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Membrane Transport

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Learning Objectives

- Understand the different mechanisms of membrane transport
- Explain simple diffusion using O_2 and CO_2 as examples
- Describe facilitated diffusion for glucose, Na^+, and K^+ transport
- Analyze primary active transport via Na^+-K^+ pump
- Examine secondary active transport through Na^+-glucose cotransport
- Explore LDL receptor-mediated endocytosis mechanism
- Compare energy requirements and clinical significance of each transport type

Overview of Transport Mechanisms

Passive transport	• Simple diffusion (O_2, CO_2) • Facilitated diffusion (Glucose, Ions)
Active transport	• Primary (Na^+-K^+ pump) • Secondary (Na^+-Glucose cotransport)
Vesicular Transport	• LDL receptor mediated endocytocis

Membrane structure and selective permeability

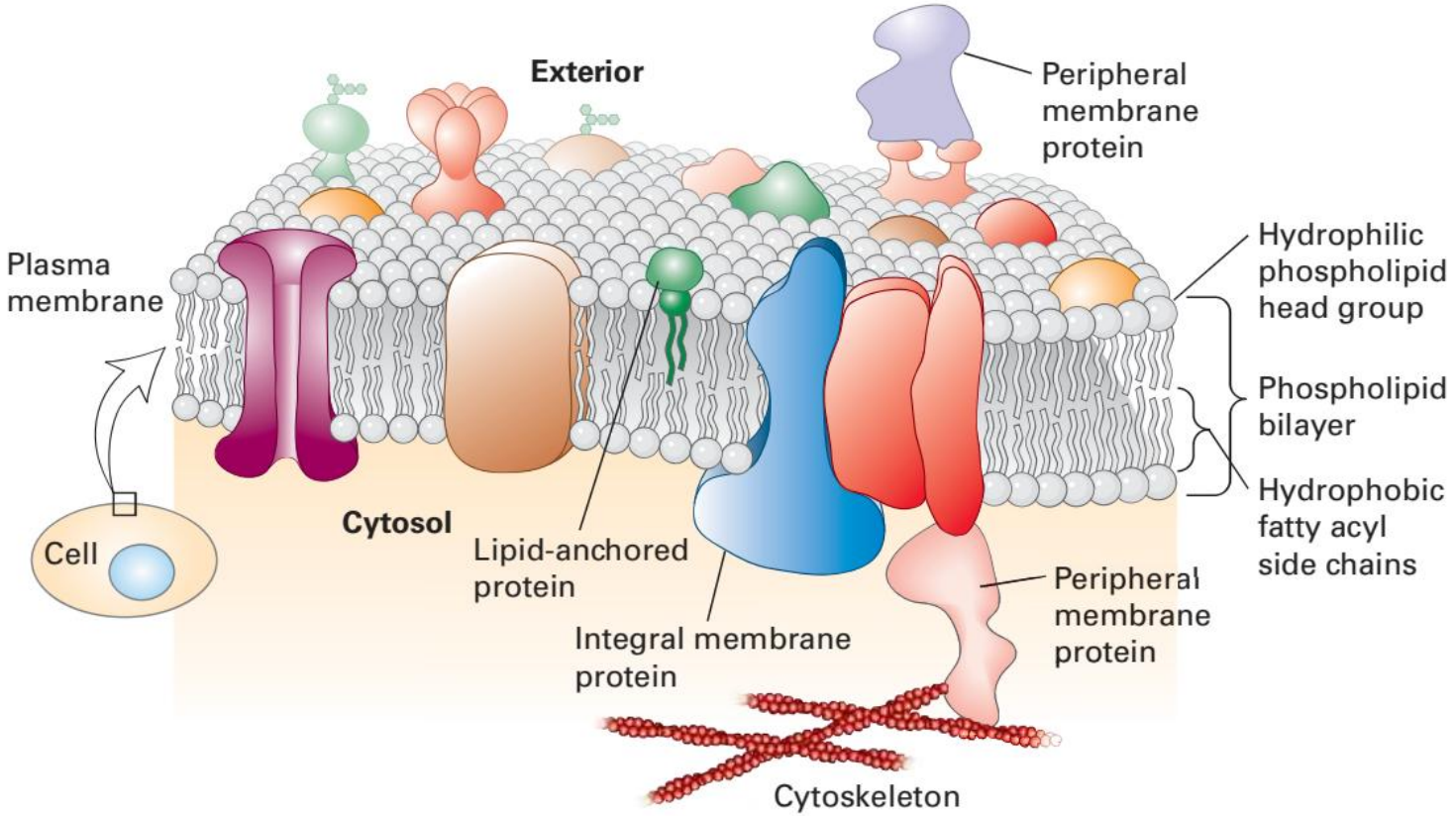


Image source: Lodish et al., 2016. Molecular Cell Biology, 8th Edn.

- **Plasma Membrane Composition:**
  - Phospholipid bilayer (hydrophobic core)
  - Intrinsic proteins (spanning membrane)
  - Peripheral proteins (surface-associated)
  - Cholesterol (membrane fluidity regulation)
- **Why Selective Permeability?**
  - Hydrophobic lipid bilayer impermeable to ions and polar molecules
  - Transport proteins create selective pathways
  - Controls what enters/exits the cell
  - Essential for homeostasis

Permeability of PM

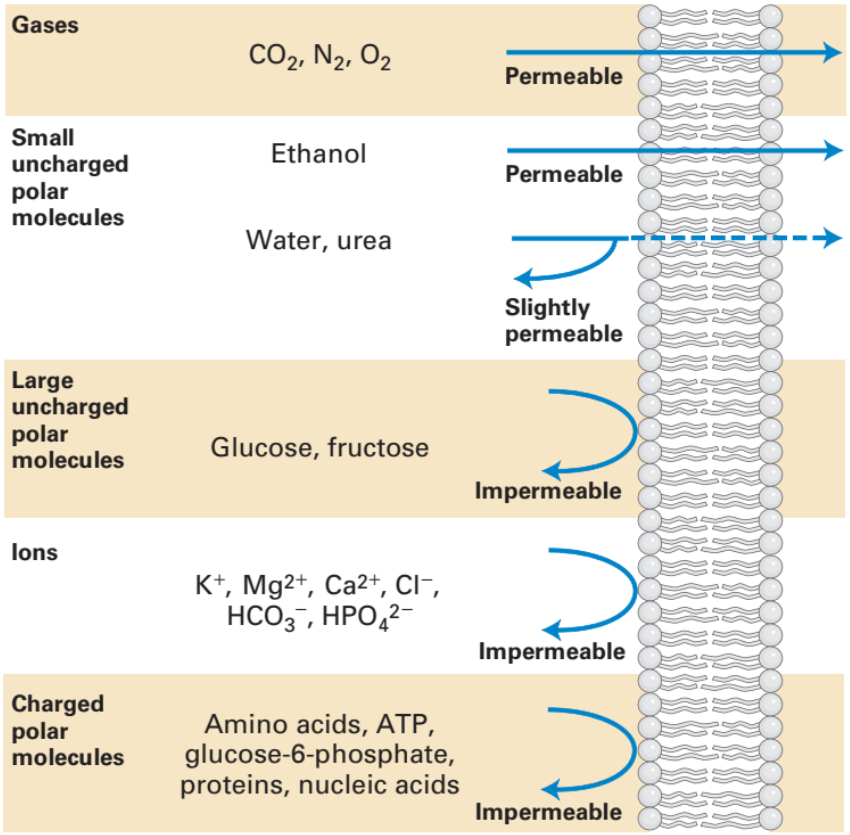


FIGURE 11-1 Relative permeability of a pure phospholipid bilayer to various molecules and ions. A pure phospholipid bilayer is permeable to many gases and to small, uncharged, water-soluble (polar) molecules. It is slightly permeable to water, and essentially impermeable to ions and to large polar molecules.

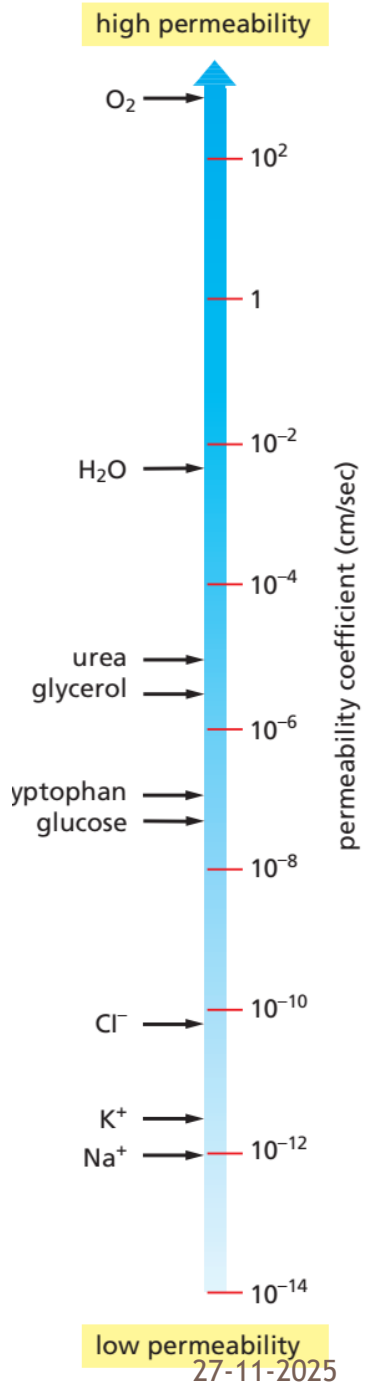
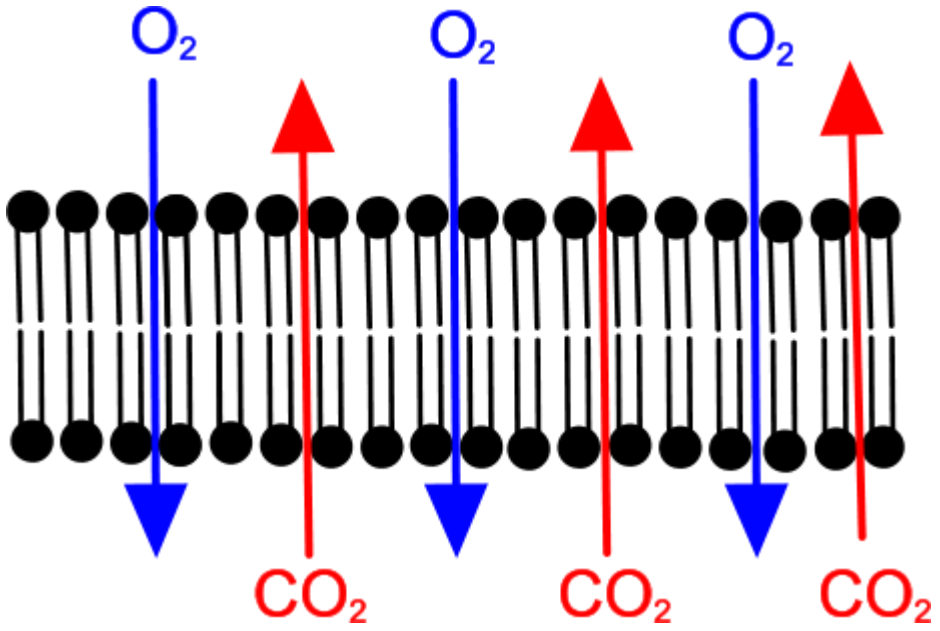


