9.60		5.98	3.8	9.1
Isoleucine	Ile	I	131	2.36	9.68		6.02	4.5	5.3
Methionine	Met	M	149	2.28	9.21		5.74	1.9	2.3
Aromatic R groups									
Phenylalanine	Phe	F	165	1.83	9.13		5.48	2.8	3.9
Tyrosine	Tyr	Y	181	2.20	9.11	10.07	5.66	−1.3	3.2
Tryptophan	Trp	W	204	2.38	9.39		5.89	−0.9	1.4
Polar, uncharged R groups									
Serine	Ser	S	105	2.21	9.15		5.68	−0.8	6.8
Proline	Pro	P	115	1.99	10.96		6.48	1.6	5.2
Threonine	Thr	T	119	2.11	9.62		5.87	−0.7	5.9
Cysteine	Cys	C	121	1.96	10.28	8.18	5.07	2.5	1.9
Asparagine	Asn	N	132	2.02	8.80		5.41	−3.5	4.3
Glutamine	Gln	Q	146	2.17	9.13		5.65	−3.5	4.2
Positively charged R groups									
Lysine	Lys	K	146	2.18	8.95	10.53	9.74	−3.9	5.9
Histidine	His	H	155	1.82	9.17	6.00	7.59	−3.2	2.3
Arginine	Arg	R	174	2.17	9.04	12.48	10.76	−4.5	5.1
Negatively charged R groups									
Aspartate	Asp	D	133	1.88	9.60	3.65	2.77	−3.5	5.3
Glutamate	Glu	E	147	2.19	9.67	4.25	3.22	−3.5	6.3

*A scale combining hydrophobicity and hydrophilicity of R groups; it can be used to measure the tendency of an amino acid to seek an aqueous environment (− values) or a hydrophobic environment (+ values). See Chapter 12. From Kyte, J. & Doolittle, R.F. (1982) *J. Mol. Biol.* **157,** 105–132.

†Average occurrence in over 1150 proteins. From Doolittle, R.F. (1989) Redundancies in protein sequences. In *Prediction of Protein Structure and the Principles of Protein Conformation* (Fasman, G.D., ed) Plenum Press, NY, pp. 599–623.

Hydropathy Plots

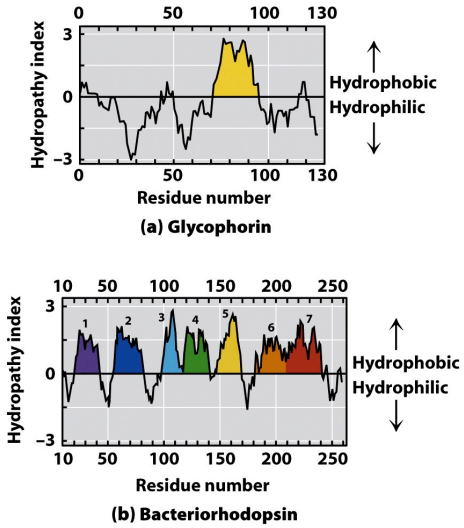

Figure 11-11
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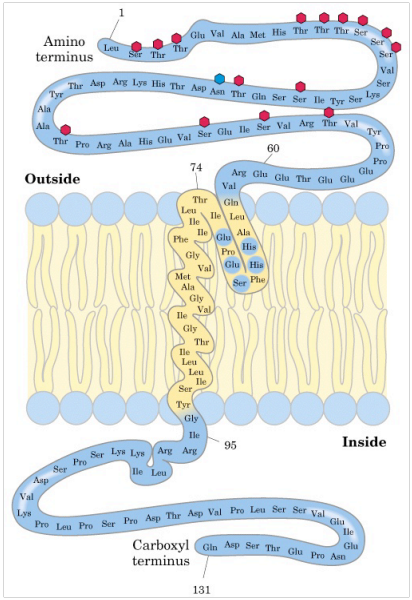
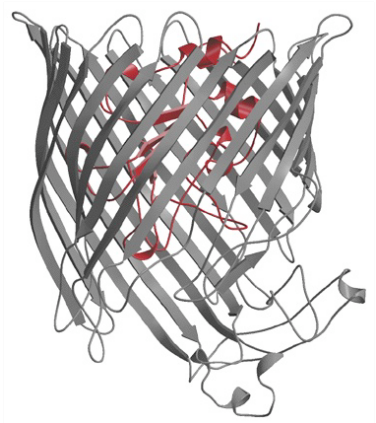
Glycophorin in the erythrocyte



