2 The Cell Membrane

The cell's organelles and its intracellular solutes (some inorganic and some organic) are contained within the cell by its membrane. The membrane has limited and selective permeability; it maintains the intracellular concentration of electrolytes and biologic compounds that is distinctly different from that of the extracellular fluid. Cell membrane function is thus an essential one for the health and survival of the cell.

Membrane Composition

Membranes are complex structures composed of lipids, proteins, and carbohydrates. The cell membrane contains proteins and lipids in a *mass ratio* of 50:50. An average membrane protein is several times larger than the average lipid molecule, but lipid molecules are ~50 times more numerous than protein molecules. The ratio is not absolute and varies from membrane to membrane. The exact ratio between the two varies with the function of the cell. For example, the myelin sheath of nerves has ~75% lipids and 25% proteins, whereas membranes involved in energy transduction, such as the inner mitochondrial membrane, have 75% proteins and 25% lipids.

The major membrane lipids are phospholipids, glycosphingolipids, and cholesterol. Membrane phospholipids are of two types: the phosphoglycerides (**Fig. 2.1A**), which are more abundant, and the sphingomyelins (**Fig. 2.1B**), which are prominent in the myelin sheath. Glycosphingolipids present in the membrane include cerebrosides and gangliosides (**Figs. 2.1C** and **2.1D**). Both are derivatives of sphingosine. Cholesterol is also present in the cell membrane, where it plays an important role in determining membrane fluidity (see below).

The plasma membrane contains over 100 different proteins: enzymes, transport proteins, structural proteins, antigens (e.g., for histocompatibility), and receptors for various molecules. The external side of membrane proteins has oligosaccharide chains (carbohydrates) attached to them.

Membrane Structure

Lipid Bilayer

Membrane lipids are amphipathic; that is they contain both hydrophobic and hydrophilic regions. The hydrophilic (polar) region is their globular head; the hydrophobic (nonpolar) regions are their fatty acid tails. The membrane lipids are organized into a continuous bilayer (as seen in **Fig. 2.2A**) in which the hydrophobic regions of the phospholipids are shielded from the aqueous environment, while the hydrophilic regions are immersed in water. Proteins are found inserted into this lipid bilayer and are classified into integral proteins and peripheral proteins.

Integral proteins are anchored to membranes through a direct interaction with the lipid bilayer. Some of them span the entire thickness of the membrane, often traversing the membrane several times (**Fig. 2.2B**). Others are located more on the outside or inside of the membrane.

Integral proteins are amphipathic, consisting of two hydrophilic ends separated by an intervening hydrophobic region that traverses the hydrophobic core of the bilayer. The hydrophilic ends of the integral protein are found outside the membrane, on either its external or internal surface. Integral