Figure 11–2 **Permeability coefficients for the passage of various molecules through synthetic lipid bilayers.** The rate of flow of a solute across the bilayer is directly proportional to the difference in its concentration on the two sides of the membrane. Multiplying this concentration difference (in mol/cm^3) by the permeability coefficient (in cm/sec) gives the flow of solute in moles per second per square centimeter of bilayer. A concentration difference of tryptophan of 10^{-4} mol/cm^3 (10^{-4} mol / 10^{-3} L = 0.1 M), for example, would cause a flow of 10^{-4} mol/cm^3 × 10^{-7} cm/sec = 10^{-11} mol/sec through 1 cm^2 of bilayer, or 6 × 10^4 molecules/sec through 1 μm^2 of bilayer.

Simple Diffusion

- **Definition & Characteristics:**
  - Movement from **high to low concentration**
  - No energy (ATP) required
  - No transport proteins needed
  - Molecules: Small, nonpolar, lipid-soluble
- **O_2 Transport (Oxygen Diffusion):**
  - Alveolar air → Higher O_2 concentration
  - Capillary blood → Lower O_2 concentration
  - O_2 crosses endothelial cells via simple diffusion
  - Binds to hemoglobin in red blood cells
  - No ATP required; purely concentration-gradient driven
- **CO_2 Transport (Carbon Dioxide Removal):**
  - **Cellular Respiration:** Mitochondria produce CO_2
  - **Tissue → Blood Gradient:** CO_2 concentration higher in tissue than in capillary blood
  - **Diffusion Across Cell Membrane:** CO_2 crosses via simple diffusion
  - **Transport in Blood:** Converted to HCO_3^- in red blood cells
  - **Lung Excretion:** Expelled during respiration



Different kinds of transport

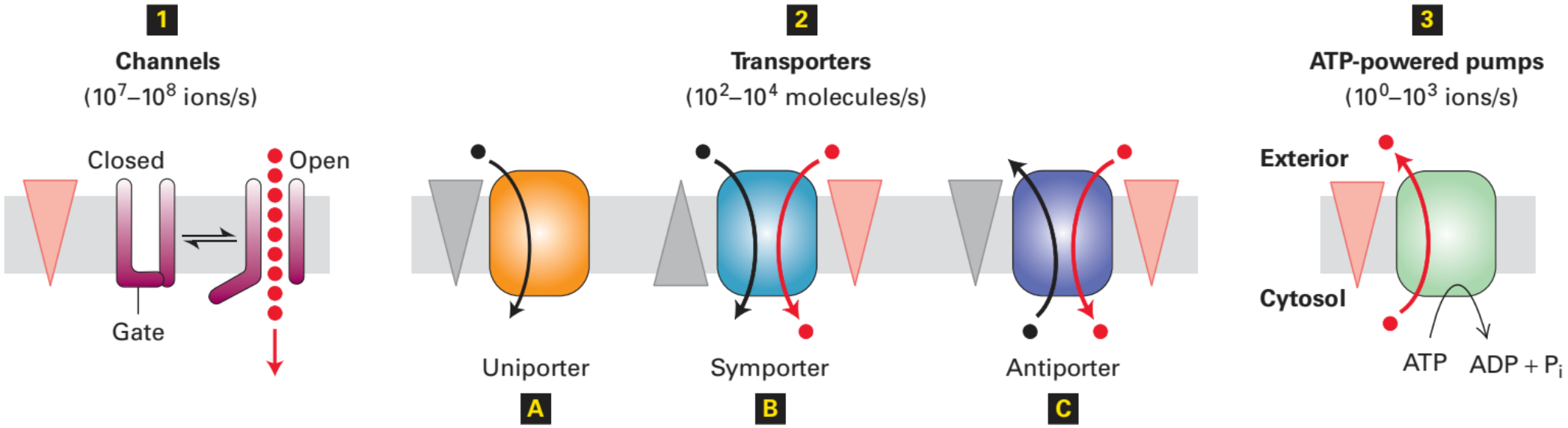
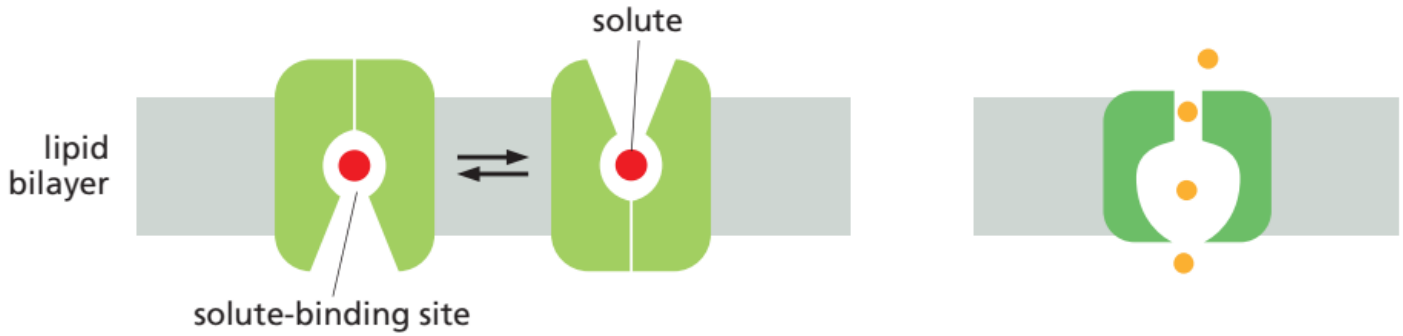


FIGURE 11-2 Overview of membrane transport proteins. Gradients are indicated by triangles with the tip pointing toward lower concentration, electric potential, or both. 1 Channels permit movement of specific ions (or water) down their electrochemical gradient. 2 Transporters, which fall into three groups, facilitate movement of specific small molecules or ions. Uniporters transport a single type of molecule down its concentration gradient 2A. Cotransport proteins (symporters, 2B, and antiporters, 2C) catalyze the movement of one molecule *against* its concentration gradient (black circles), driven by movement of one or more ions down an electrochemical gradient (red circles). 3 Pumps use the energy released by ATP hydrolysis to power movement of specific ions or small molecules (red circles) against their electrochemical gradient. Differences in the mechanisms of transport by these three major classes of proteins account for their varying rates of solute movement.

Facilitated Diffusion

- Protein-mediated transport of **polar and charged molecules** DOWN their concentration gradient. Molecules cannot cross the hydrophobic lipid bilayer alone; **specific transport proteins provide the pathway**.
- **TWO CLASSES OF TRANSPORT PROTEINS**
  - **CARRIER PROTEINS**
    - Bind molecule → Conformational change → Release inside cell
    - Highly specific
    - Diffusion rate: Moderate
    - **Transports:** sugars, amino acids, and nucleosides
  - **CHANNEL PROTEINS**
    - Form **open pores** allowing rapid, free diffusion
    - **Examples:**
      - **Aquaporins** → Water (kidney, plants)
      - **Ion Channels** → Na^+, K^+, Ca^{2+}, Cl^- (nerve/muscle)



(A) TRANSPORTER

(B) CHANNEL PROTEIN

FACILITATED DIFFUSION - GLUCOSE TRANSPORT

- **Definition:** Protein-mediated transport DOWN concentration gradient; NO direct ATP hydrolysis
- **Glucose Transporter (GLUT) Function:**
  - Glucose concentration: Higher in blood, lower inside cells
  - GLUT proteins bind glucose on extracellular side
  - Conformational change → Glucose enters cell interior
  - Concentration gradient provides energy
  - Release on intracellular side
- **Primary GLUT Isoforms:**
  - **GLUT1:** Brain, red blood cells (basal glucose uptake)
  - **GLUT2:** Liver, pancreatic β-cells (glucose sensing)
  - **GLUT4:** Muscle, adipose tissue (insulin-responsive; insulin ↑ GLUT4 at membrane)
- **Key Features:**
  - Selective for glucose
  - Saturable (limited by number of GLUT proteins)
  - Faster than simple diffusion
  - No energy cost to cell