For type III or IV proteins:

- α-helical sequence of 20 to 25 amino acid residues
- β-sheet sequence of 7 to 9 amino acid residues
- α-helical: average 3.6 amino acids for 0.54 nm
- β-sheet: average 2 amino acids for 0.65 to 0.7 nm



Porin FhuA, with 22 antiparallel β strands forming channel for iron ion bound to the carrier ferrichrome

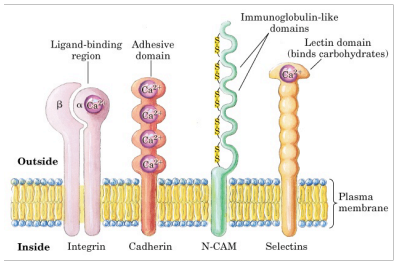
Cell-cell interaction & adhesion

Integrins: heterodimeric, for binding collagen & fibronectin receptors & signal transducers, and regulate platelet aggregation at the site of a wound, tissue repair, activity of immune cells, and the invasion of tissue by a tumor

Cadherins for homophilic interaction

Immunoglobulin-like protein for both homophilic & heterophilic interaction

Selectins for binding polysaccharides.



Membrane fusion

Specific fusion of two membranes requires:

a) They recognize each other
b) Their surfaces become closely apposed, which requires the removal of water molecules normally associated with the polar head groups of lipids
c) Their bilayer structures become locally disrupted
d) The two bilayers fuse to form a single continuous bilayer
e) The fusion process is triggered at the appropriate time or in response to a specific signal

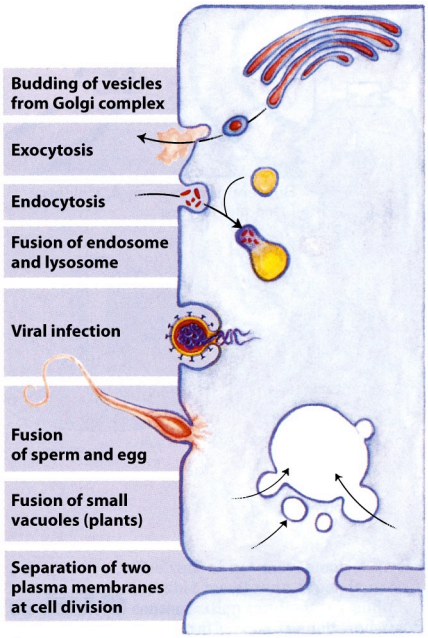


Figure 11-22
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Solute Transport across Membranes

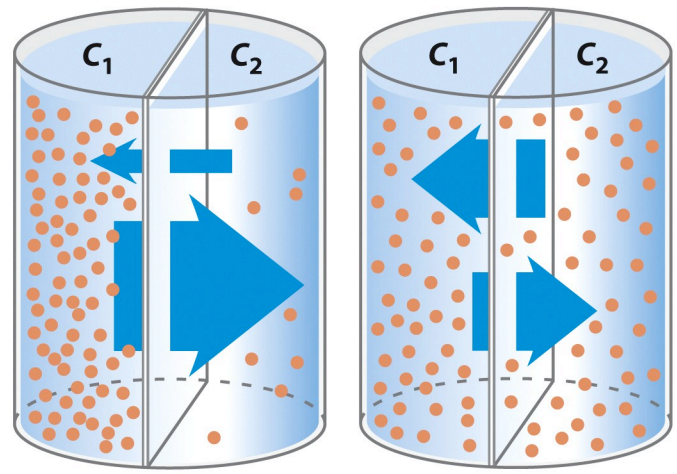
Solute mediated by transmembrane channels, carriers or pumps

Passive transport & active transport

Passive Transport

Membrane potential (V_m) & electric gradient

Electrochemical gradient or electrochemical potential



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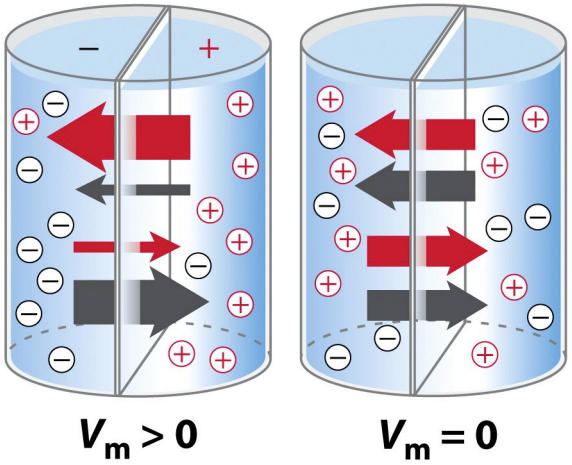

