Chapter 11 Biological Membrane and Transport

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What are Membranes?

- Composed of a variety of lipids and proteins
- Some membrane lipids and proteins are glycosylated
- All cells have the cell membrane, which separates the cell from its surrounding

Functions of Membranes

- Define the boundaries of the cell
- Allow import and export
  - Selective import of nutrients (e.g. lactose)
  - Selective export of waste and toxins (e.g. antibiotics)
- Retain metabolites and ions within the cell
- Sense external signals and transmit information into the cell
- Provide compartmentalization within the cell
  - separate energy-producing reactions from energy-consuming ones
  - keep proteolytic enzymes away from important cellular proteins

11.1 The Composition and Architecture of Membranes

Each Type of Membrane Has Characteristic Lipids and Proteins

- Cells clearly have mechanisms to control the kinds and amounts of membrane lipid they synthesize and to target specific lipids to particular organelles.
- Plasma membranes are enriched in cholesterol and contain no detectable cardiolipin (Fig. 11–2).

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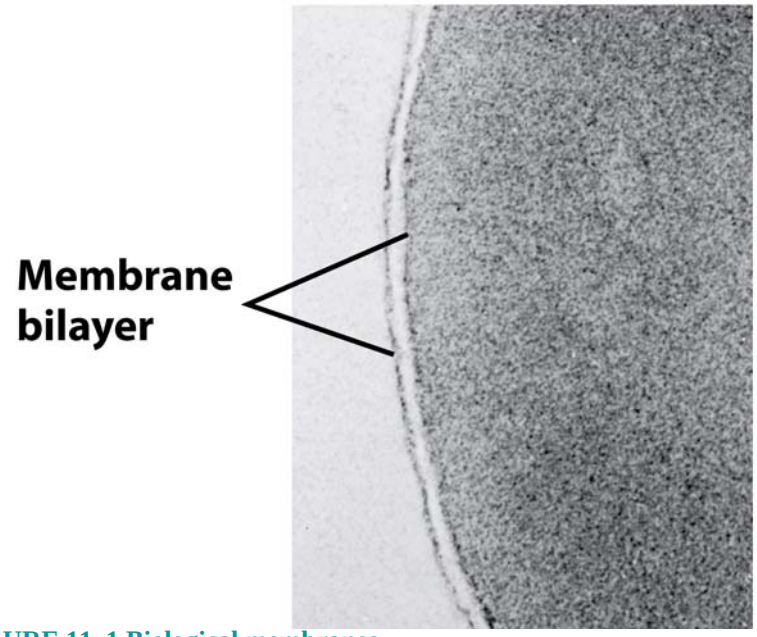

FIGURE 11–1 Biological membranes.

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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	—	—

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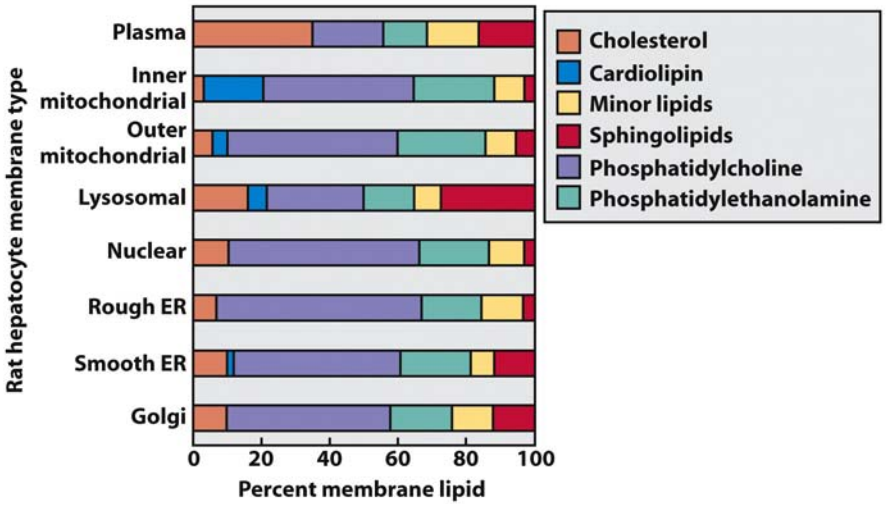

FIGURE 11–2 Lipid composition of the plasma membrane and organelle membranes of a rat hepatocyte.

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All Biological Membranes Share Some Fundamental Properties

- **Fluid mosaic model for the structure of biological membranes:**
- **Phospholipids and sterols form a bilayer in which the nonpolar regions of the lipid molecules in each layer face the core of the bilayer and their polar head groups face outward, interacting with the aqueous phase on either side.**
- **Proteins are embedded in this bilayer sheet, held by hydrophobic interactions between the membrane lipids and hydrophobic domains in the proteins.**
- **Membrane is fluid (lipid and protein molecules free to move laterally in the plane of membrane)**

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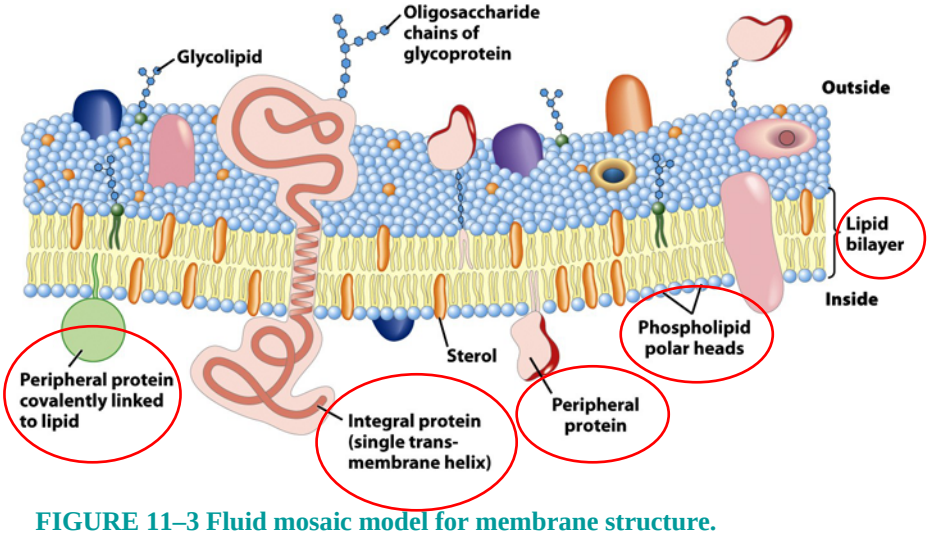

FIGURE 11–3 Fluid mosaic model for membrane structure.

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A Lipid Bilayer Is the Basic Structural Element of Membranes

Three types of lipid aggregate:

(1) Micelles:

- **Forms in the solution of amphipathic molecules that have larger head than tail**
  - **Fatty acids**
  - **Sodium dodecyl sulfate**
- **Each micelle has from a few dozen to few thousand lipid molecules**
- **Aggregation occurs when the concentration of molecules is higher than a certain threshold**

(2) Bilayer:

in which two lipid monolayers (leaflets) form a two dimensional sheet.

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(3) **Vesicle (Lyposome)**:

- **Small bilayers will spontaneously seal into spherical vesicles**
- **Vesicle membranes can contain artificially inserted proteins**
- **The central aqueous cavity can enclose dissolved molecules**
- **They are useful artificial carriers of molecules (e.g. drugs)**
- **Vesicles fuse readily with cell membranes or with each other**

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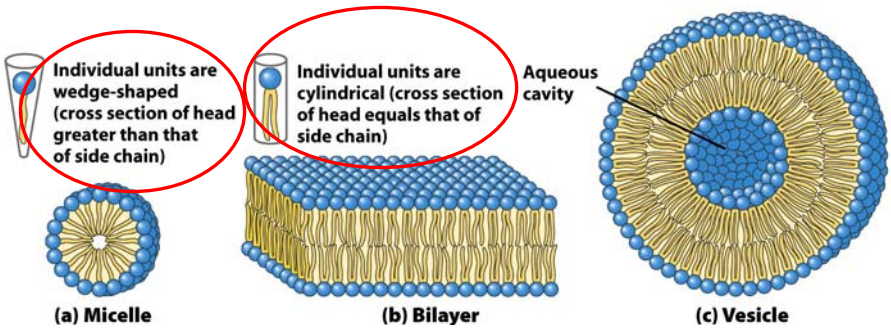

Micelles: lysophospholipids (phospholipids lacking one fatty acid), SDS

bilayer: phospholipids (glycerophospholipids and sphingolipids)

vesicle: the edge of lipid bilayer contacts with H2O

↓

unstable

↓

form vesicles

FIGURE 11–4 Amphipathic lipid aggregates that form in water.

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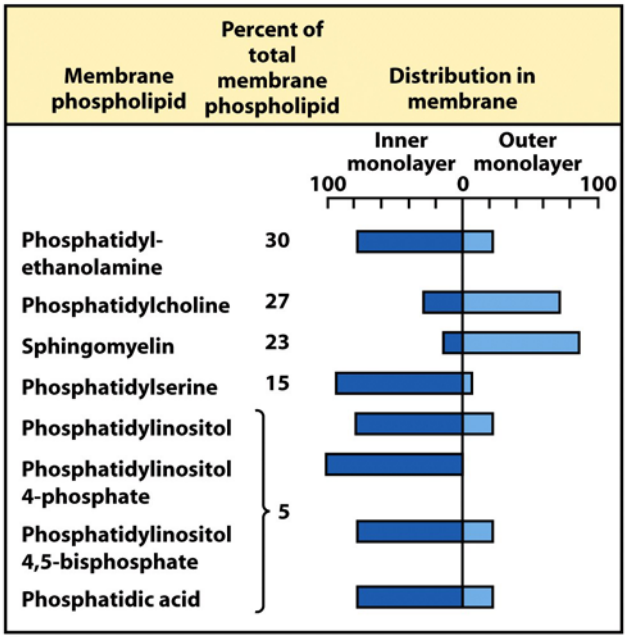
Common Features of Membranes

- Sheet-like flexible structure, 30-100 Å (3-10 nm) thick
- Main structure is composed of two leaflets of lipids (bilayer)
  - Except of archaebacteria: monolayer of bifunctional lipids
- Form spontaneously in aqueous solution and are stabilized by non-covalent forces, esp. hydrophobic effect
- Protein molecules span the lipid bilayer
- Asymmetric
  - Some lipids are found preferably “inside”
  - Some lipids are found preferably “outside”
  - Carbohydrate moieties are always outside the cell
  - Electrically polarized (inside negative ~ -60mV)
- Fluid structures: 2-dimensional solution of oriented lipids



Functions of Proteins in Membranes

- **Receptors: detecting signals from outside**
  - **Light (opsin)**
  - **Hormones (insulin receptor)**
  - **Neurotransmitters (acetylcholine receptor)**
  - **Pheromones (taste and smell receptors)**
- **Channels, gates, pumps**
  - **Nutrients (maltoporin)**
  - **Ions (K-channel)**
  - **Neurotransmitters (serotonin reuptake protein)**
- **Enzymes**
  - **Lipid biosynthesis (some acyltransferases)**
  - **ATP synthesis (F_0F_1 ATPase/ATP synthase)**

Three Types of Membrane Proteins Differ in Their Association with the Membrane

- **Integral membrane proteins are very firmly associated with the lipid bilayer, and are removable only by agents that interfere with hydrophobic interactions.**
- **Peripheral membrane proteins associate with the membrane through electrostatic interactions and hydrogen bonding with the hydrophilic domains of integral proteins and with the polar head groups of membrane lipids.**
- **Amphitropic proteins are found both in the cytosol and in association with membranes.**

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Peripheral membrane proteins are easily solubilized

- **Peripheral membrane proteins:** can be relieved by mild conditions, e.g. change pH or ionic strength, add urea. If covalently linked to membrane lipid, use phosphilipase C to cleave the linkage
- **Integral membrane proteins:** use detergent.