FACILITATED DIFFUSION - GLUCOSE TRANSPORT

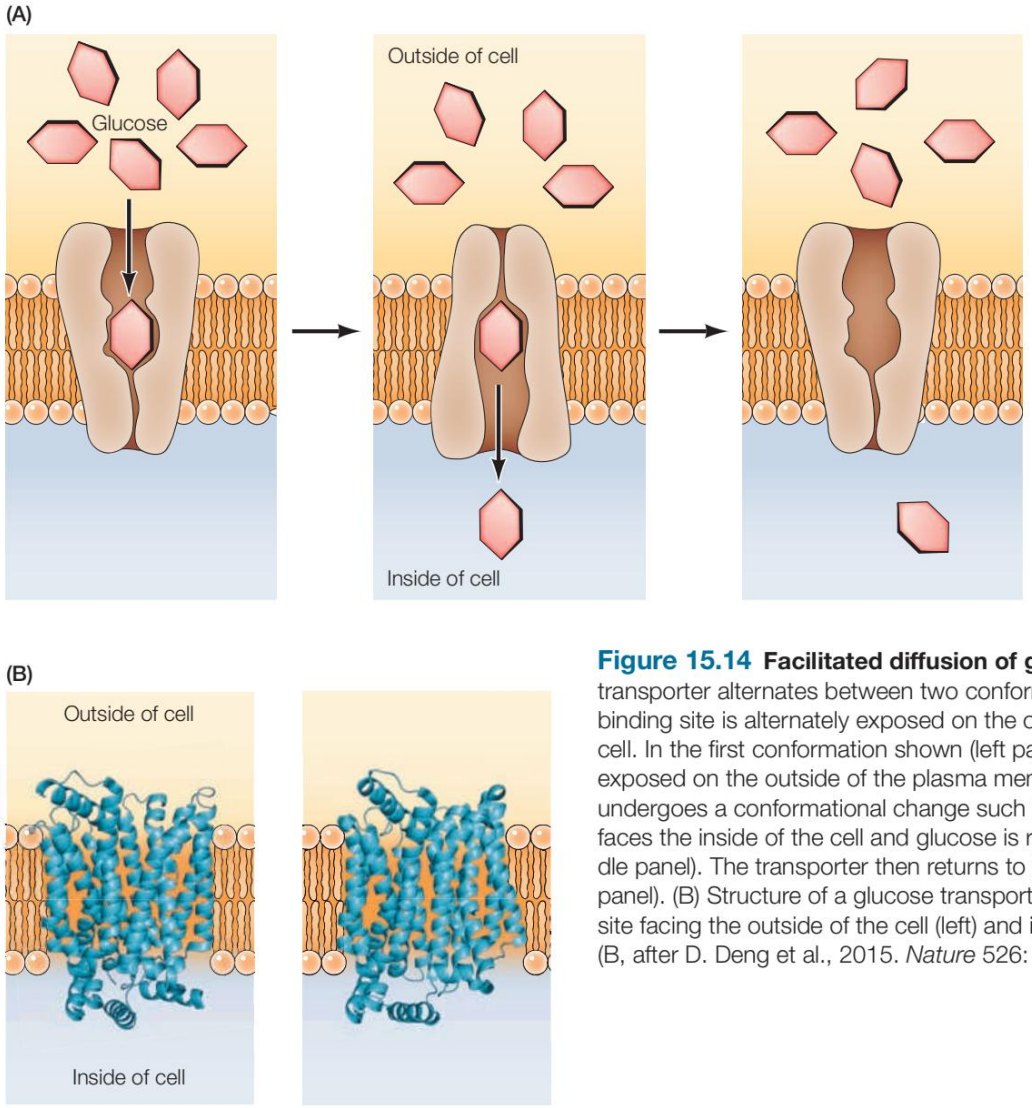


Figure 15.14 Facilitated diffusion of glucose (A) The glucose transporter alternates between two conformations in which a glucose-binding site is alternately exposed on the outside and the inside of the cell. In the first conformation shown (left panel) glucose binds to a site exposed on the outside of the plasma membrane. The transporter then undergoes a conformational change such that the glucose-binding site faces the inside of the cell and glucose is released into the cytosol (middle panel). The transporter then returns to its original conformation (right panel). (B) Structure of a glucose transporter with the glucose-binding site facing the outside of the cell (left) and inside of the cell (right). (B, after D. Deng et al., 2015. *Nature* 526: 391.)

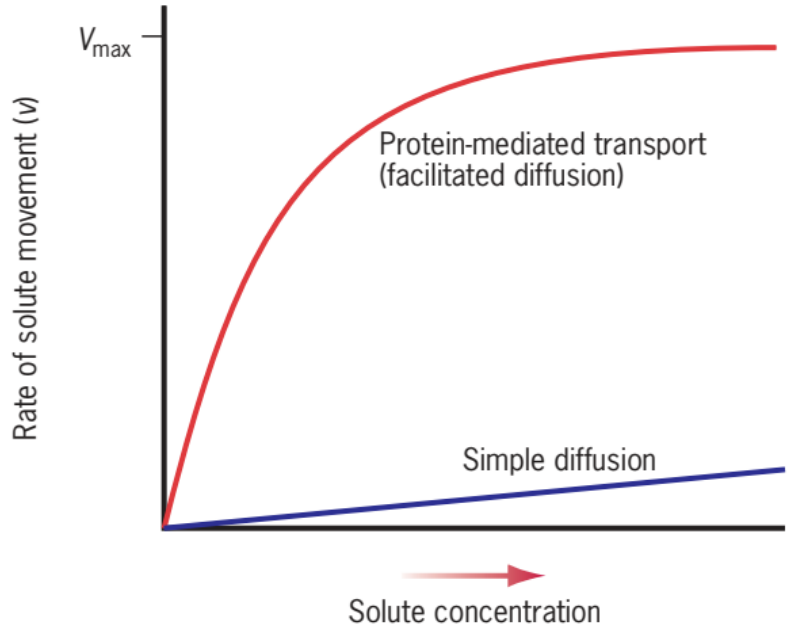


FIGURE 4.45 The kinetics of facilitated diffusion as compared to that of simple physical diffusion.

Facilitated Diffusion: Ion Channels (Na^+ & K^+)

Key Features:

- **Ion channels:** Allow rapid ion transport
- **K^+ channels:** Potassium leaks OUT (high inside → low outside)
- **Na^+ channels:** Sodium leaks IN (high outside → low inside)
- **Selectivity:** Each channel selective for specific ion size and charge
- **Speed:** Very rapid (millions of ions/second)

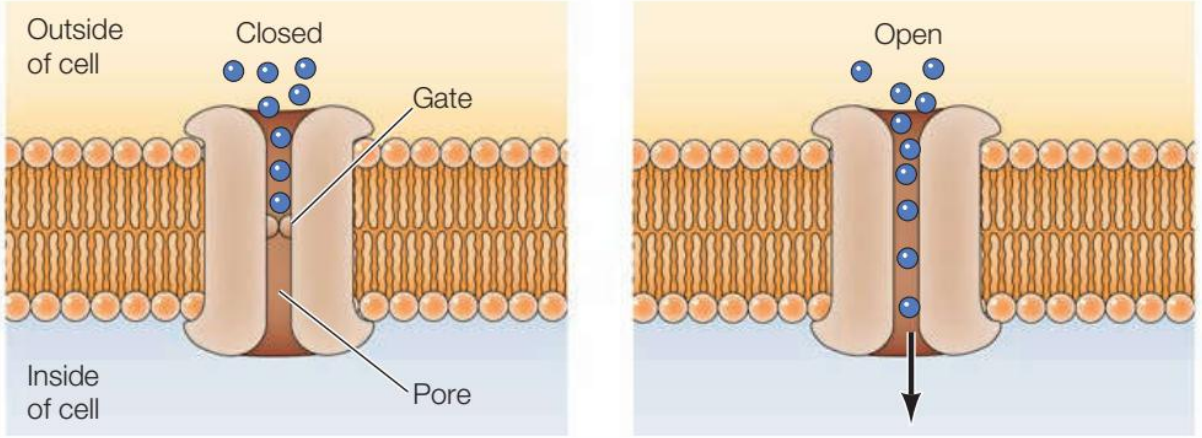


Figure 15.16 Model of an ion channel In the closed conformation, the flow of ions is blocked by a gate. Opening of the gate allows ions to flow rapidly through the channel. The channel contains a narrow pore that restricts passage to ions of the appropriate size and charge.