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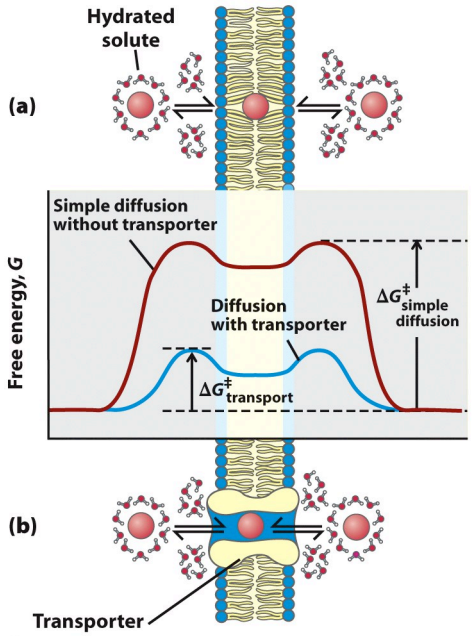
Membrane: selectively permeable

The energy of activation for translocation of a polar solute across the bilayer is so large that pure lipid bilayers are virtually impermeable to polar and charged species over periods of time relevant to cells.

Transmembrane passage of polar compounds and ions is made possible by membrane proteins that lower the activation energy for transport by providing an alternative path for specific solutes through the lipid bilayer.
These proteins are called transporters or permeases.

Transporters span the lipid bilayers at least once, and usually several times, forming a transmembrane channel lined with hydrophilic amino acid side chains. The channel provides an alternative path for a specific substrate to move across the lipid bilayer without its having to dissolve in the bilayer, further lowering the activation energy for transmembrane diffusion.



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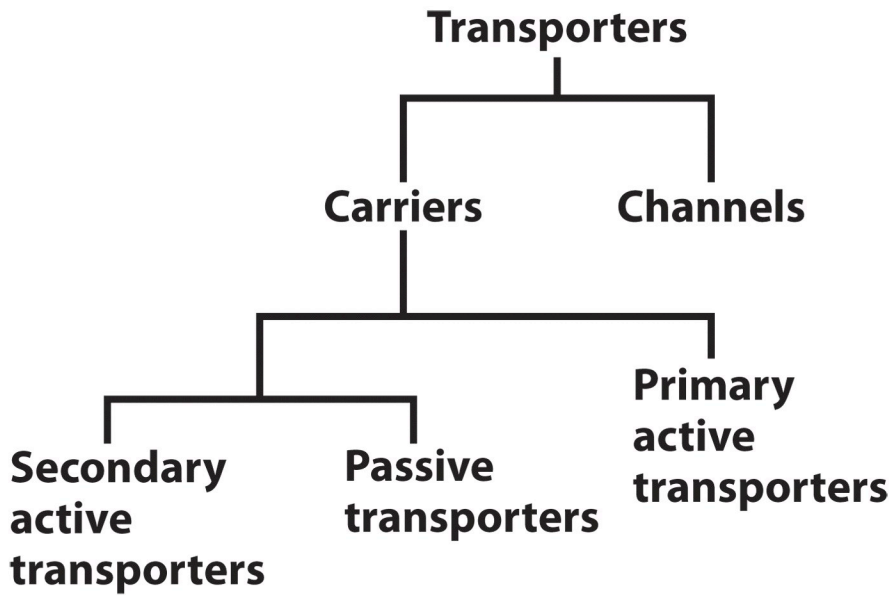

Figure 11-28
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$$S_{out} + T_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S_{out} \bullet T_1$$

$$k_{-4} \downarrow\uparrow k_4 \qquad\qquad k_{-2} \uparrow\downarrow k_2$$

$$S_{in} + T_2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} S_{in} \bullet T_2$$