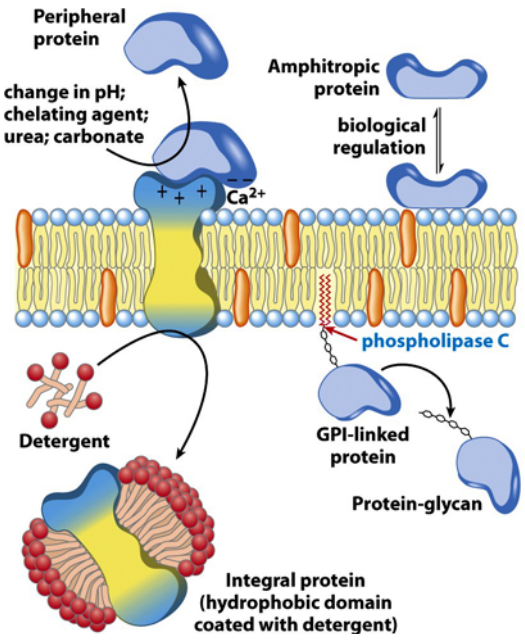

FIGURE 11–6 Peripheral, integral, and amphitropic proteins.

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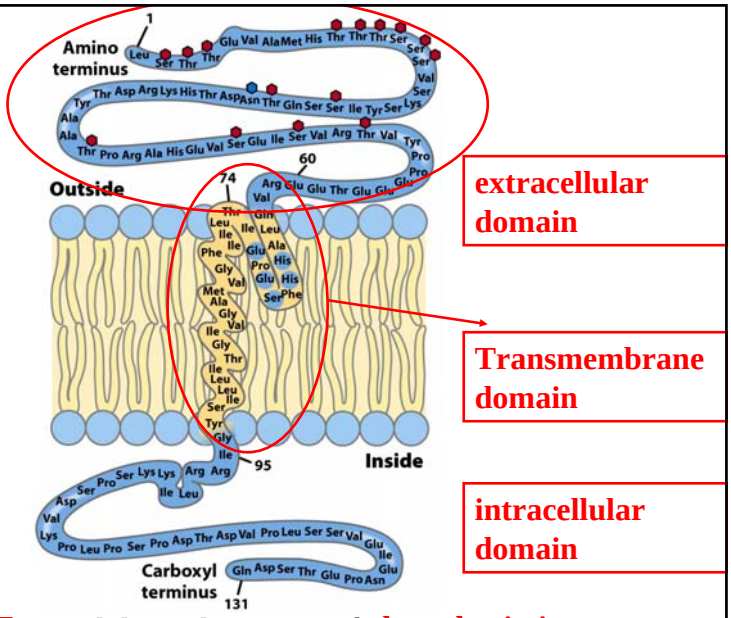

FIGURE 11–7 Transbilayer disposition of glycophorin in an erythrocyte. One hydrophilic domain, containing all the sugar residues, is on the outer surface.

Integral Proteins Are Held in the Membrane by Hydrophobic Interactions with Lipids

- **The firm attachment of integral proteins to membranes is the result of hydrophobic interactions between membrane lipids and hydrophobic domains of protein (Figure 11-8).**

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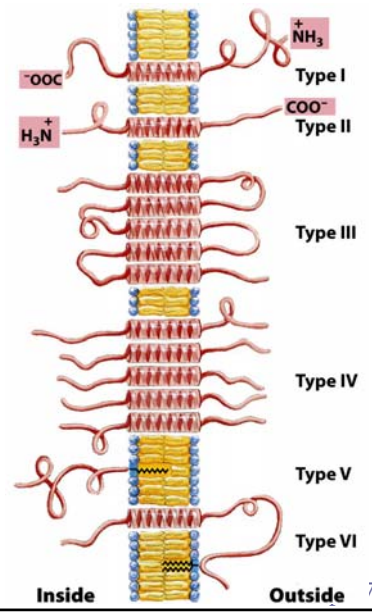
Integral Proteins are held in the membrane by hydrophobic interactions with lipidsIntegral membrane proteins

FIGURE 11–8 Integral membrane proteins. Integral proteins can be classified into 6 categories:
Type I and II: one transmembrane helix.
Type III: multi-transmembrane helices in a single polypeptide chain
Type IV: transmembrane domains from different polypeptides assemble to form a channel
Type V: held to the bilayer through covalently linked lipids
Type VI:contain both transmembrane helices and GPI-anchor



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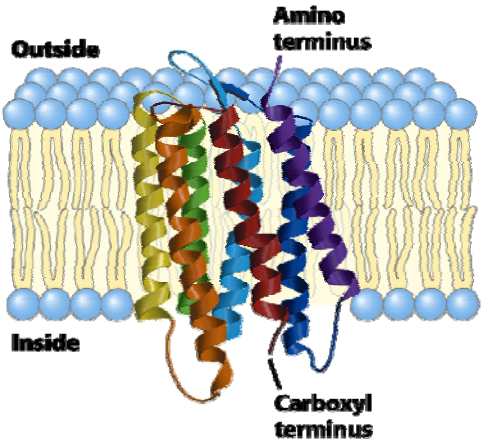
Bacteriorhodopsin: light-driven proton pump



seven transmembrane domains
(each ~ 20 a.a., make an a-helix that spans the bilayer

FIGURE 11–9 Bacteriorhodopsin, a membrane-spanning protein.

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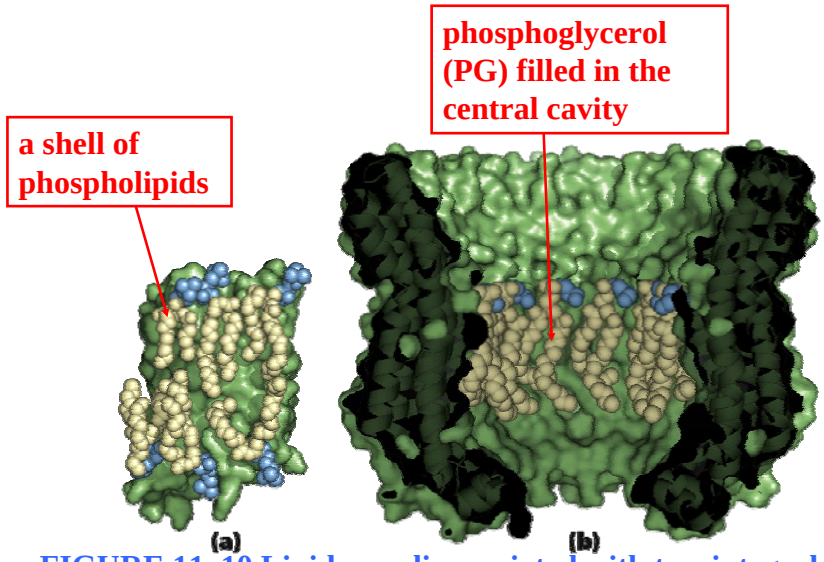

FIGURE 11–10 Lipid annuli associated with two integral membrane proteins. (a) sheep aquaporin (b) F_o integral protein complex of V-type Na^+-ATPase: 10 identical subunits, each contains 4 transmembrane helices

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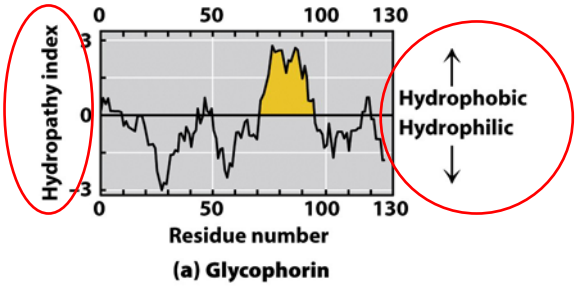
The topology of an integral protein can be sometimes be predicted from its sequence

- Lipid bilayer thickness ~ 30Å
- A-helix: 5.4 Å/patch and 3.6 residues/turn
- 30Å / 5.4 Å x 3.6 residues = 20 residues (per transmembrane helix)

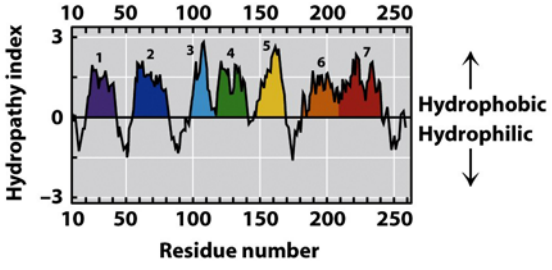
- **Hydropathy Index:** the relative polarity of each amino acid side chain determined by measuring the free energy change accompanying the movement of an amino acid from a hydrophobic solvent to water (Table 3-1).