TABLE 4.3 Ion Concentrations Inside and Outside of a Typical Mammalian Cell

	Extracellular concentration	Intracellular concentration	Ionic gradient
Na^+	150 mM	10 mM	15×
K^+	5 mM	140 mM	28×
Cl^-	120 mM	10 mM	12×
Ca^{2+}	10^{-3} M	10^{-7} M	10,000×
H^+	$10^{-7.4}$ M (pH of 7.4)	$10^{-7.2}$ M (pH of 7.2)	Nearly 2×

Active transport

- This kind of transport requires energy
- Solutes moves against concentration gradient

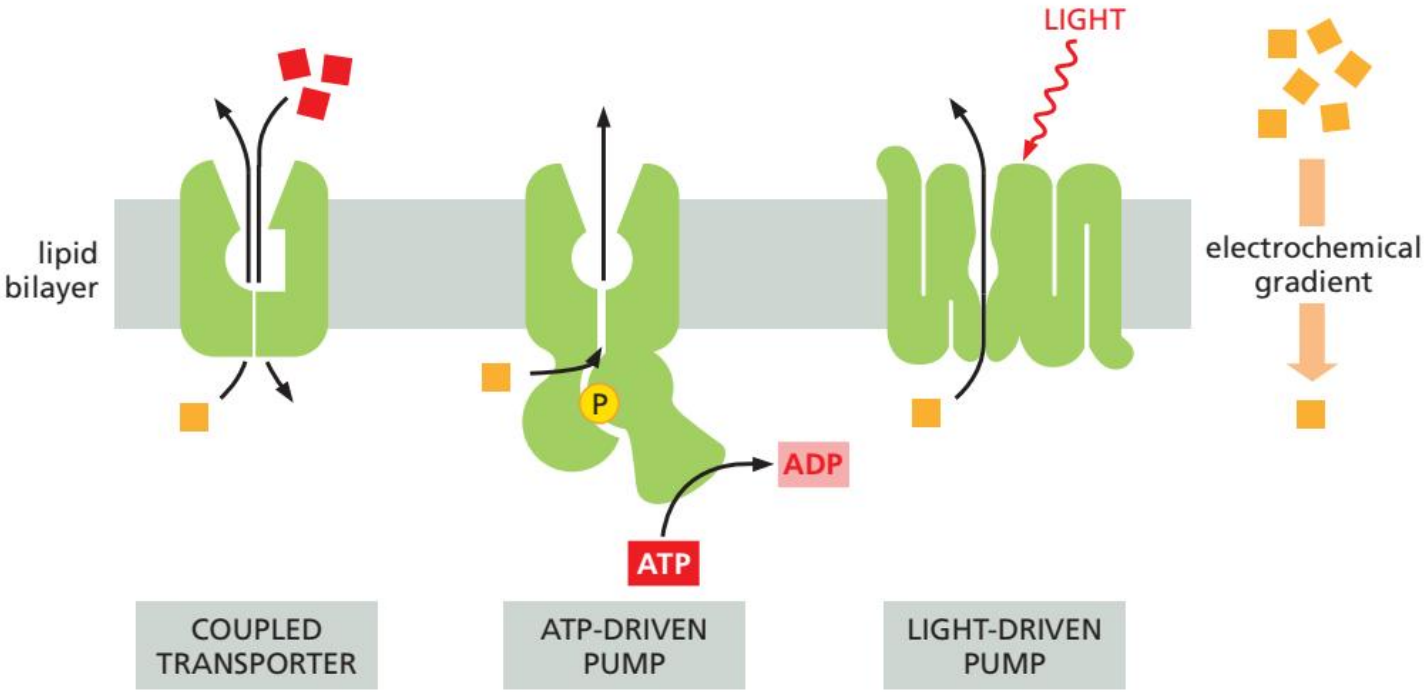
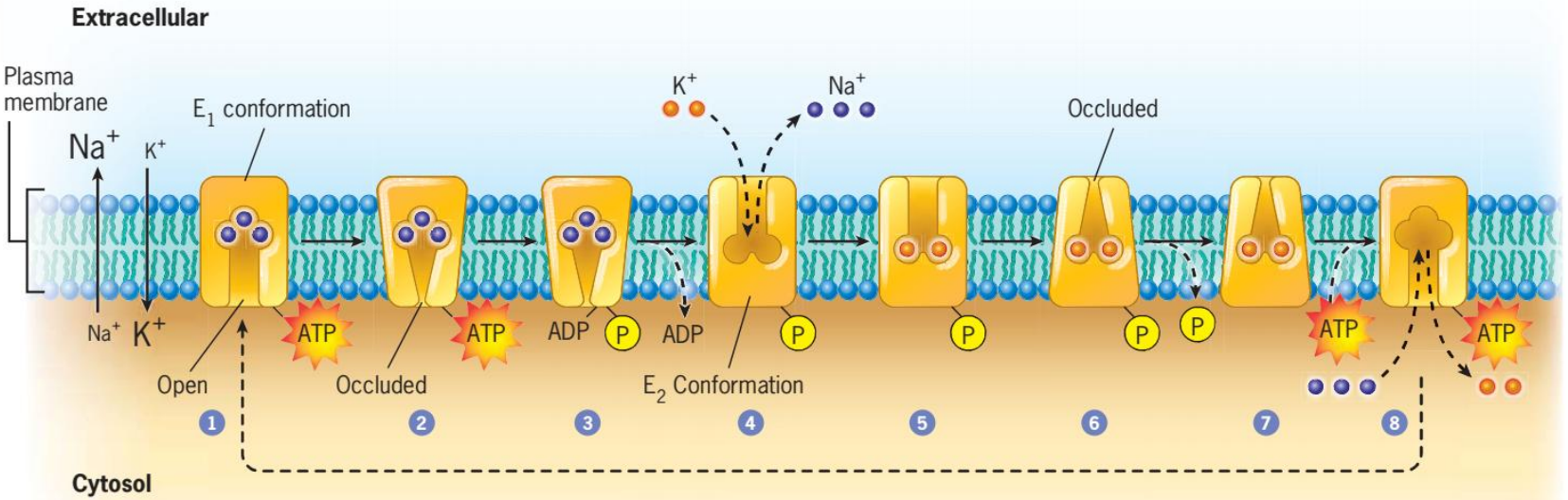


Figure 11–7 Three ways of driving active transport. The actively transported molecule is shown in *orange*, and the energy source is shown in *red*. Redox driven active transport is discussed in Chapter 14 (see Figures 14–18 and 14–19).

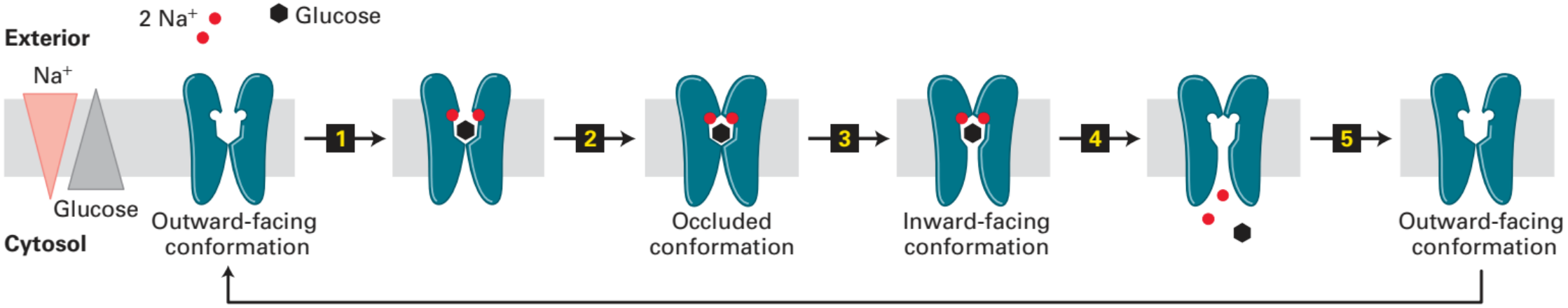
PRIMARY ACTIVE TRANSPORT - Na^+-K^+-ATPase PUMP

- **ATP-Driven Ion Pumping Against Gradients**
- **Definition:** Direct ATP hydrolysis drives transport against electrochemical gradients**Pumping Cycle (P-type ATPase):**
  - **ATP Binding:** Pump-ATP complex formed; 2 K^+ binding sites accessible from outside
  - **Na^+ Binding:** 3 intracellular Na^+ bind to pump
  - **Autophosphorylation:** Terminal phosphate of ATP transfers to aspartate residue (P-ATPase mechanism)
  - **Conformational Change:** Exposes K^+ binding sites outside; closes Na^+ sites inside
  - **K^+ Binding:** 2 extracellular K^+ bind; 3 Na^+ released to extracellular space
  - **Dephosphorylation:** Phosphate hydrolysis returns pump to initial state; K^+ released inside
- **Cellular Energy Consumption:**
  - ~1/3 of cellular ATP devoted to Na^+-K^+ pump
  - Higher in neurons and kidney tubules (up to 70% ATP)
  - Maintains steep Na^+ and K^+ gradients
  - Essential for nerve/muscle function, glucose uptake, cell volume regulation
- **Electrogenic Effect:**
  - Net extrusion of 3 positive charges vs 2 positive charges entering
  - Creates net outward current
  - Contributes ~10% to membrane potential (rest from K^+ gradient)



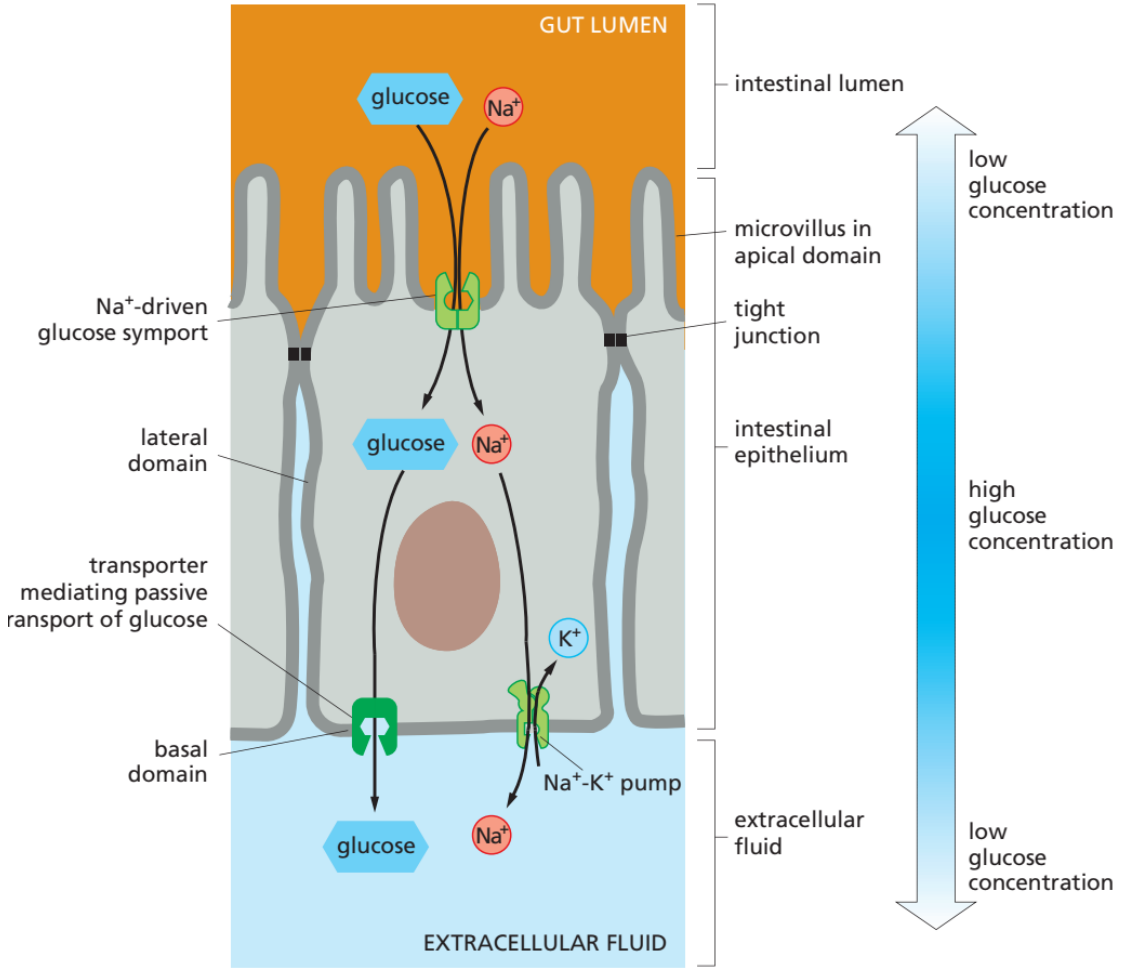
Secondary Active Transport: Na^+-Glucose Cotransport