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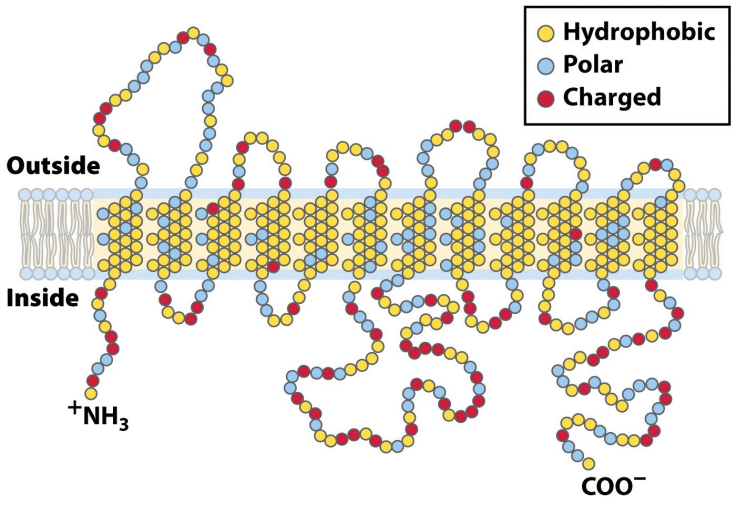
Erythrocyte's Glucose Transporter

Type III integral protein with MW of 45,000 and 12 hydrophobic segments, each of which form a membrane-spanning helix



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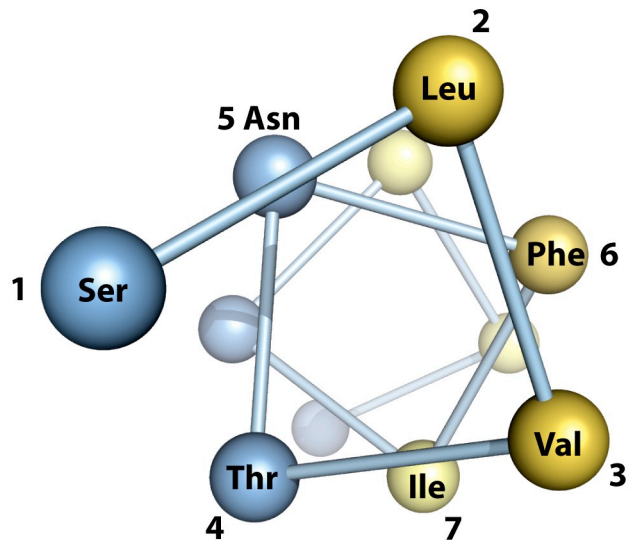

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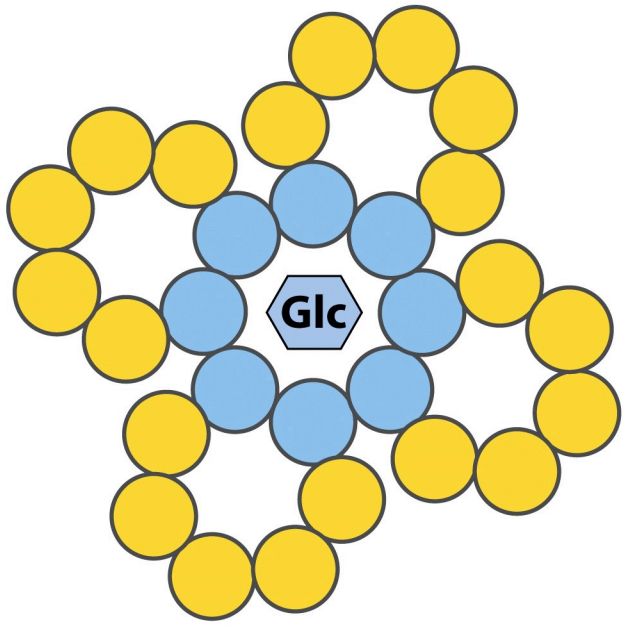

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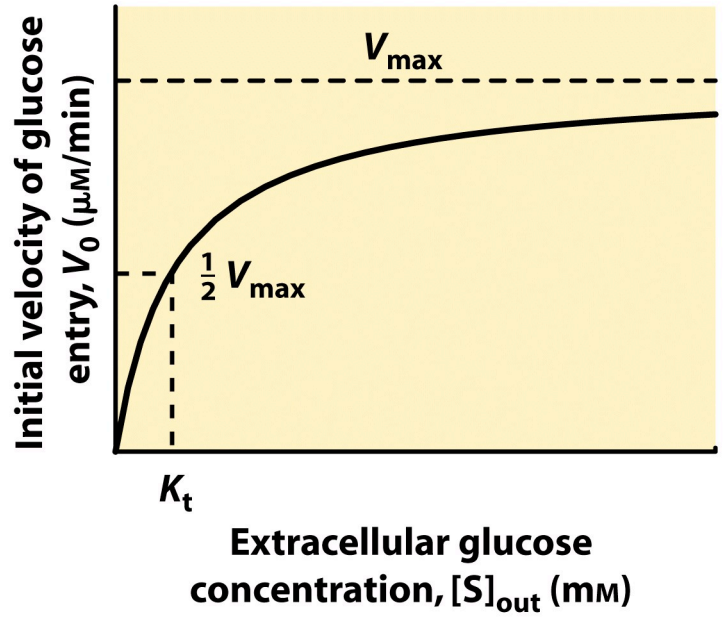