To predict the secondary structure of a transmembrane protein

(1) Scan the hydropathy index along the sequence
(2) Choose the “window” size (can be 7-20 residues)
(3) 將平均hydropathy index 置於中間
e.g. choose window size 7
sequence 1 ~ 7　將平均hydropathy index置於 4
sequence 2 ~ 8　將平均hydropathy index置於 5
sequence 3 ~ 9　將平均hydropathy index置於 6
(4) A region with more than 20 residues of high average hydropathy index is a “transmembrane helix domain”



(a) Glycophorin



(b) Bacteriorhodopsin

- **A further remarkable feature of many transmembrane proteins of known structure is the presence of Tyr and Trp residues at the interface between lipid and water (Fig. 11–12).**
- **Not all integral membrane proteins are composed of transmembrane helices. Another structural motif common in bacterial membrane proteins is the β barrel, in which 20 or more transmembrane segments form sheets that line a cylinder (Fig. 11–13).**

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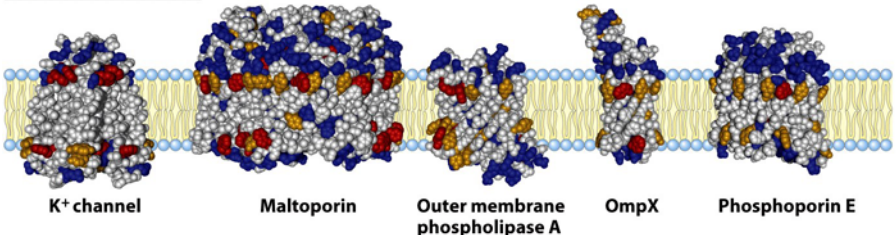

- **Tyr (in orange) and Trp (red) residues of membrane proteins clustering at the interface between water and lipid. The side chains of these residues serve as membrane interface anchors**
- **Positive-inside rule: the positively charged Lys, Arg, His residues (blue) more commonly on the cytoplasmic face of the membrane**

FIGURE 11–12 Tyr and Trp residues of membrane proteins clustering at the water-lipid interface.

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β Barrel Integral Membrane Proteins

(1) **Like α-helical transmembrane domain, β-sheet transmembrane domain form due to : no water molecules to form H-bond with the polar C=O and NH bonds in the hydrophobic environment.**

(2) **Every second residue is hydrophobicresidue (recall the structure of β-sheet)**

(3) **Hydropathy index can not used in the β-barrel membrane domain prediction**

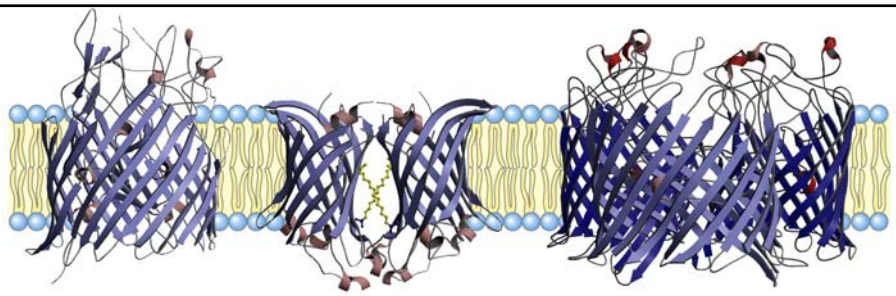

FIGURE 11–13 Membrane proteins with β--barrel structure.

(1) **Porins, proteins that allow certain polar solutes to cross the outer membrane of gramnegative bacteria such as *E. coli*, have many-stranded barrels lining the polar transmembrane passage.**

(2) **20 or more anti-parallel β-strands form a transmembrane channel**

(3) **Only 7-9 residues in β-structure are needed to span a membrane**

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Covalently Attached lipids anchor some perpheral membrane proteins

(1) **Some membrane proteins contain one or more covalently linked lipids including long chain fatty acids, isoprenoids, GPI (acted as hydrophobic anchor into membrane)**

- **Inner phase of plasma membrane:**

  (a) Fatty acid 接在 Cys (Ser) side chain上 S (O)上

  e.g. palmitoyl group is attached to a Cys residue by thioester linkage

  (b) an N-myristoyl group is generally attached to an amino-terminal Gly

  (c) the farnesyl and geranylgeranyl groups attached to carboxyl-terminal Cys residues are isoprenoids of 15 and 20 carbons, respectively.

(3) extracellular face of the plasma membrane :

Fatty acid 接在 :

Glycosyl phosphatidylinositol (GPI) anchors are derivatives of phosphatidylinositol in which the inositol bears a short oligosaccharide covalently joined to the carboxyl-terminal residue of a protein through phosphoethanolamine.

Glycosyl phosphatidylinositol (GPI) anchors : phosphatidylinositol in which the inositol bears a short oligosaccharide covalently joined to the carboxyl-terminal residue of a protein through phosphoethanolamine.

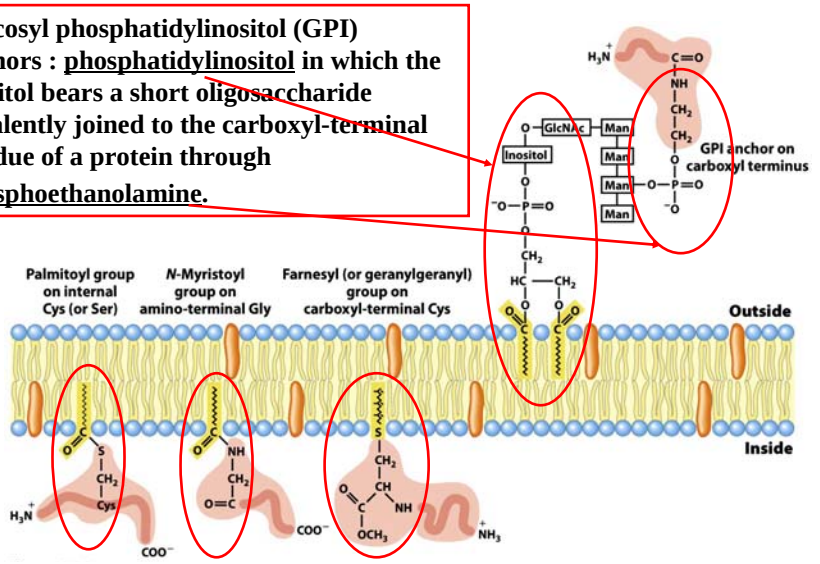

FIGURE 11-14 Lipid-linked membrane proteins. Covalently Attached lipids anchor membrane proteins to the lipid bilayer.

11.2 Membrane Dynamics

Acyl Groups in the Bilayer Interior Are Ordered to Varying Degrees

- **Although the lipid bilayer structure is quite stable, its individual phospholipid and sterol molecules have much freedom of motion (Fig. 11–15).**
- **The structure and flexibility of the lipid bilayer depend on the kinds of lipids present, and change with temperature. Below normal physiological temperatures, the lipids in a bilayer form a semisolid gel phase.**

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- In this liquid-disordered state, or fluid state (Fig. 11–15b), the interior of the bilayer is more fluid than solid and the bilayer is like a sea of constantly moving lipid. At intermediate (physiological) temperatures, the lipids exist in a liquid-ordered state.

Transbilayer Movement of Lipids Requires Catalysis

- At physiological temperatures, diffusion of a lipid molecule from one leaflet of the bilayer to the other (Fig. 11–16a) occurs very slowly if at all in most membranes.

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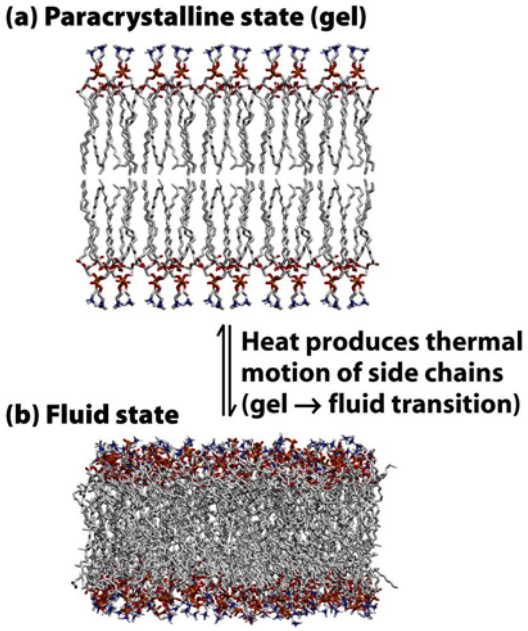

FIGURE 11–15 Two extreme states of bilayer lipids.

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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
Lehninger Principles of Biochemistry, Fifth Edition

- Several families of proteins, including the flippases, floppases, and scramblases.
- **Flippases** catalyze translocation of the *amino*phospholipids phosphatidylethanolamine and phosphatidylserine from the extracellular to the cytosolic leaflet of the plasma membrane.
- **Floppases** move plasma membrane phospholipids from the cytosolic to the extracellular leaflet.
- **Scramblases** are proteins that move any membrane phospholipid across the bilayer down its concentration gradient.

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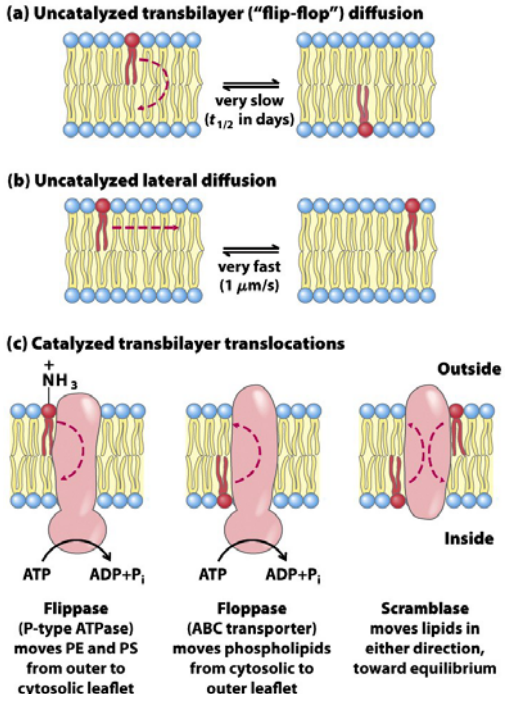

FIGURE 11–16
Motion of single phospholipids in a bilayer.