- **Energy Source:** Na^+ electrochemical gradient (NOT direct ATP)
- **Transport Mechanism:**
- **Na^+ Gradient Established:** Na^+-K^+ pump maintains low intracellular Na^+
- **Cotransporter Binding:** Both Na^+ AND glucose bind SGLT1 simultaneously
- **Coupled Movement:** Na^+ moves DOWN its gradient (favorable, releases energy)
- **Glucose Movement:** Glucose moves UP its gradient (unfavorable) using Na^+ energy
- **Transcript:** Both enter cell interior; Na^+ continues to Na^+-K^+ pump for recycling



Epithelial Glucose Absorption:

- **Apical Membrane (intestinal lumen side):**
  - SGLT1 cotransporters pump glucose ACTIVELY into cell
  - Glucose accumulates intracellularly (against concentration gradient)
  - Driven by Na^+ gradient
- **Basolateral Membrane (blood side):**
  - GLUT2 glucose uniporters allow glucose to exit PASSIVELY
  - Glucose moves from high (intracellular) to low (blood) concentration
  - No energy required
  - **Net Result**: Glucose transcellular transport from lumen to blood



LDL Receptor-Mediated Endocytosis: Overview

- **What is LDL?**
  - **LDL**: Low-Density Lipoprotein
  - Spherical particles ~22 nm diameter
  - Core: ~1500 cholesteryl ester molecules
  - Surface: Phospholipid monolayer + apolipoprotein B (recognition protein)
  - Function: Transport cholesterol from liver to peripheral tissues
- **Why Cells Need Cholesterol:**
  - Membrane synthesis and repair
  - Steroid hormone synthesis (adrenal glands, gonads)
  - Bile acid synthesis (liver)
  - Vitamin D synthesis (skin)
- **LDL Receptor-Mediated Endocytosis:**
  - Selective, efficient uptake mechanism
  - *100-fold enhancement vs simple diffusion*
  - Receptor clustering in specialized membrane domains
  - Energy-dependent (requires ATP for later events, not direct ATP use for uptake)

LDL-cholesterol

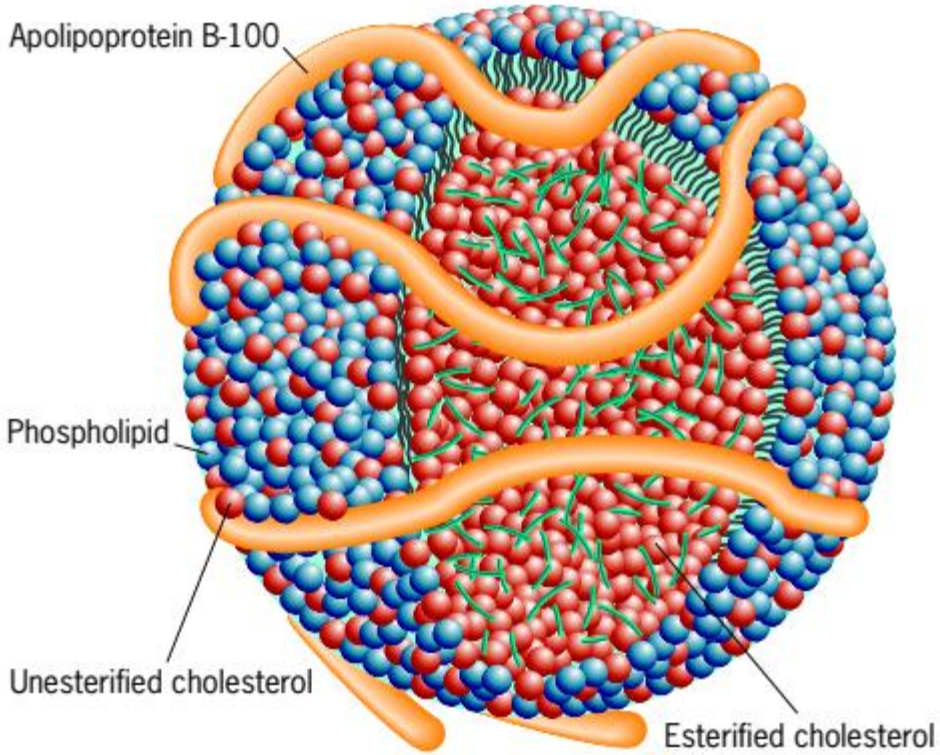


Figure 8.44 **LDL cholesterol.** Each particle consists of esterified cholesterol molecules, surrounded by a mixed monomolecular layer of phospholipids and cholesterol, and a single molecule of the protein apolipoprotein B-100, which interacts specifically with the LDL receptor projecting from the plasma membrane.

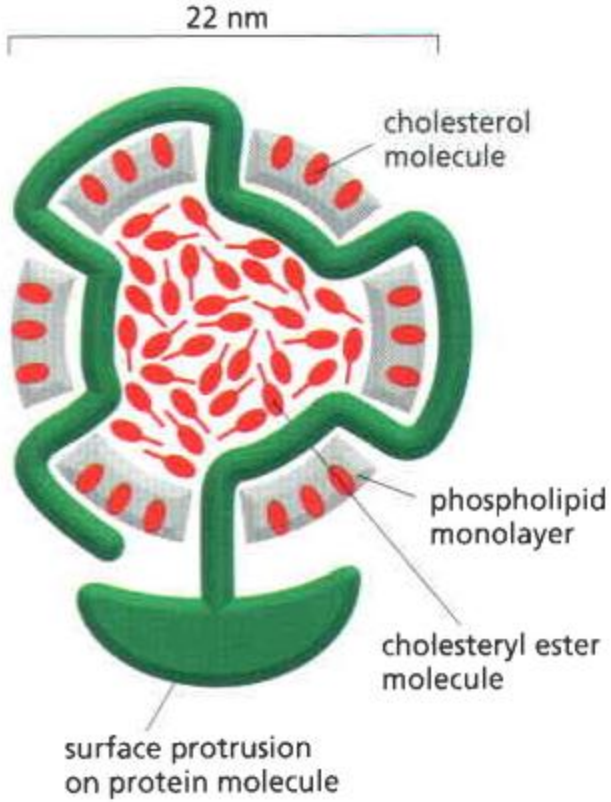


Figure 13–50 A low-density lipoprotein (LDL) particle. Each spherical particle has a mass of 3×10^6 daltons. It contains a core of about 1500 cholesterol molecules esterified to long-chain fatty acids. A lipid monolayer composed of about 800 phospholipid and 500 unesterified cholesterol molecules surrounds the core of cholesterol esters. A single molecule of a 500,000-dalton protein organizes the particle and mediates the specific binding of LDL to cell-surface LDL receptors.

Clathrin

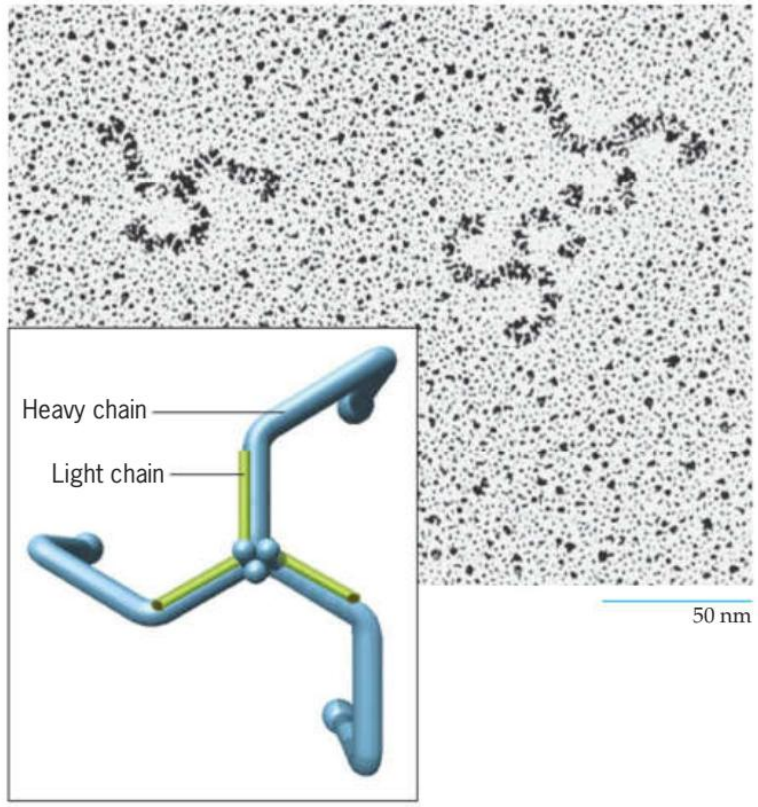


FIGURE 8.39 Clathrin triskelions. Electron micrograph of a metal-shadowed preparation of clathrin triskelions. Inset shows the triskelion is composed of three heavy chains. The inner portion of each heavy chain is linked to a smaller light chain.