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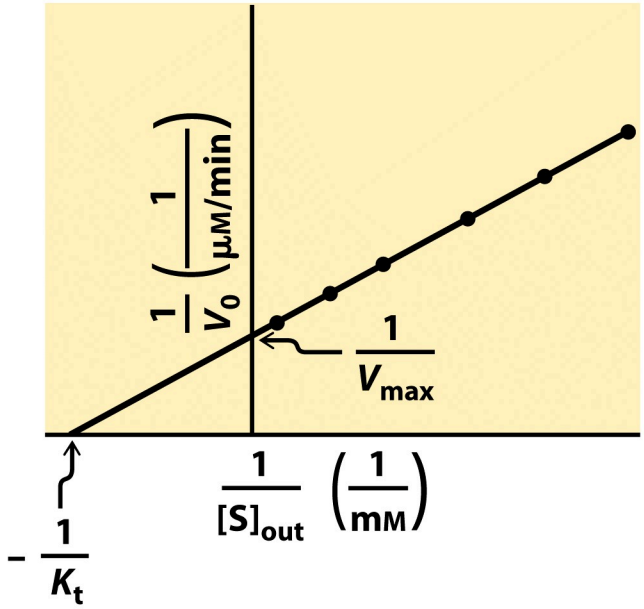

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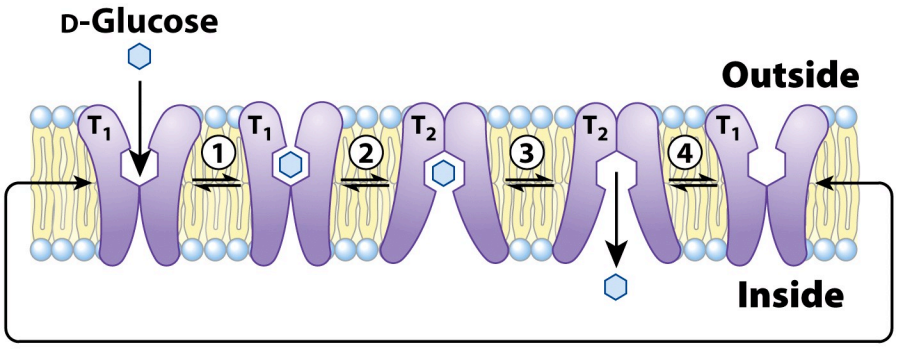

Figure 11-31
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Hallmarks of passive transport