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Study of Membrane Dynamics: FRAP

- **Fluorescence Recovery After Photobleaching (FRAP) allows to monitor lateral lipid diffusion by monitoring the rate of fluorescence return**
- **From the rate of return of lipids, the diffusion coefficient of a lipid in the leaflet can be determined**
- **Rates of lateral diffusion are high (up to 1 μm/sec):**
  - **a lipid can circumnavigate *E.coli* cell in one second**

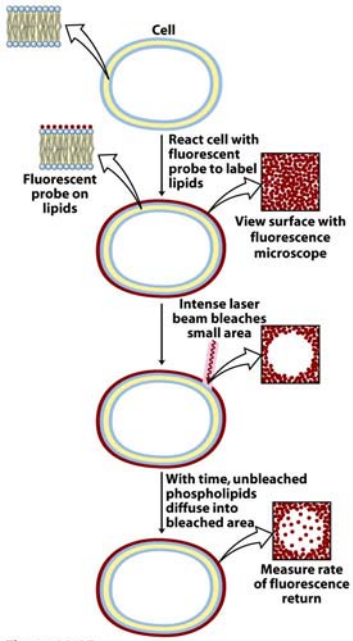


Figure 11-17
Lehninger Principles of Biochemistry, Fifth Edition

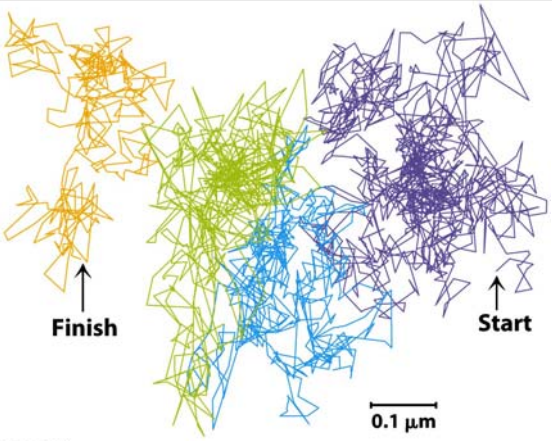


FIGURE 11-18 Hop diffusion of individual lipid molecules. The motion of a single fluorescently labeled lipid molecule in a cell surface is recorded on video by fluorescence microscopy, with a time resolution of 25 µs (equivalent to 40,000 frames/s). The track shown here represents a molecule followed for 56 ms (2,250 frames); the trace begins in the purple area and continues through blue, green, and orange. The pattern of movement indicates rapid diffusion within a confined region (about 250 nm in diameter, shown by a single color), with occasional hops into an adjoining region. This finding suggests that the lipids are corralled by molecular fences that they occasionally jump

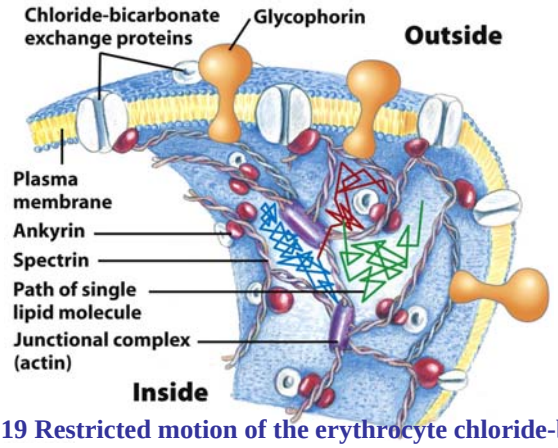


FIGURE 11-19 Restricted motion of the erythrocyte chloride-bicarbonate exchanger and glycophorin. The proteins span the membrane and are tethered to spectrin, a cytoskeletal protein, by another protein, ankyrin, limiting their lateral mobility. Ankyrin is anchored in the membrane by a covalently bound palmitoyl side chain (see Figure 11-14). Spectrin, a long, filamentous protein, is cross-linked at junctional complexes containing actin. A network of cross-linked spectrin molecules attached to the cytoplasmic face of the plasma membrane stabilizes the membrane, making it resistant to deformation. This network of anchored membrane proteins may form the "corral" suggested by the experiment shown in Figure 11-18; the lipid tracks shown here are confined to regions defined by the tethered membrane proteins.

Membrane Rafts

- Lipid distribution in a single leaflet is not random and even
- Some regions contain clusters of glycosphingolipids with longer than usual tails
- These regions are more ordered and contain specific doubly- or triply-acylated proteins
- Rafts allow segregation of proteins in the membrane

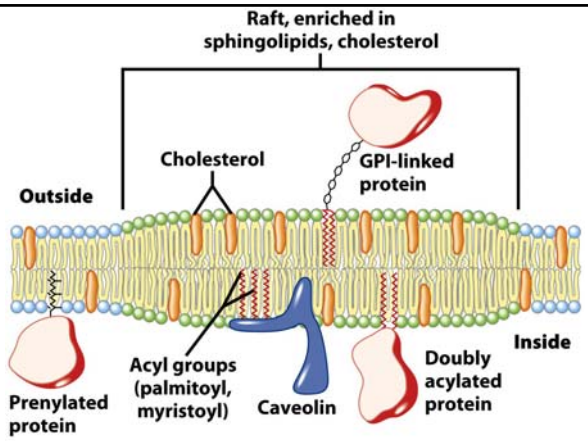


FIGURE 11-20a Membrane microdomains (rafts). (a) Stable associations of sphingolipids and cholesterol in the outer leaflet produce a microdomain, slightly thicker than other membrane regions, that is enriched with specific types of membrane proteins. GPI-linked proteins are common in the outer leaflet of these rafts, and proteins with one or several covalently attached long-chain acyl groups are common in the inner leaflet. Caveolin is especially common in inwardly curved rafts called caveolae (see Figure 11-21).

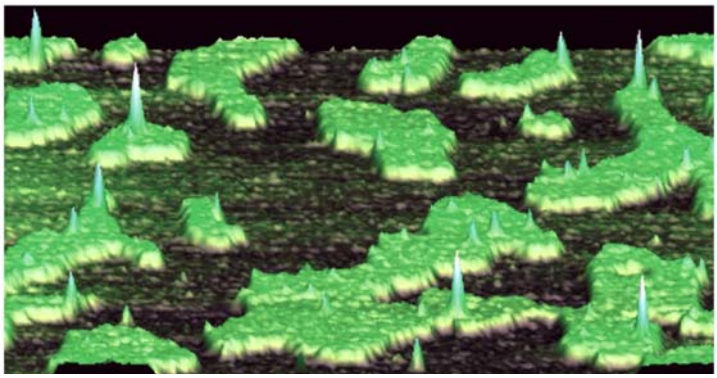
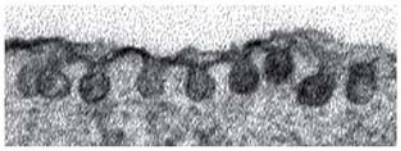


FIGURE 11-20b Membrane microdomains (rafts). (b) In this artificial membrane—reconstituted (on a mica surface) from cholesterol, synthetic phospholipid (dioleoylphosphatidylcholine), and the GPI-linked protein placental alkaline phosphatase—the greater thickness of raft regions is visualized by atomic force microscopy (see Box 11-1). The rafts protrude from a lipid bilayer ocean (the black surface is the top of the upper monolayer); sharp peaks represent GPI-linked proteins. Note that these peaks are found almost exclusively in the rafts.



(a)

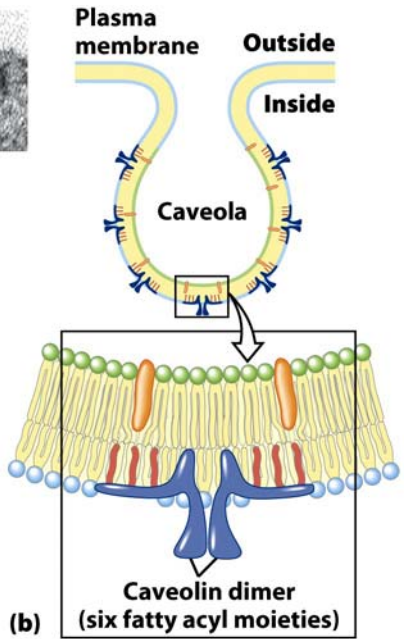


FIGURE 11-21 Caveolin forces inward curvature of a membrane. Caveolae are small invaginations in the plasma membrane, as seen in (a) an electron micrograph of an adipocyte surface-labeled with an electron-dense marker. (b) Each caveolin monomer has a central hydrophobic domain and three long-chain acyl groups (red), which hold the molecule to the inside of the plasma membrane. When several caveolin dimers are concentrated in a small region (a raft), they force a curvature in the lipid bilayer, forming a caveola. Cholesterol molecules in the bilayer are shown in orange.

Membrane Fusion

- Membranes can fuse with each other without losing continuity
- Fusion can be spontaneous or protein-mediated
- Examples of protein-mediated fusion are
  - Entry of influenza virus into the host cell
  - Release of neurotransmitters at nerve synapses

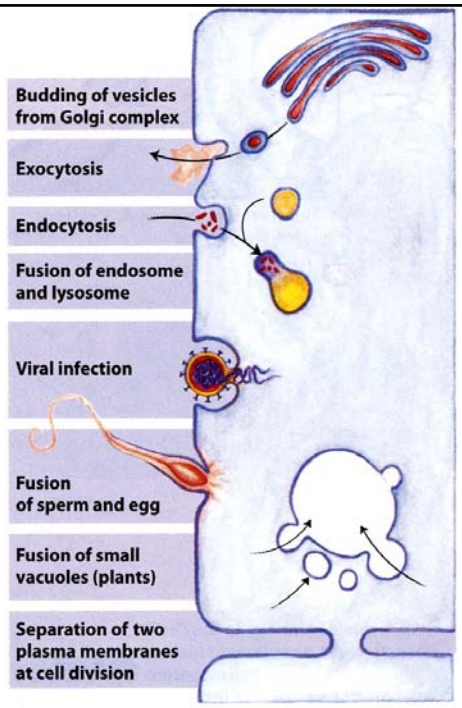


FIGURE 11–22 Membrane fusion. The fusion of two membranes is central to a variety of cellular processes involving organelles and the plasma membrane.

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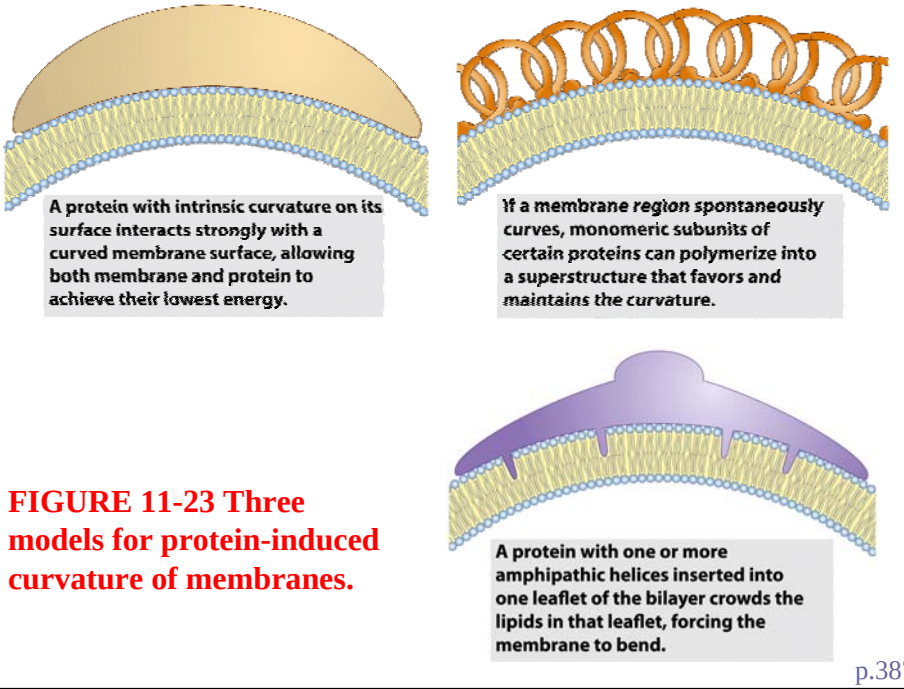

FIGURE 11-23 Three models for protein-induced curvature of membranes.