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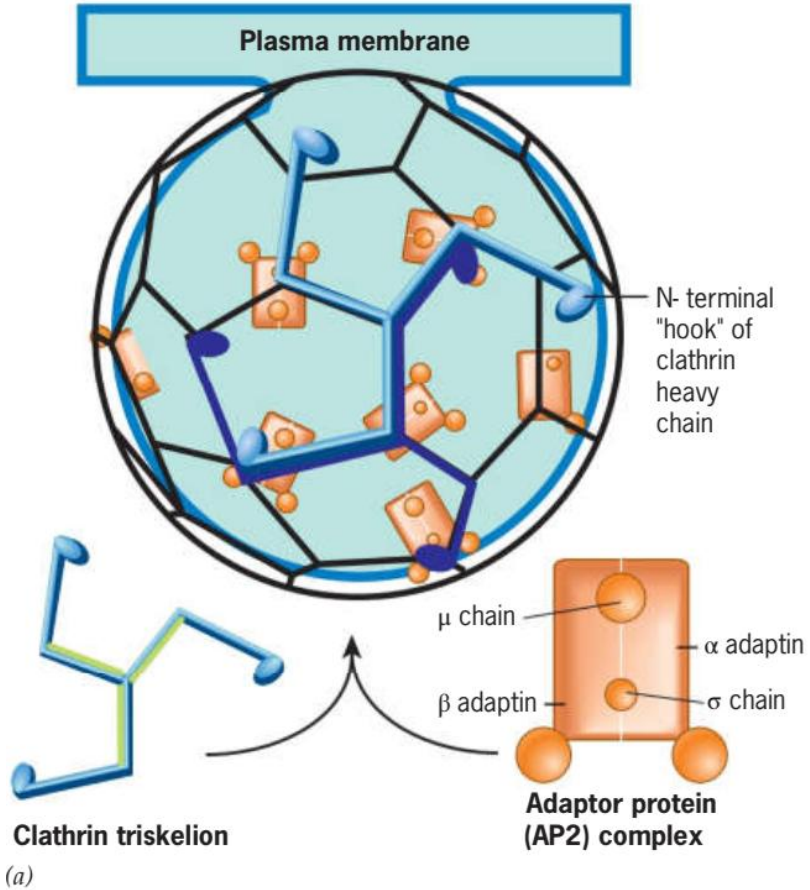
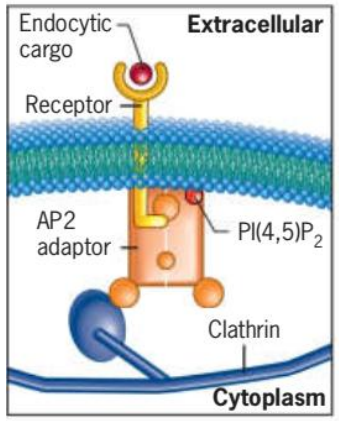




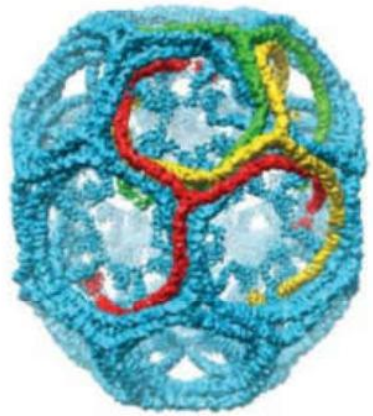
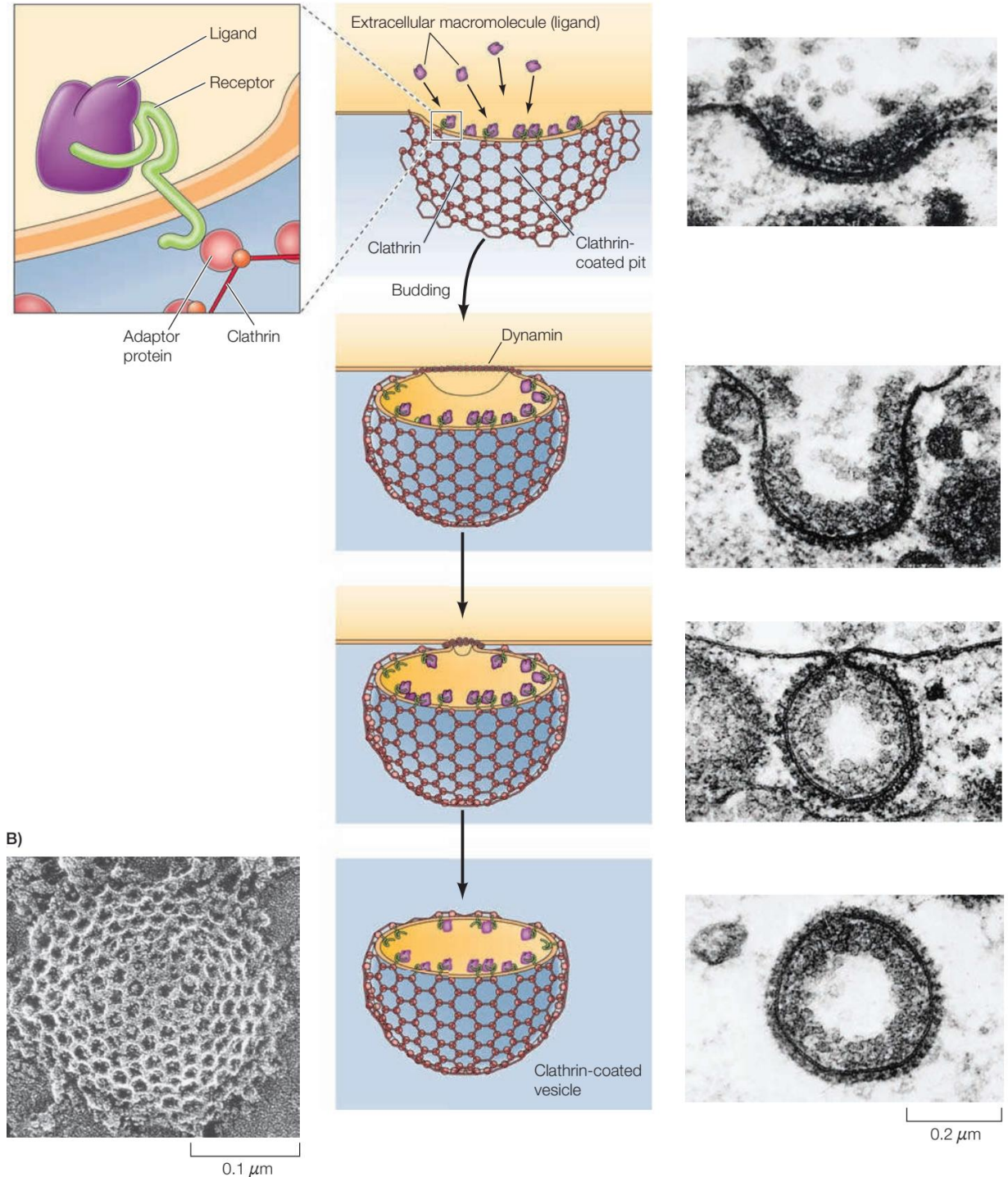


FIGURE 8.40 Molecular organization of a coated vesicle. (*a*) Schematic drawing of the surface of a coated vesicle showing the arrangement of triskelions and adaptors in the outer clathrin coat. The sides of the polygons are formed by parts of the legs of overlapping triskelions. The N-terminus of each clathrin heavy chain forms a "hook" that projects toward the surface of the membrane where it engages an adaptor. Each adaptor, which consists of four different polypeptide subunits, can bind a diverse array of accessory proteins that are not shown in this illustration. Both the hooks and adaptors are situated at the vertices of the polyhedrons. (*Note:* Not all of the triskelions of the lattice are shown in this figure; if they were, every vertex would have a clathrin hub, hook, and associated adaptor.) (*b*) Schematic drawing of a cross section through the surface of a coated vesicle showing the interactions of the AP2 adaptor complexes with both the clathrin coat and membrane receptors. Recruitment of AP2 adaptors to the plasma membrane is facilitated by the presence of $PI(4,5)P_2$ molecules in the inner (cytosolic) leaflet of the membrane as shown in Figure 8.42. Each receptor is bound to a ligand being internalized. (*c*) Reconstruction of a clathrin cage containing 36 triskelions showing the overlapping arrangement of several of these trimeric molecules (shown in different colors).

SOURCE: (*a*) *Annual Review of Biochemistry*. Volume 65, 1996 by Richardson, Charles C., Abelson, John N., Raetz, Christian R. H. copyright 1997 Reproduced with permission of Annual Reviews, Inc. In the format textbook via copyright clearance center; (*b–c*) From Alexander Fotin et al., *Nature* 432:574, 2004, courtesy of Stephen C. Harrison; © 2004. Reprinted with permission from Macmillan Publishers Ltd.