High rates of diffusion down a concentration gradient

Saturability

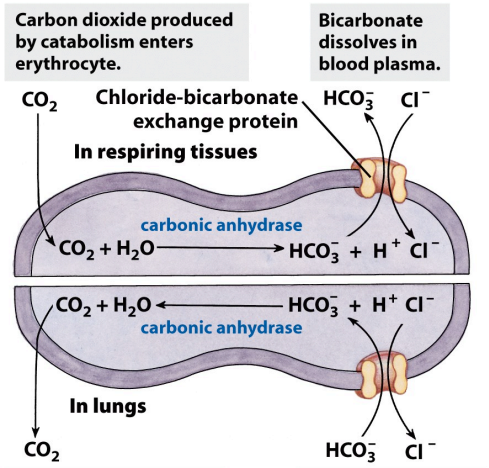
Specificity

chloride-bicarbonate exchanger

Anion exchange protein

Obligatorily transport one bicarbonate and one chloride

Cotransport systems: simultaneously carry two solutes across a membrane



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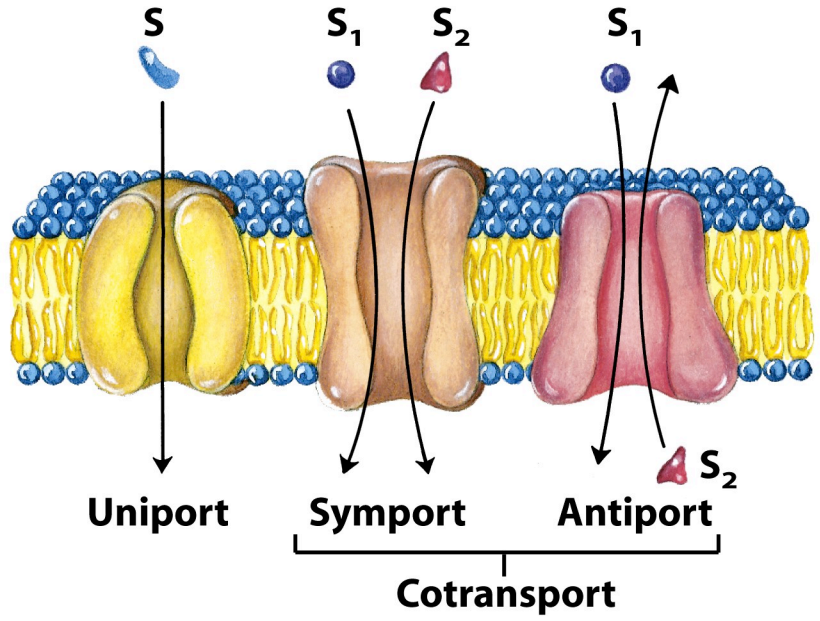

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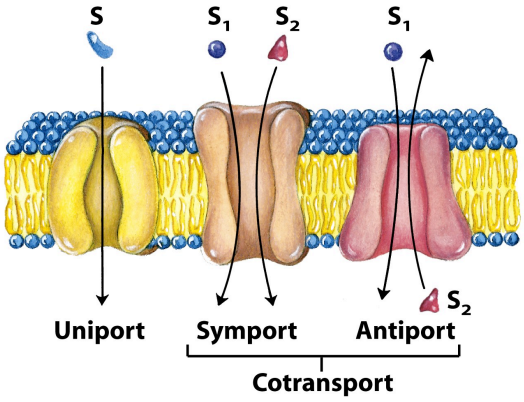
Antiport systems: transporters that carry two substrates moving in opposite directions

Symport systems: transporters that carry two substrates moving simultaneously in the same direction.

Uniport systems: transporters that carry only one substrate



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Active transport

Active transport results in solute movement against a concentration or electrochemical gradient, thus it is thermodynamically unfavorable or endergonic process, and must be coupled with other energy releasing processes.

Primary active transport (coupled with energy)

Secondary active transport (coupled with concentration flow)

(Major energy-consuming process)

Four types of transporters

Different in structure, mechanism, localization in specific tissues and intracelluar compartments

table 12–4

Four Classes of Transport ATPases

	Organism or tissue	Type of membrane	Role of ATPase
P-type ATPases			
Na^+K^+	Animal tissues	Plasma	Maintains low $[Na^+]$, high $[K^+]$ inside cell; creates transmembrane electrical potential
H^+K^+	Acid-secreting (parietal) cells of mammals	Plasma	Acidifies contents of stomach
H^+	Fungi *(Neurospora)*	Plasma	Create H^+ gradient to drive secondary transport of extracellular solutes into cell
H^+	Higher plants	Plasma	
Ca^{2+}	Animal tissues	Plasma	Maintains low $[Ca^{2+}]$ in cytosol
Ca^{2+}	Myocytes of animals	Sarcoplasmic reticulum (endoplasmic reticulum)	Sequesters intracellular Ca^{2+}, keeping cytosolic $[Ca^{2+}]$ low
Cd^{2+}, Hg^{2+}, Cu^{2+}	Bacteria	Plasma	Pumps heavy metal ions out of cell
V-type ATPases			
H^+	Animals	Lysosomal, endosomal, secretory vesicles	Create low pH in compartment, activating proteases and other hydrolytic enzymes
H^+	Higher plants	Vacuolar	
H^+	Fungi	Vacuolar	
F-type ATPases			
H^+	Eukaryotes	Inner mitochondrial	Catalyze formation of ATP from ADP + P_i
H^+	Higher plants	Thylakoid	
H^+	Prokaryotes	Plasma	
Multidrug transporter			
	Animal tumor cells	Plasma	Removes a wide variety of hydrophobic natural products and synthetic drugs from cytosol, including vinblastine, doxorubicin, actinomycin D, mitomycin, taxol, colchicine, and puromycin

1. P-type ATPase: ATP driven cation transporters, reversibly phosphorylated by ATP during the transport cycle, with similar amino acid sequence, can be inhibited by phosphate analog vanadate. Generally have two types of integral protein subunits. The α-subunit is essential, has Asp residue phosphorylated during transport.
2. V-type ATPase: responsible for acidifying intracelluar compartments in many organisms via proton-transporting, also called proton pump. To acidify the vacuoles of fungi and higher plants, as well as lysosomes, endosomes, the Golgi complex, and secretory vesicles in animal cells. All have an integral (transmembrane) domain as proton channel and a peripheral domain containing the ATP-binding site and the ATPase activity.