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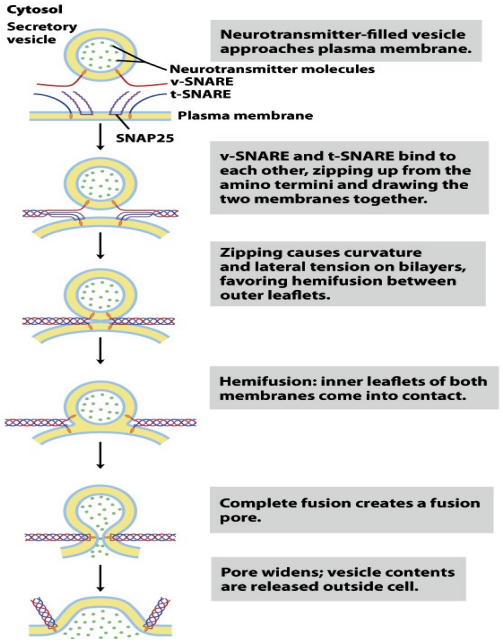
Neurotransmitter Release



Integral Proteins of the Plasma Membrane Are Involved in Surface Adhesion, Signaling, and Other Cellular Processes

- **Integrins are surface adhesion proteins that mediate a cell's interaction with the extracellular matrix and with other cells.**
- **Other plasma membrane proteins involved in surface adhesion are the cadherins, which undergo homophilic interactions with identical cadherins in an adjacent cell. Selectins have extracellular domains that, in the presence of Ca^{2+}, bind specific polysaccharides on the surface of an adjacent cell.**

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11.3 Solute Transport across Membranes

- Some solutes passively diffuse through the lipid membrane
- Passive diffusion of polar molecules involves desolvation and thus has a high activation barrier
- Transport across the membrane can be facilitated by proteins that provide an alternative diffusion path
- Such proteins are called transporters or permeases

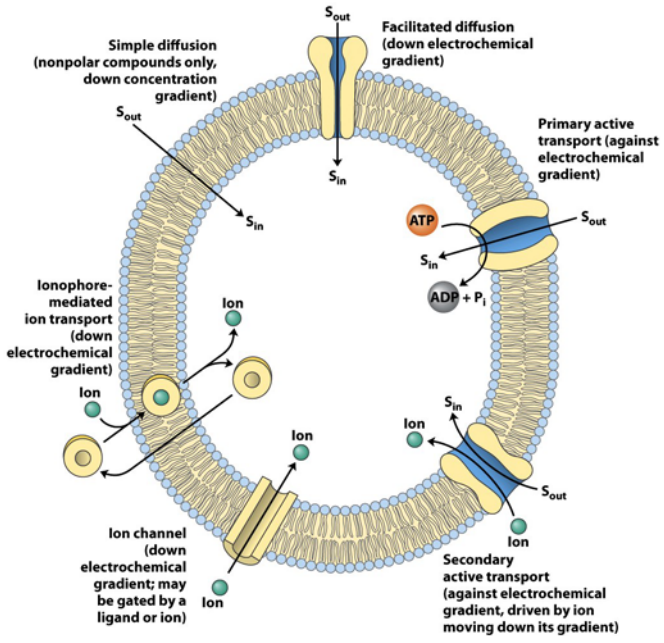

FIGURE 11–25 Summary of transport types. p.389

Passive Transport Is Facilitated by Membrane Proteins

- When two aqueous compartments containing unequal concentrations of a soluble compound or ion 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 (Fig. 11–26a).

p.390

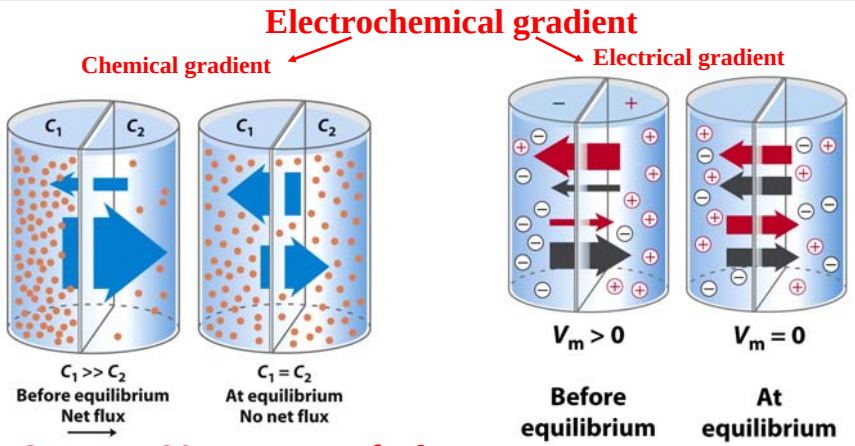

FIGURE 11-26 Movement of solutes across a permeable membrane.
(a) Net movement of an electrically neutral solute is toward the side of lower solute concentration until equilibrium is achieved. The solute concentrations on the left and right sides of the membrane are designated C_1 and C_2. The rate of transmembrane movement (indicated by the arrows) is proportional to the concentration gradient, C_2/C_1.
(b) Net movement of an electrically charged solute is dictated by a combination of the electrical potential (V_m) and the chemical concentration difference (C_2/C_1) across the membrane; net ion movement continues until this electrochemical potential reaches zero.

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Passive Transport Is Facilitated by Membrane Proteins

- The direction of a charged solute tends to move across a membrane depends on:

  (1) chemical gradient (the difference in solute concentration)
  (2) electrical gradient across the membrane (called electrochemical gradient or electrochemical potential)
- Membrane proteins lower the activation energy for transport of polar compounds and ions by providing an alternative path through the bilayer for specific solutes. Proteins that bring about this **facilitated diffusion**, or **passive transport**, are not enzymes in the usual sense
- Membrane proteins that speed the movement of a solute across a membrane by facilitating diffusion are called **transporters** or **permeases**.

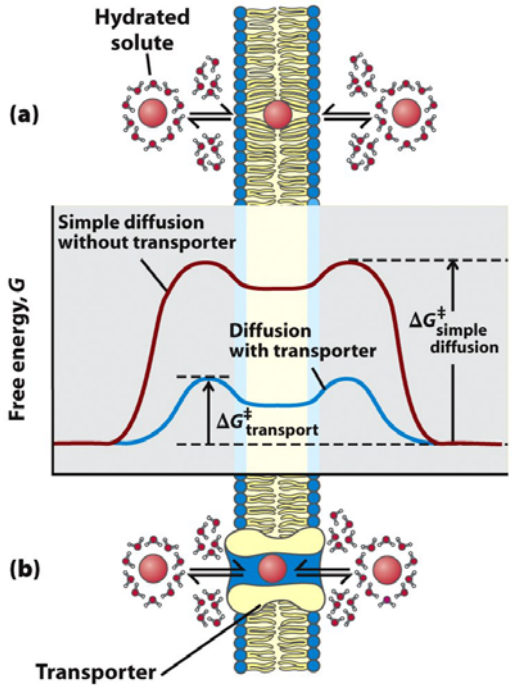


FIGURE 11–27 Energy changes accompanying passage of a hydrophilic solute through the lipid bilayer of a biological membrane.

p.390

Transporters Can Be Grouped into Superfamilies Based on Their Structures

- Transporters fall within two very broad categories: carriers and channels (Fig. 11–28). **Carriers** bind their substrates with high stereospecificity, catalyze transport at rates well below the limits of free diffusion, and are saturable in the same sense as are enzymes.
- **Channels** generally allow transmembrane movement at rates orders of magnitude greater than those typical of carriers, rates approaching the limit of unhindered diffusion.

p.391

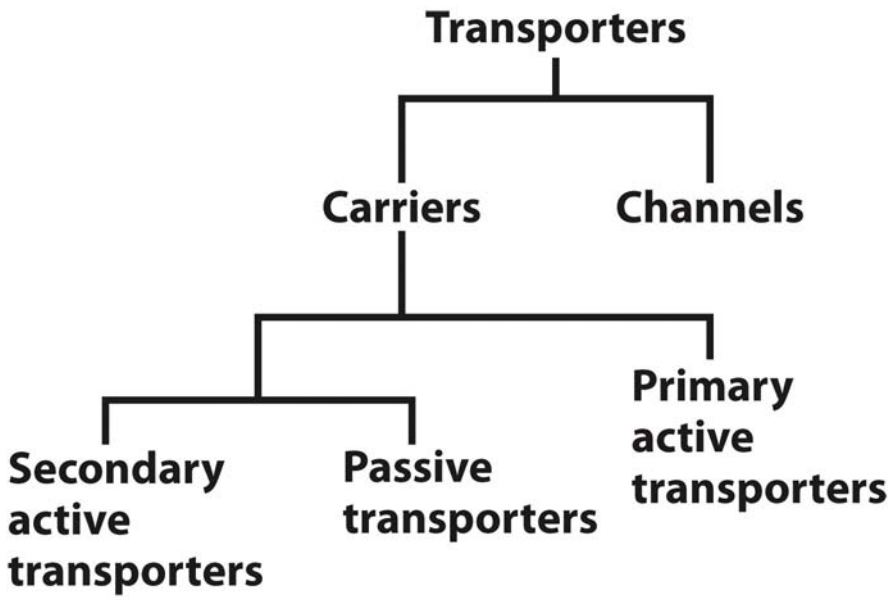
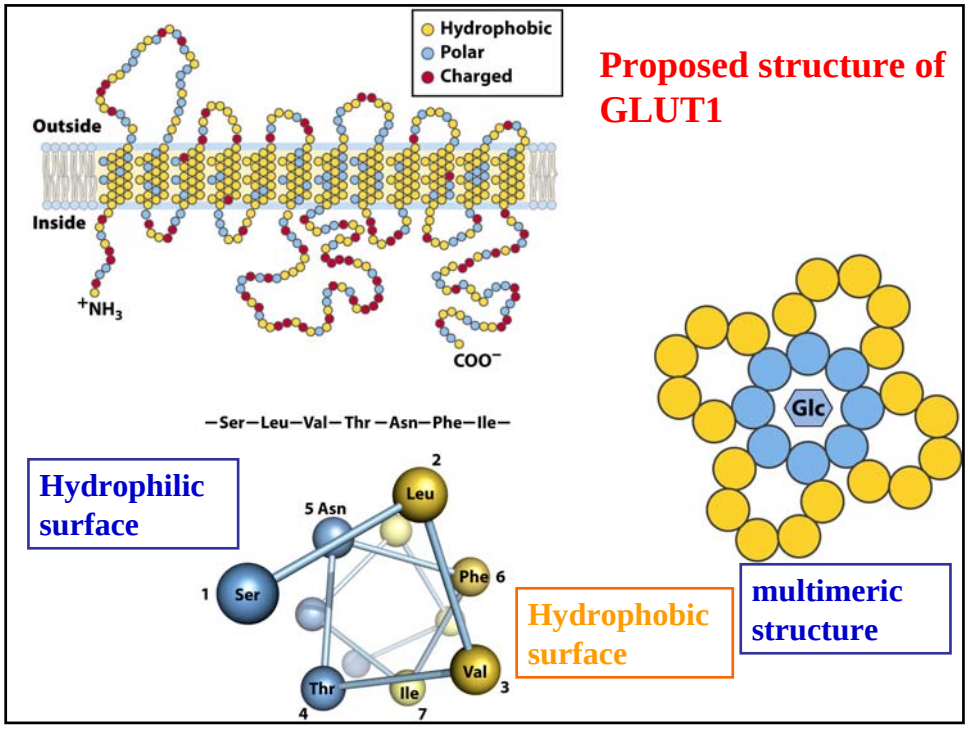