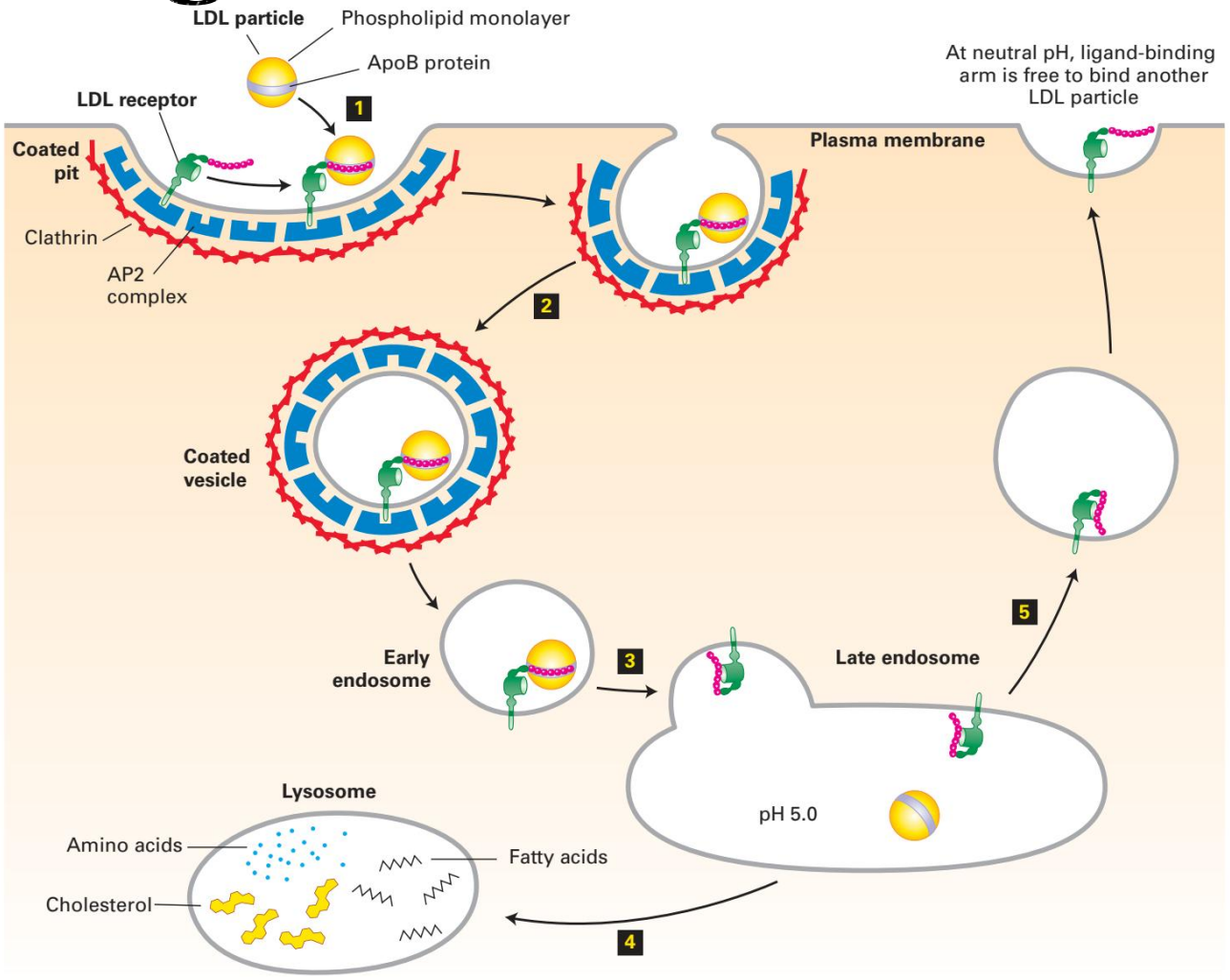
LDL Endocytosis: Binding & Coated Pit Formation

1. **LDL Binding:** LDL particles in blood bind to LDL receptors on plasma membrane surface
2. **Receptor Clustering:** Bound LDL-receptor complexes migrate and cluster in specialized regions called coated pits
3. **Coated Pits:** Regions rich in clathrin protein on cytoplasmic side. Contain 20× more LDL receptors than rest of membrane
4. **Invagination:** Coated pits indent inward, forming depression in membrane



LDL Endocytosis: Vesicle Formation & Sorting

FIGURE 14-29 Endocytic pathway for internalizing low-density lipoprotein (LDL). Step 1: A cell-surface LDL receptor binds to an ApoB protein embedded in the phospholipid outer layer of an LDL particle. Interaction between the NPXY sorting signal in the cytosolic tail of the LDL receptor and the AP2 complex incorporates the receptor-ligand complex into a forming endocytic vesicle. Step 2: Clathrin-coated pits containing receptor-LDL complexes are pinched off by the same dynamin-mediated mechanism used to form clathrin/AP1-coated vesicles on the *trans*-Golgi network (see Figure 14-19). Step 3: After the vesicle coat is shed, the uncoated endocytic vesicle (early endosome) fuses with a late endosome. The acidic pH in this compartment causes a conformational change in the LDL receptor that leads to release of the bound LDL particle. Step 4: The late endosome fuses with a lysosome, and the proteins and lipids of the free LDL particle are broken down into their constituent parts by enzymes in the lysosome. Step 5: The LDL receptor is recycled to the cell surface, where at the neutral pH of the exterior medium, the receptor undergoes a conformational change so that it can bind another LDL particle. See M. S. Brown and J. L. Goldstein, 1986, *Science* **232**:34, and G. Rudenko et al., 2002, *Science* **298**:2353.



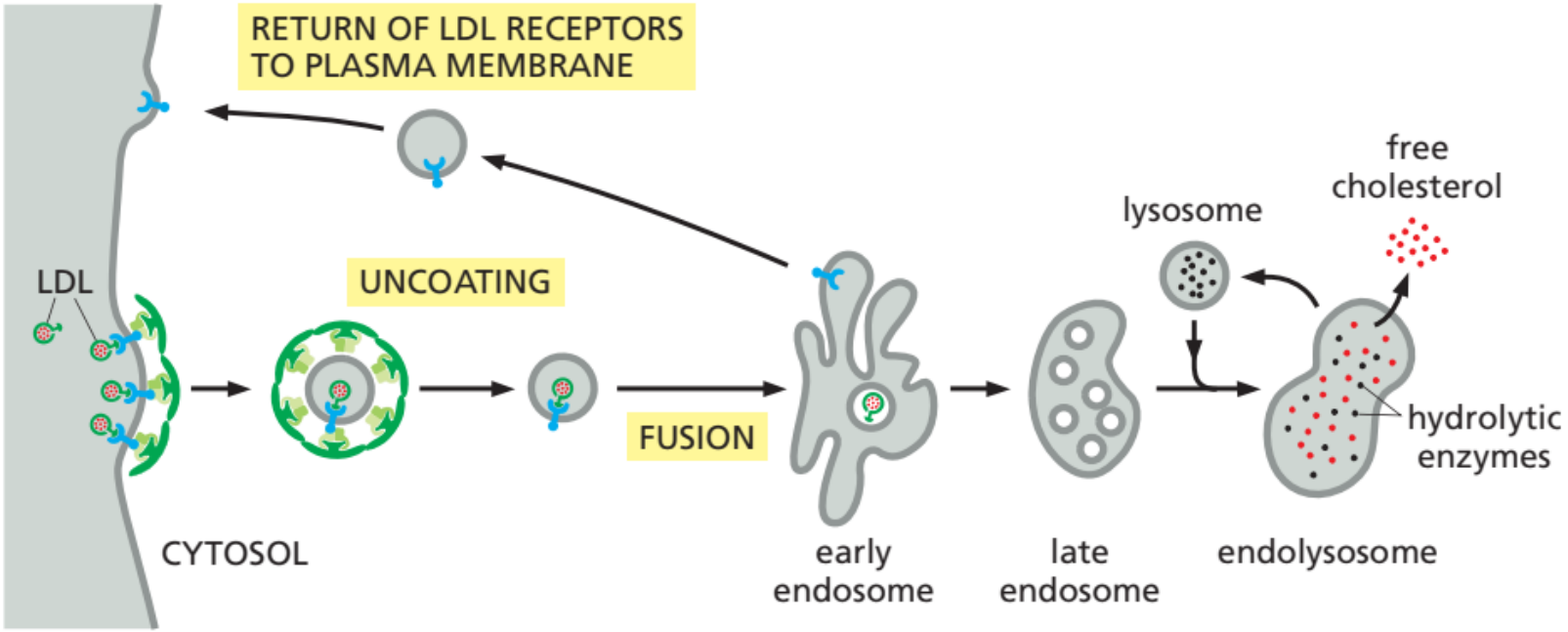
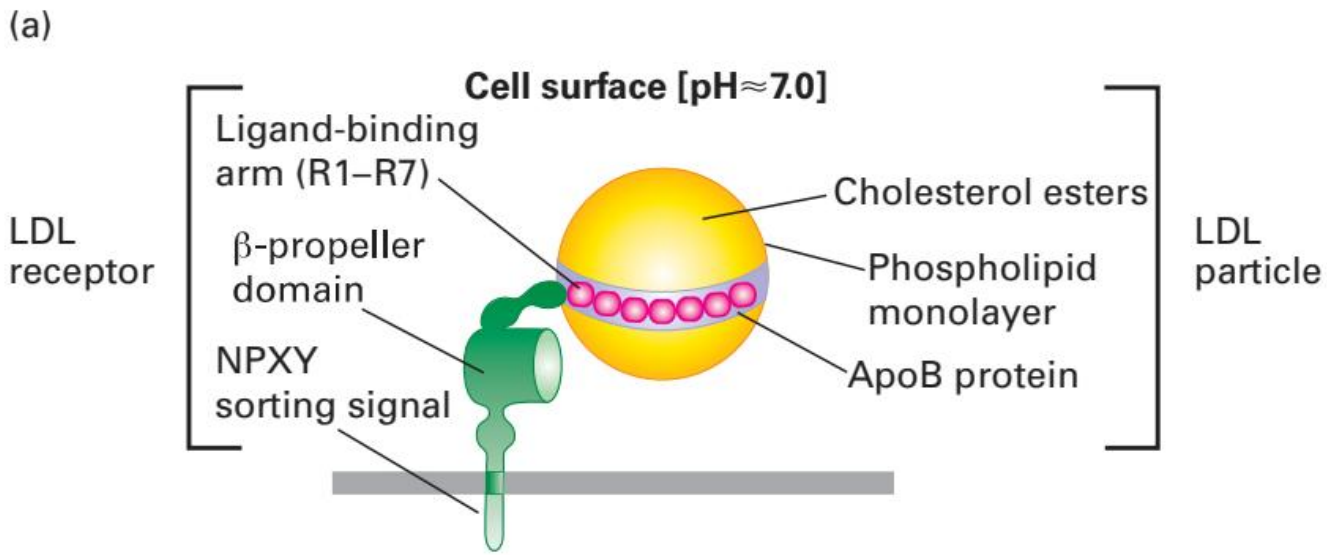
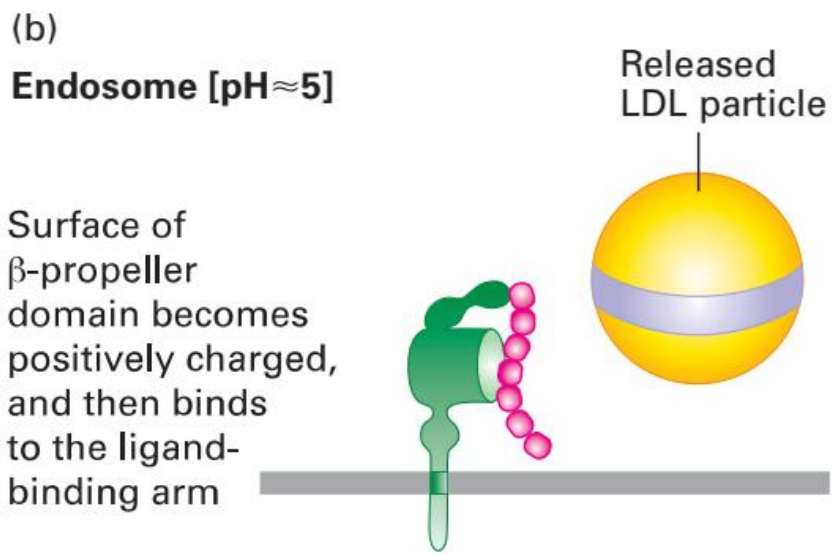