3. F-type ATPase: central role in energy-conserving reactions in bacteria, mitochondria and chloroplasts. Catalyzes the uphill trans-membrane passage of protons driven by ATP hydrolysis, as well as the reverse reaction, in which downhill proton flow drives ATP synthesis. (ATP synthases).
4. Multidrug transporter: responsible for removing different drugs from tumor cell cytosol, preventing their growth-inhibitory effect.

Na^+K^+ ATPase

P-type ATPase that cotransport Na^+ and K^+

Na^+: lower in the cell than in the surrounding medium

K^+: higher in the cell than in the surrounding medium

$$ATP + Enz_I \longrightarrow ADP + P{-}Enz_{II}$$

$$H_2O + P{-}Enz_{II} \longrightarrow Enz_I + Pi$$

$$ATP + H_2O \longrightarrow ADP + Pi$$

transmembrane potential of -50 to -70 mV

Na^+K^+ ATPase

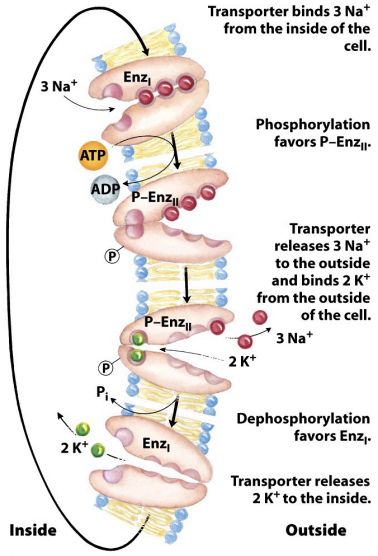

Figure 11-37
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TABLE 11–4 Cotransport Systems Driven by Gradients of Na^+ or H^+

Organism/ tissue/cell type	Transported solute (moving against its gradient)	Cotransported solute (moving down its gradient)	Type of transport
E. coli	Lactose	H^+	Symport
	Proline	H^+	Symport
	Dicarboxylic acids	H^+	Symport
Intestine, kidney (vertebrates)	Glucose	Na^+	Symport
	Amino acids	Na^+	Symport
Vertebrate cells (many types)	Ca^{2+}	Na^+	Antiport
Higher plants	K^+	H^+	Antiport
Fungi (*Neurospora*)	K^+	H^+	Antiport

Table 11-4
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Ion gradient for secondary active transport

Cells contain transport systems that couple the spontaneous, downhill flow of Na^+, H^+ ions to the simultaneous uphill pumping of another ion, sugar or amino acids.

For example, glucose:
Chemical potential
Electrical potential

Poison that collapses the ion gradient across cellular membrane

Ionophores, ion bearers

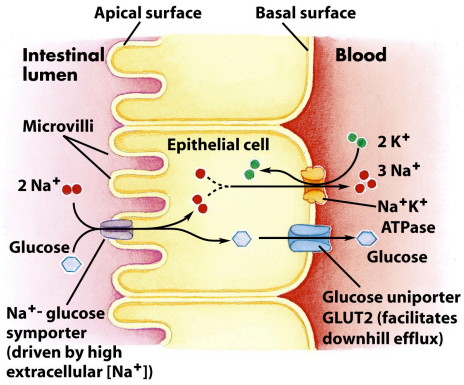

Figure 11-44
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Ion selective channels

Move inorganic ions across membrane quickly.

Determine the plasma membrane's permeability to specific ions, and together with ion pumps such as Na/K ATPase, regulate the cytosolic concentration of ions and the membrane potential.

Characters: the rate of flux through channels can be orders of magnitude greater than the turnover number for a transporter, 10^7 to 10^8 ions per channel per second.

Not saturable

"Gated", open or close in response to some cellular event

Ion channels

Ligand-gated channels: allosteric proteins change conformation when bind to some extracellular or intracellular small molecules

Acetylcholine receptor

Voltage-gated ion channels: response to a change in transmembrane electrical potential

K^+ channel

David L. Nelson and Michael M. Cox

- ***LEHNINGER***
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CHAPTER 12
Biosignaling

Biosignaling

- Signal response pathways
- Types of signals
- Biosignaling characters

Signals from receptor to cell response

Autocrine: acting on the same cell that produces the signals

Paracrine: acting on a near neighbour

Endocrine: carried in the bloodstream from the producer cell to a distant target cell.