FIGURE 11–28 Classification of transporters.

p.391



Glucose Transporter of Erythrocyte mediates passive transport

Glucose transporter (Glu T1, in erythrocytes)

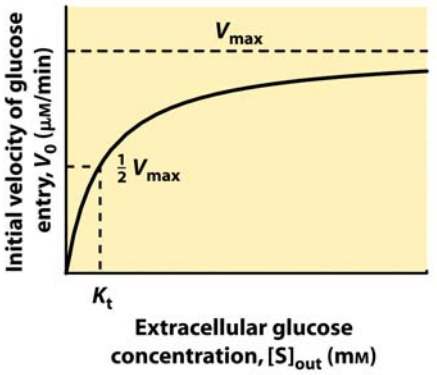
(1)12 transmembrane domain proposed

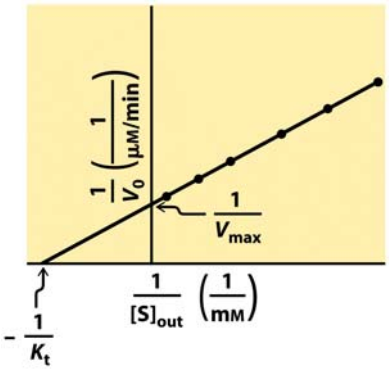
(2)From helical wheel disgram, we can see each helical segment contains two surfaces: hydrophobic and hydrophilic surfaces.

(3)Proposed three dimensional structure:

5 or 6 helical segments arranged as a channel-like structure

hydrophilic surface toward inward and can form H-bond with solute glucose





Analogous to Michaelis-Menten Equation:

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

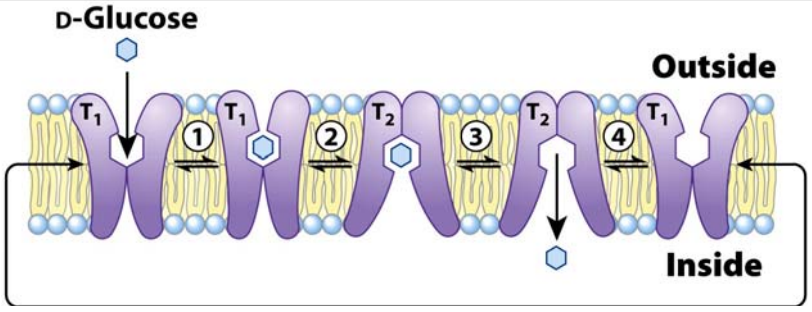
$$k_{-4} \uparrow\downarrow k_4 \qquad k_{-2} \uparrow\downarrow k_2$$

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

$$V_0 = \frac{V_{max}[S]_{out}}{K_t + [S]_{out}} \qquad \frac{1}{V_0} = \frac{K_t}{V_{max}} \frac{1}{[S]} + \frac{1}{V_{max}}$$

$$\left(K_t = \frac{k_2 + k_{-1}}{k_1}; when\, k_2 << k_{-1}\right.$$

$$\left. K_t = \frac{k_{-1}}{k_1} = dissociation const\right)$$



$$V_0 = \frac{V_{max}[S]_{out}}{K_t + [S]_{out}}$$

For Glu T1,

Kt = 1.5mM for D-Glucose

Kt = 20 – 30 mM for D-Mannose & D-Galactose

Kt = 1.5mM for L-Glucose

GluT1: (1) high rates for diffusion down a conc. gradient

(2) specificity (3) saturability

[Blood sugar]= 4.5 to 5mM, about 3x Kt, therefore $V_0 \sim V_{max}$

TABLE 11–3 Glucose Transporters in the Human Genome

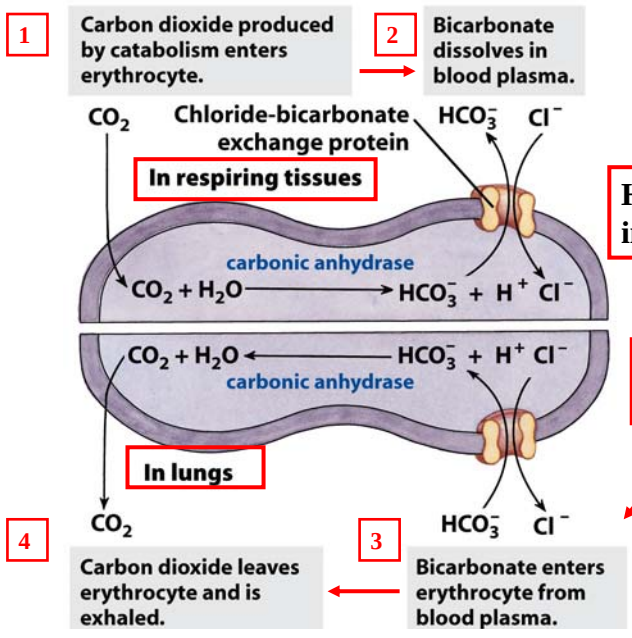
Transporter	Tissue(s) where expressed	Gene	Role*
GLUT1	Ubiquitous	*SLC2A1*	Basal glucose uptake
GLUT2	Liver, pancreatic islets, intestine	*SLC2A2*	In liver, removal of excess glucose from blood; in pancreas, regulation of insulin release
GLUT3	Brain (neuronal)	*SLC2A3*	Basal glucose uptake
GLUT4	Muscle, fat, heart	*SLC2A4*	Activity increased by insulin
GLUT5	Intestine, testis, kidney, sperm	*SLC2A5*	Primarily fructose transport
GLUT6	Spleen, leukocytes, brain	*SLC2A6*	Possibly no transporter function
GLUT7	Liver microsomes	*SLC2A7*	—
GLUT8	Testis, blastocyst, brain	*SLC2A8*	—
GLUT9	Liver, kidney	*SLC2A9*	—
GLUT10	Liver, pancreas	*SLC2A10*	—
GLUT11	Heart, skeletal muscle	*SLC2A11*	—
GLUT12	Skeletal muscle, adipose, small intestine	*SLC2A12*	—

*Dash indicates role uncertain.

The Chloride-Bicarbonate Exchanger Catalyzes Electroneutral Cotransport of Anions across the Plasma Membrane

- The **chloride-bicarbonate exchanger (cotransport system)**, also called the **anion exchange (AE) protein**, increases the rate of HCO_3^- transport across the erythrocyte membrane more than a millionfold. Entry and exit of HCO_3^- and Cl^- without changes in the transmembrane electrical potential (called "electroneutral").
- When two substrates move in opposite directions, the process is **antiport**. In **symport**, two substrates are moved simultaneously in the same direction. Transporters that carry only one substrate, are known as **uniport** systems.

p.393



HCO_3^- is more soluble in blood than CO2

HCO_3^- then transferred to lung

FIGURE 11–32 Chloride-bicarbonate exchanger of the erythrocyte membrane.

p.395

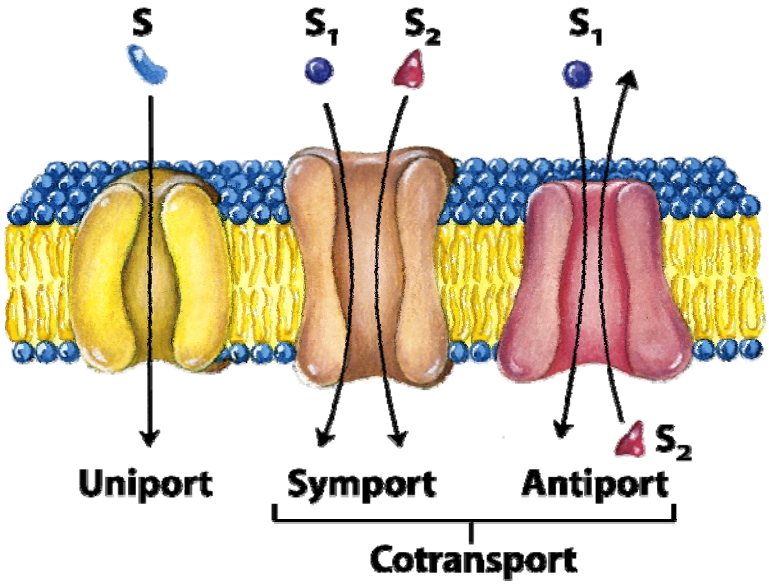


FIGURE 11–33 Three general classes of transport systems.

p.395

Active Transport Results in Solute Movement against a Concentration or Electrochemical Gradient

- In **primary active transport**, solute accumulation is coupled directly to an exergonic chemical reaction, such as conversion of ATP to ADP + P_i (Fig. 11–34).
- **Secondary active transport** occurs when endergonic (uphill) transport of one solute is coupled to the exergonic (downhill) flow of a different solute that was originally pumped uphill by primary active transport.

p.395

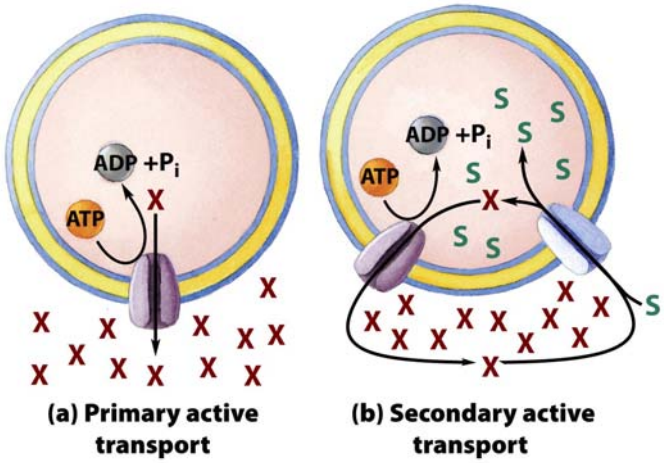


FIGURE 11–34 Two types of active transport. (a) In primary active transport, the energy released by ATP hydrolysis drives solute movement against an electrochemical gradient. (b) In secondary active transport, a gradient of ion X (often Na^+) has been established by primary active transport. Movement of X down its electrochemical gradient now provides the energy to drive cotransport of a second solute (S) against its electrochemical gradient.