Figure 13–52 The receptor-mediated endocytosis of LDL. Note that the LDL dissociates from its receptors in the acidic environment of the early endosome. After a number of steps, the LDL ends up in endolysosomes and lysosomes, where it is degraded to release free cholesterol. In contrast, the LDL receptors are returned to the plasma membrane via transport vesicles that bud off from the tubular region of the early endosome, as shown. For simplicity, only one LDL receptor is shown entering the cell and returning to the plasma membrane. Whether it is occupied or not, an LDL receptor typically makes one round trip into the cell and back to the plasma membrane every 10 minutes, making a total of several hundred trips in its 20-hour life-span.





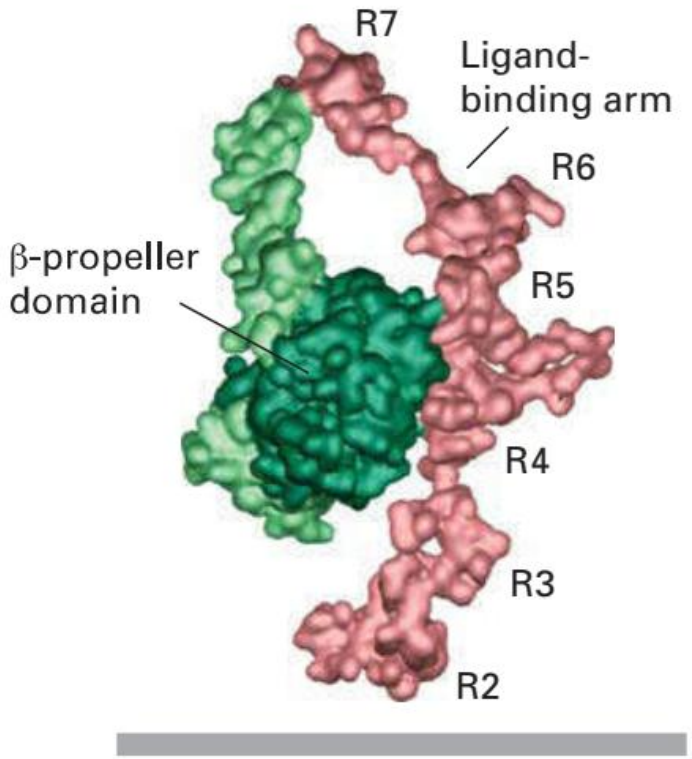


FIGURE 14-30 Model for pH-dependent binding of LDL particles by the LDL receptor. Schematic depiction of an LDL receptor at the neutral pH found at the cell surface (a) and at the acidic pH found in the interior of the late endosome (b). (a) At the cell surface, apoB-100 on the surface of an LDL particle binds tightly to the receptor. Of the seven cysteine-rich repeats (R1–R7) in the ligand-binding arm, R4 and R5 appear to be most critical for LDL binding. (b, *top*) Within the endosome, histidine residues in the β-propeller domain of the LDL receptor become protonated. The positively charged propeller can bind with high affinity to the ligand-binding arm, which contains negatively charged residues, causing release of the LDL particle. (b, *bottom*) Experimental electron density and C_α backbone trace model of the extracellular region of the LDL receptor at pH 5.3 based on x-ray crystallographic analysis. In this conformation, extensive hydrophobic and ionic interactions occur between the β propeller and the R4 and R5 repeats. [Part (b) data from G. Rudenko et al., 2002, *Science* **298**:2353, PDB ID 1n7d.]

LDL Endocytosis: Cellular Significance

- **When Cell has SUFFICIENT Cholesterol:**
  - Lysosomal free cholesterol accumulates
  - Cholesterol activates SREBP (Sterol Regulatory Element-Binding Protein)
  - SREBP inhibits transcription of LDL receptor gene
  - Fewer LDL receptors synthesized and inserted into membrane
  - Cell takes up LESS cholesterol
  - Cellular cholesterol synthesis also decreases
- **When Cell NEEDS Cholesterol:**
  - Cholesterol levels drop
  - SREBP activation decreases
  - LDL receptor gene transcription INCREASES
  - More receptors displayed on cell surface
  - Enhanced LDL uptake
  - Cellular cholesterol increases
- **Clinical Relevance - Familial Hypercholesterolemia (FH):**
  - **Genetic Defects in LDL Pathway:**
    - **Complete Loss:** No functional LDL receptors → blood cholesterol ~600-1000 mg/dL (normal <200)
    - **Partial Defect:** Receptors absent from coated pits (can't internalize)
    - **Binding Site Defect:** Receptors present but can't bind LDL
    - **Result:** LDL accumulates in blood → deposits in arteries (atherosclerotic plaques)
  - **Pathological Consequence:**
    - Premature atherosclerosis (teens-20s)
    - Heart attacks in young patients
    - Coronary artery disease severity correlates with cholesterol levels
    - Treatment: Statins (↓ cholesterol synthesis), PCSK9 inhibitors (↑ receptor recycling)

Transport Type	Energy Source	Gradient Direction	Speed	Example	Location
Simple Diffusion	None (concentration gradient)	Down (high → low)	Slow-moderate	O_2, CO_2	Lung, tissues
Facilitated Diffusion	None (protein-assisted)	Down (high → low)	Fast	Glucose (GLUT), ions (channels)	Muscle, adipose, all cells
Primary Active Transport	ATP hydrolysis (direct)	UP (against gradient)	Moderate	Na^+-K^+-ATPase pump	All cells (especially neurons)
Secondary Active Transport	Ion gradient (coupled)	UP for solute, DOWN for ion	Fast	Na^+-Glucose cotransport (SGLT1)	Intestine, kidney
Endocytosis	ATP (for coat proteins, dynamin)	Inward vesiculation	Slow	LDL receptor-mediated	All cells (especially macrophages)

Comparative Table: All Transport Types

Key Distinctions:

Passive: No energy; transport DOWN gradients only

Active: Requires energy; can transport AGAINST gradients

Endocytosis: Unique membrane invagination mechanism; can internalize large particles/macromolecules

Clinical Applications & Real-World Examples

- **Drug Absorption:**
  - Many drugs use glucose transporters for intestinal absorption
  - Understanding transport mechanisms improves drug delivery
- **Diabetes Treatment:**
  - **SGLT2 inhibitors:** Block glucose reabsorption in kidney → glucose excreted in urine → lower blood sugar
  - Target: Secondary active transport in kidney tubules
- **Cholesterol Management:**
  - **Statins:** Increase LDL receptor expression → more LDL uptake → lower blood cholesterol
  - Prevents cardiovascular disease
- **Genetic Disorders:**
  - **Familial hypercholesterolemia:** Defective LDL receptors → high cholesterol

Conclusion

- **Transport mechanisms** are fundamental to cell survival and function
- Different mechanisms suit different molecules based on **size, polarity, and cellular needs**
- Regulation of transport maintains **cellular homeostasis**
- Understanding transport is key to understanding **physiology and diseases**
- Clinical applications: From **drug delivery** to treating genetic disorders

Suggested Reading

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