TABLE 12–1 Some Signals to Which Cells Respond

Antigens	Light
Cell surface glycoproteins/ oligosaccharides	Mechanical touch
Developmental signals	Neurotransmitters
Extracellular matrix components	Nutrients
Growth factors	Odorants
Hormones	Pheromones
	Tastants

Table 12-1
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The end result of a signaling pathway is the phosphorylation of a few specific target-cell proteins, which changes their activities and thus the activities of the cell

Characters of signal transduction

- **Specificity: precise molecular complementarity between the signal and receptor molecules, mediated by weak forces occuring in the enzyme-substrate, protein-ligand and antigen-antibody interactions.**
- **Sensitivity**

1) **High affinity of receptors for signal molecules**
2) **Cooperativity in the ligand-receptor interaction**
3) **Amplification of the signal by enzyme cascades.**

- **Adaptation/Desensitization (saturation): When receptor is continuously stimulated by signal, the threshold would be leveled up.**
- **Integration: The ability of the system to receive multiple signals and produce a unified response appropriate to the needs of the cell or organism.**

Specificity

Signal molecule fits binding site on its complementary receptor; other signals do not fit.

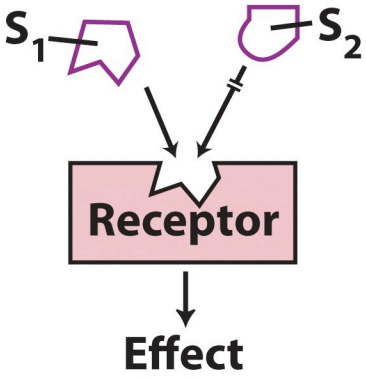

Figure 12-1a
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Amplification

When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.

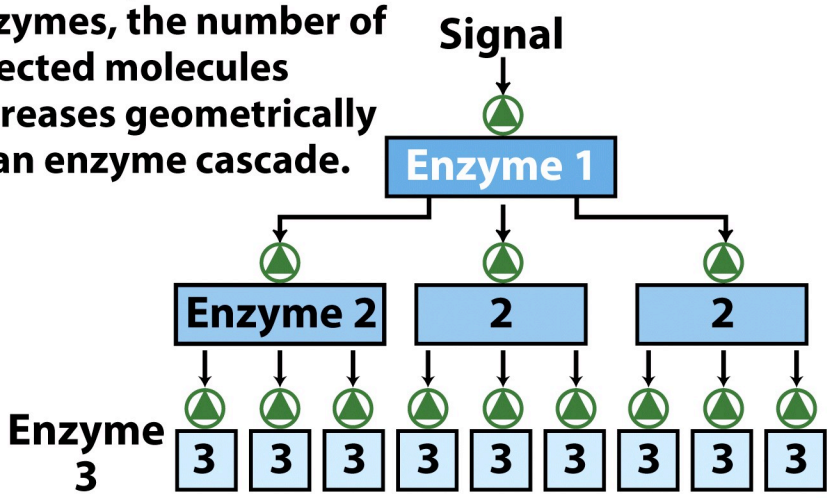

Figure 12-1b
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Desensitization/Adaptation

Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.

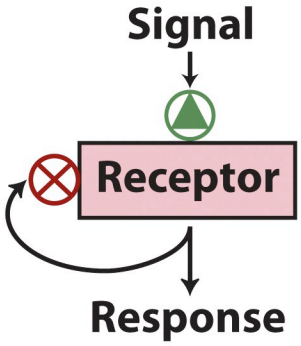

Figure 12-1c
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Integration

When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger X, or the membrane potential V_m, the regulatory outcome results from the integrated input from both receptors.

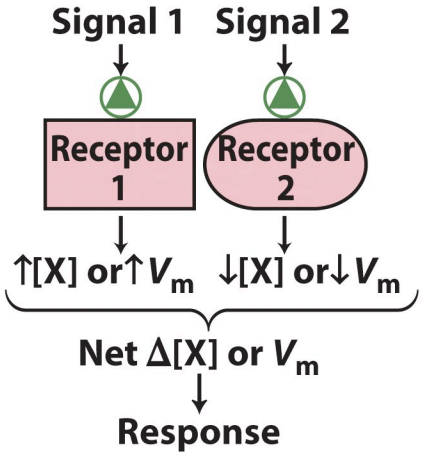

Figure 12-1d
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