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Active Transport Results in Solute Movement against a Concentration or Electrochemical Gradient

Recall $\Delta G = \Delta G^o + RT \ln Q$ **; Q: reaction quoient**

For a transport system: **Q =** $\frac{[S]_{in}}{[S]_{out}}$ **or =** $\frac{[S]_{out}}{[S]_{in}}$

$\because \Delta G^o = 0$ **(since no bonds are made or broken)**

Free energy change for transport:

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

Ex. 11-1: pumping uncharged solute against 10^{-4} fold

$$\Delta G_t = RT \ln \frac{C_2}{C_1} = 8.314 * 298 * \ln(1.0 * 10^{-4})$$

= 23 kJ/mol

(I) For a transport process of 'uncharged' solutes:

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

(II) For a transport process of 'charged' solutes:

$$\therefore \Delta G_t = RT \ln \frac{C_2}{C_1} + zF\Delta\psi$$

Z : charge of the solute

$\Delta\psi$ **: transmembrane electrical potential (in volts)**

(for eukaryotic cells, $\Delta\psi$ **= 50 to 200mV**

Ex. 11-2: pumping charged solute

$$\Delta G_t = RT \ln \frac{C_2}{C_1} + zF\Delta\psi = 8.314 * 310 * \ln\left(\frac{1.0*10^{-3}}{1.0*10^{-7}}\right)$$

$$+ 2 * 96500 * 0.050 \quad \textbf{= 33kJ/mol}$$

There are at least four general types of transport ATPase

(I)P-Type ATPases Undergo Phosphorylation during Their Catalytic Cycles

- The family of active transporters called **P-type ATPases** are **cation transporters** that are reversibly phosphorylated by ATP as part of the transport cycle.
- In animal tissue, the Na^+K^+ATPase and Ca^{2+} ATPase are ubiquitous P-type ATPase that maintain the differences in the ionic composition of cytosol and extracellular medium.
- The **plasma membrane Ca^{2+} pump** moves calcium ions out of the cell, and another P-type pump in the endoplasmic reticulum moves Ca^{2+} into the ER lumen.

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- The **sarcoplasmic and endoplasmic reticulum calcium (SERCA) pumps** are P-type ATPases closely related in structure and mechanism.
- A variation on this basic mechanism is seen in the **Na^+K^+ ATPase** of the plasma membrane, discovered by Jens Skou in 1957.

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ATP-drive Ca^{2+} pumps (P-type ATPase) maintain a low conc. of calcium in the cytosol

- Calcium ions are pumped out of the cytosol by plasma membrane Ca^{2+} pump (a P-type ATPase) to maintain low conc. of calcium in the cytosol
- Calcium ions are pumped in to the lumen by endoplasmic reticulum and sacoplasmic reticulum Ca^{2+} pump (SERCA).
- SERCA conatins a single polypeptide (Mr ~ 100,000) and cycles among conformations (see Fig. 11-36).
- Two calcium ions bind to a transmembrane domain. Phosphorylation on Asp351 mediates conformational change and controls calcium release/binding.

p.396

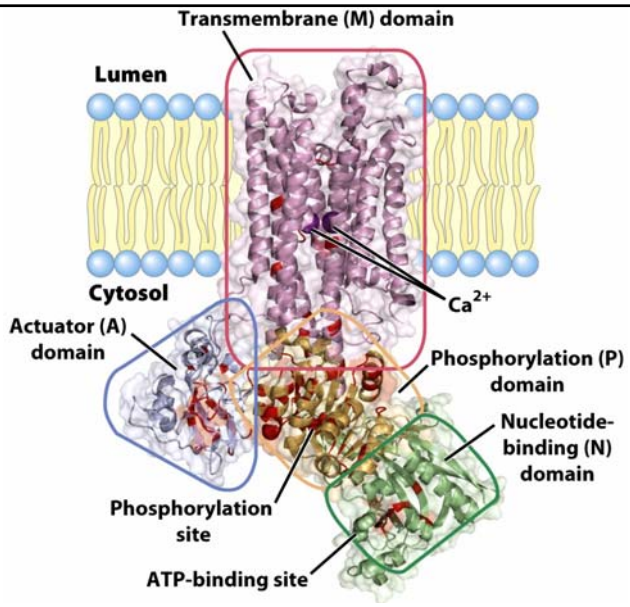

FIGURE 11–35 The Ca^{2+} pump of sarcoplasmic reticulum: a SERCA pump.

p.397

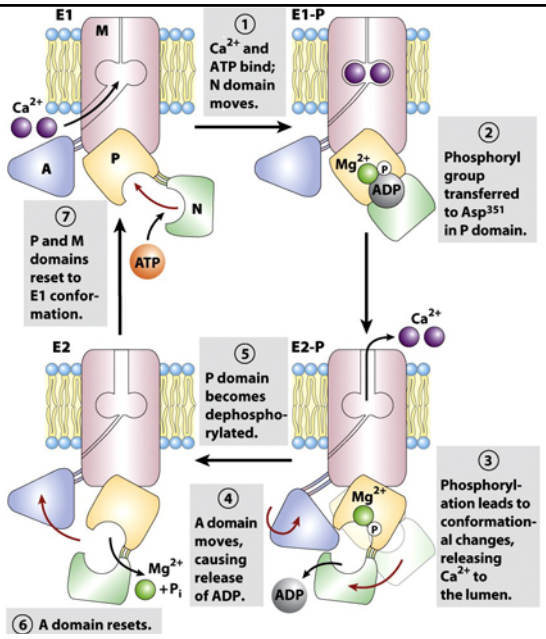

FIGURE 11–36 Postulated mechanism of the SERCA pump.

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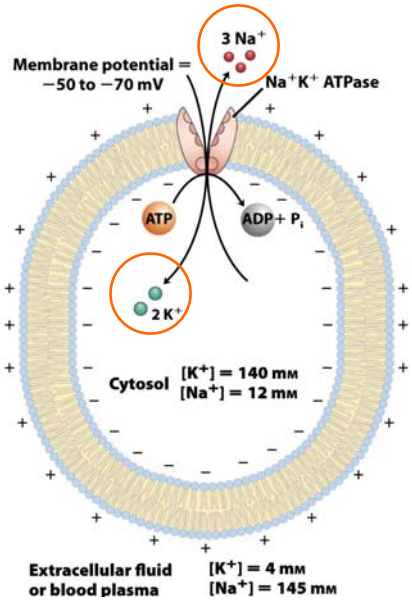
A P-Type ATPases catalyzes active cotransport of Na^+ and K^+



Jens Skou discovered **Na^+K^+ ATPase** of the plasma membrane in 1957.

- 1 molecule of ATP hydrolyzed to ADP,
- 2 molecules of K+ move inwards
- 3 Na+ move outwards.

FIGURE 11–38 Role of the Na^+K^+ ATPase in animal cells.

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(1)ATP + EnzI → ADP + P-EnzII
(2)P-EnzII + H_2O → EnzI + Pi

Net:
ATP+ H_2O → ADP +Pi

(1)EnzI binds 3 Na^+
(2) P-EnzII binds to 2 K^+
"cycle between two conformations"

(3)Ouabian (箭毒 , a steroid derivative) can bind to Na^+K^+ ATPase and prevent the conformational change, then prohibit the cycling Na^+K^+ ATPase

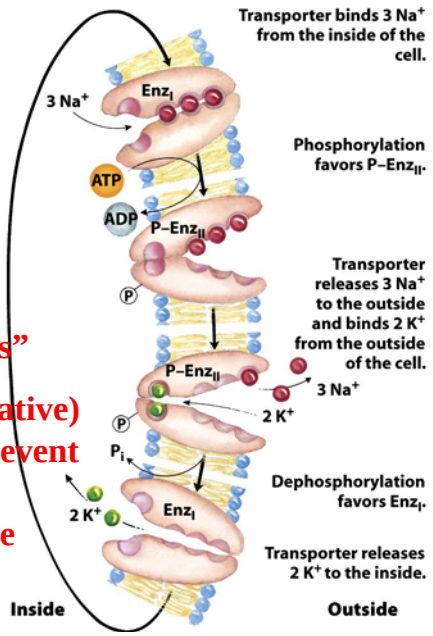


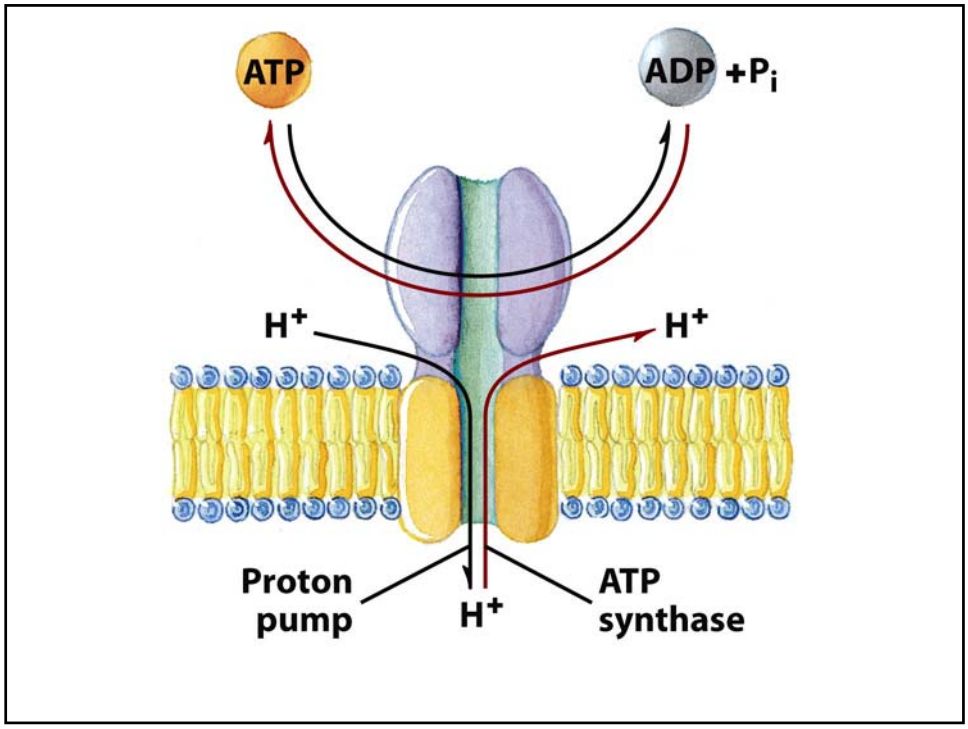
FIGURE 11–37 Postulated mechanism of the Na^+K^+ ATPase.