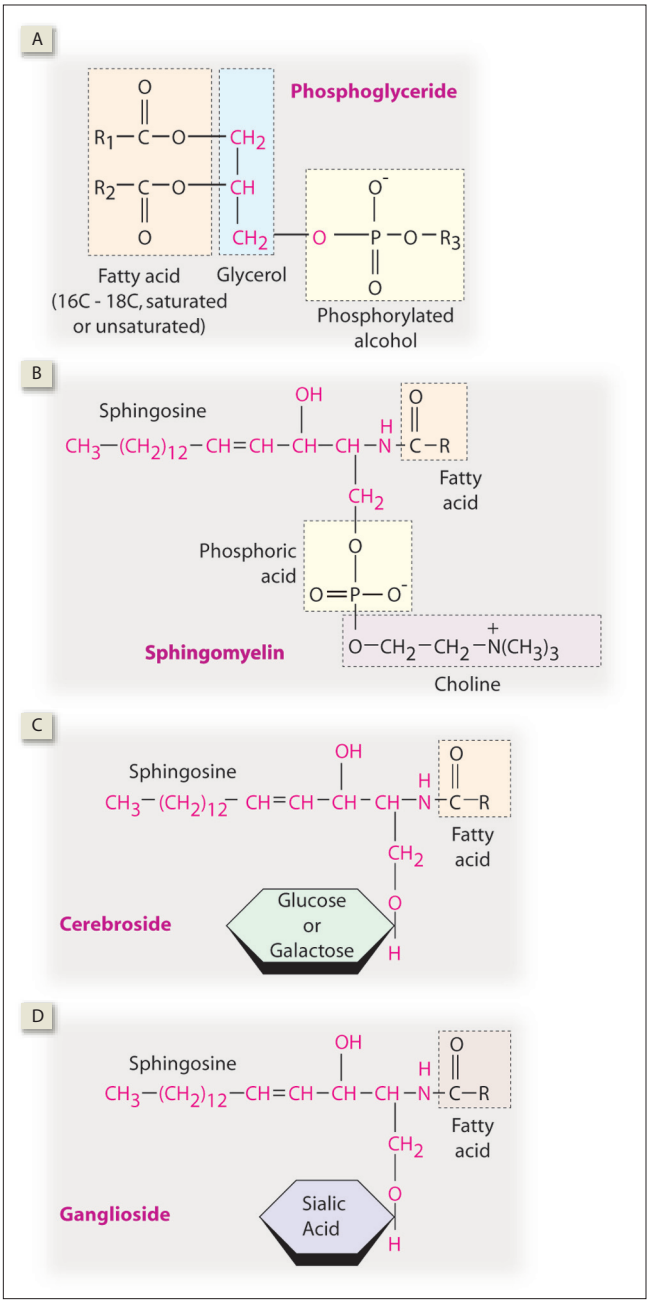

Fig. 2.1 **(A,B)** Chemical structure of membrane phospholipids and **(C,D)** glycosphingolipids.

proteins serve as (1) *channels,* which permit the passage of selected ions through the membrane; (2) *carriers* (or transporters), which translocate substances across the membrane by binding to them; (3) *pumps,* which are carriers that split adenosine triphosphate (ATP) and use the energy derived for membrane transport of substrates; (4) *receptors* (located on the outside), which bind to specific molecules and generate a chemical signal initiating intracellular reactions; and (5) *enzymes* catalyzing reactions at the membrane surfaces, both outer and inner.

Peripheral proteins do not interact directly with the phospholipids in the bilayer. They are associated with integral proteins via electrostatic interactions. They are located on both surfaces of the membrane. Peripheral proteins serve as cell adhesion molecules (CAMs) that anchor cells to neighboring cells and to the basal lamina. They also contribute to the cytoskeleton when present on the cytoplasmic side of the membrane. For example, ankyrin, a peripheral protein located on the inside of the membrane, anchors spectrin (a cytoskeletal protein in the erythrocyte) to band-3 (an integral protein of erythrocyte membrane). Ankyrin plays an important role in the maintenance of the biconcave shape of the erythrocyte (**Fig. 2.2C**).