p.398

F-Type ATPases Are Reversible, ATP-Driven Proton Pumps

- **F-type ATPase** active transporters catalyze the uphill transmembrane passage of protons driven by ATP hydrolysis.
- **V-type ATPases**, a class of proton-transporting ATPases structurally (and possibly mechanistically) related to the F-type ATPases, are responsible for acidifying intracellular compartments in many organisms.

p.399



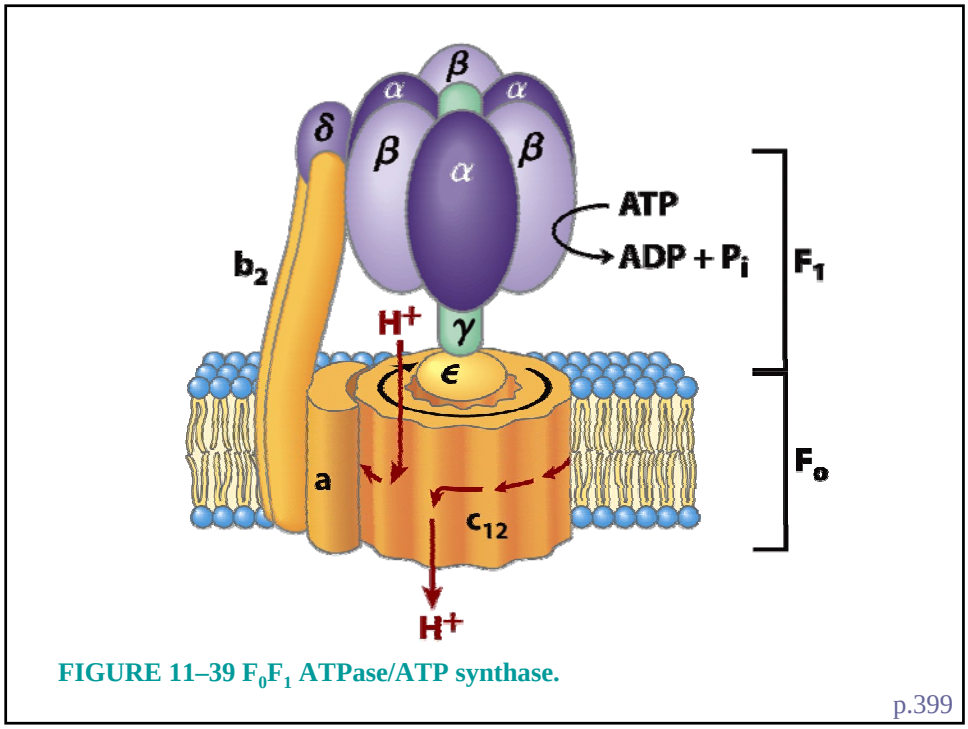


FIGURE 11–39 F_0F_1 ATPase/ATP synthase.

p.399

ABC Transporters Use ATP to Drive the Active Transport of a Wide Variety of Substrates

- **ABC transporters** (Fig. 11–41) constitute a large family of ATP-dependent transporters that pump amino acids, peptides, proteins, metal ions, various lipids, bile salts, and many hydrophobic compounds.
- One ABC transporter in humans, the **multi-drug transporter (MDR1)**, is responsible for the striking resistance of certain tumors to some generally effective antitumor drugs.

p.400

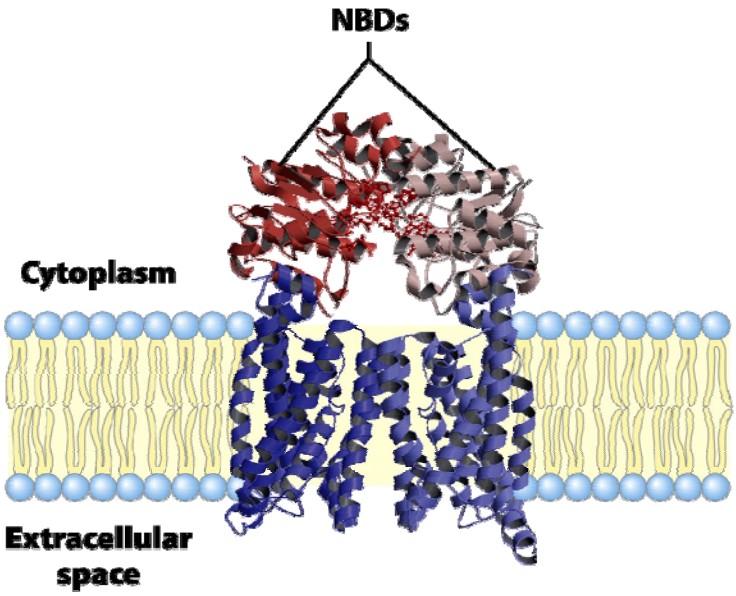


FIGURE 11–41 An ABC transporter of *E. coli.*

p.400

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

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Ion Gradients Provide the Energy for Secondary Active Transport

- **Ion gradient: e.g. Na^+K^+ ATPase 使得**

  細胞內 [Na^+] <細胞外 [Na^+] (against the gradient, therefore need the hydrolysis of ATP to provide energy)

- **Cell 利用此ion gradient由另外一個transporter 將Na^+ and其他solutes symport 進入cytosol (因爲是down the gradient, 所以不需利用ATP hydrolysis 以提供能量),此種系統稱爲secondary active transport**

- **see more examples in table 11-4**

- **Na^+K^+ ATPase and some other H^+ pump 主要功能爲提供 ion gradient for other transporter 攜帶其他solutes 進出cells.**

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Ion Gradients Provide the Energy for Secondary Active Transport

- 例子一: **The lactose transporter (lactose permease) of *E. coli* is the well-studied prototype for proton-driven cotransporters.**
- 例子二: **Na^+-glucose symporters in the apical plasma membrane take up glucose from the intestine in a process driven by the downhill flow of Na+:**

$$2Na_{out}^{+} + glucose_{out} \rightarrow 2Na_{in}^{+} + glucose_{in}$$

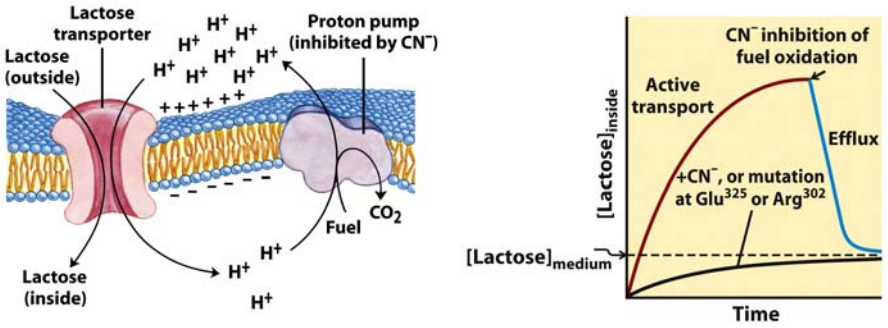

FIGURE 11–42 Lactose uptake in *E. coli.* (a) The primary transport of H^+ out of the cell, driven by the oxidation of a variety of fuels, establishes both a proton gradient and an electrical potential (inside negative) across the membrane. Secondary active transport of lactose into the cell involves symport of H^+ and lactose by the lactose transporter. The uptake of lactose against its concentration gradient is entirely dependent on this inflow of protons driven by the electrochemical gradient.

p.402

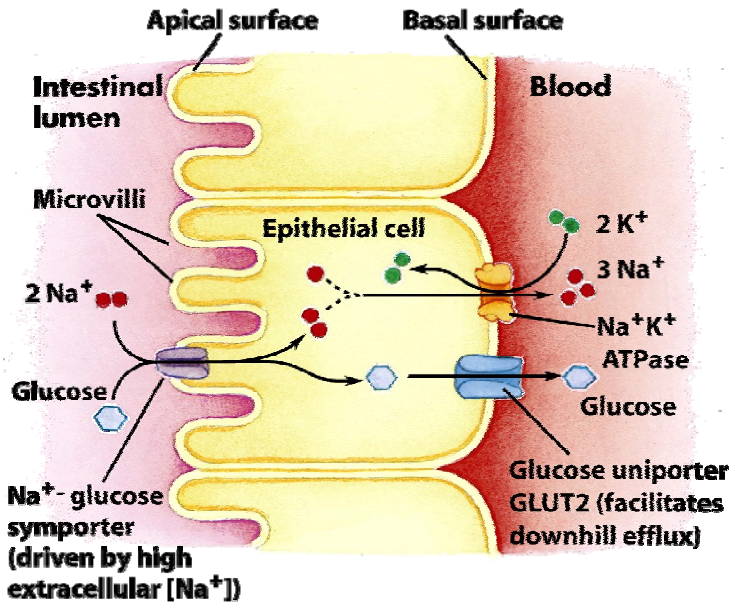

FIGURE 11–44 Glucose transport in intestinal epithelial cells.

p.403

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
Lehninger Principles of Biochemistry, Fifth Edition

Ion-Selective Channels Allow Rapid Movement of Ions across Membranes

- **Ion-selective channels** Ion channels, together with ion pumps such as the Na^+ K^+ ATPase, determine a plasma membrane's permeability to specific ions and regulate the cytosolic concentration of ions and the membrane potential.
- In **ligand-gated channels** binding of an extracellular or intracellular small molecule forces an allosteric transition in the protein.

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- **Voltage-gated ion channels**, a change in transmembrane electrical potential (V_m) causes a charged protein domain to move relative to the membrane.
- Ion channels provide hydrophilic pores through which select ions can diffuse, moving down their electrical or chemical concentration gradients; they characteristically are unsaturable, have very high flux rates, and are highly specific for one ion.

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