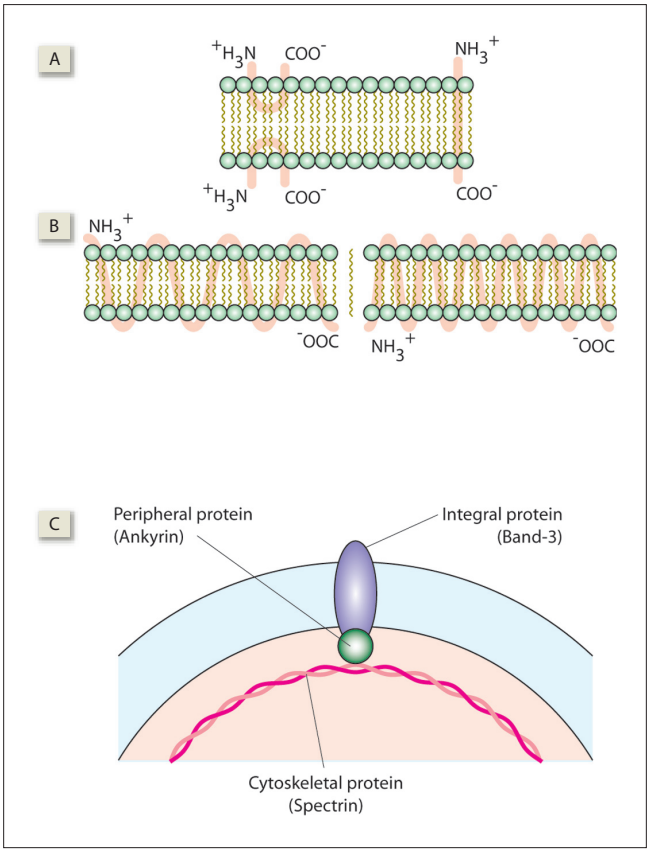

Fig. 2.2 Integral proteins. **(A)** Integral proteins with their polar residues projecting out. **(B)** A molecule of G-protein spanning the membrane seven times, and a glucose transporter molecule, spanning the membrane 12 times. **(C)** A peripheral protein anchoring the integral protein to the cytoskeletal protein of an erythrocyte.

Fluid Mosaic

The fluid mosaic model of membrane structure has been likened to icebergs (membrane proteins) floating in a sea of predominantly phospholipid molecules (**Fig. 2.3A**). Phospholipids also float about in the plane of the membrane. This diffusion, termed *translational diffusion*, can be as rapid as

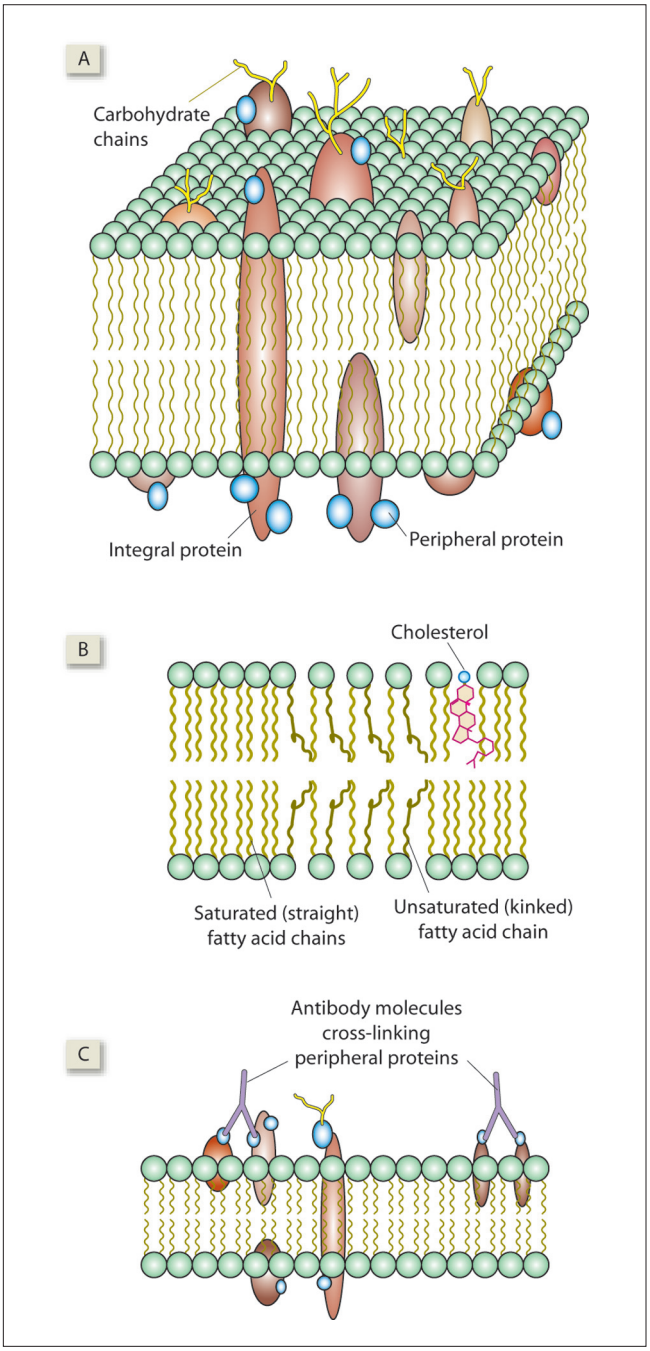

Fig. 2.3 Membrane structure. **(A)** The cell membrane showing integral and peripheral proteins. **(B)** Intercalation of kinked unsaturated fatty acid chains and cholesterol molecules spaces out the phospholipid molecules and affects membrane fluidity. **(C)** Antibody molecules cross-linking peripheral proteins. This reduces the mobility of integral proteins and reduces membrane fluidity.

several micrometers per second. Several membrane transport processes and enzyme activities depend on the optimum fluidity of the cellular membrane. As membrane fluidity increases, there is a rise in membrane permeability to water and small hydrophilic solutes. The fluidity of a cell membrane depends on the lipid composition of the membrane, the density of integral proteins, and the temperature.

Role of fatty acids | A lipid bilayer made up of only one type of phospholipid changes from a liquid state to a rigid crystalline state (gel state) at a characteristic freezing point. This change in state is known as a phase transition, and the temperature at which it occurs is called the phase transition temperature (T_m). The T_m is higher (fluidity is low) when the constituent fatty acid chains are long and mostly saturated (without double bonds). Long chains have greater interactions among themselves, making the membrane stiffer. Saturated fatty acids have straight tails, whereas unsaturated fatty acids have kinked tails. As more kinks are inserted in the tails, the membrane becomes less tightly packed, and therefore its fluidity increases (**Fig. 2.3B**), a change with consequences for membrane function.

Role of cholesterol | The presence of cholesterol in the membrane makes it possible for the cell membrane to maintain its fluidity across a wide range of temperatures. The number of cholesterol molecules in the membrane can be as high as the number of phospholipids. At high cholesterol:phospholipid ratios, the transition temperature is abolished altogether; that is, the membrane always remains fluid. Cholesterol is found among the phospholipids of the membrane, with its hydroxyl group at the aqueous interface and the remainder of the molecule among the fatty acid tails of phospholipids (**Fig. 2.3B**). At temperatures above the T_m, cholesterol partially immobilizes those portions of the fatty acid chains that lie adjacent to it and thus makes the membrane stiffer. At temperatures below the T_m, it minimizes the mutual interaction of the hydrocarbon tails of fatty acids and thereby increases membrane fluidity.

Membrane areas having a high density of integral proteins have low membrane fluidity due to protein–protein interaction. Some of the protein–protein interactions taking place within the plane of the membrane may be mediated by interconnecting peripheral proteins, such as cross-linking antibodies (**Fig. 2.3C**). These peripheral proteins may then restrict the mobility of integral proteins within the membrane.

Membrane Asymmetry

Membranes are asymmetric structures. This asymmetry is of two types: regional asymmetry and inside–outside asymmetry.

Regional asymmetry refers to the specialization of the cell membrane at different sites on the cell. For example, in renal tubules (see Chapter 53) and intestinal mucosal cells (see Chapter 70), only the membrane facing the lumen (tubular or intestinal) is thrown into folds, forming microvilli. Similarly, only the membranes that are contiguous with adjacent cells show specializations for intercellular tight junctions.

Inside–outside (transverse) asymmetry refers to the structural differences through the thickness of the cell membrane. For example, the phospholipids are not symmetrically disposed across the membrane thickness. The choline-containing phospholipids (lecithin and sphingomyelin) are located mainly in the outer molecular layer; the aminophospholipids (phosphatidylserine and cephalin) are preferentially located in the inner layer. Cholesterol is generally present in larger amounts on the outside than on the inside. Glycolipids lie exclusively on the outside of the membrane. Proteins too are differentially located in the outer, inner, or middle parts of the membrane. The carbohydrates are attached only to the membrane proteins on the outer surface. In addition, specific enzymes are located exclusively on the outside or inside of membranes, as in the mitochondrial and plasma membranes.

Membrane Disorders

Mutation of membrane proteins affects their function as receptors, transporters, ion channels, enzymes, and structural components. For example, in *hereditary spherocytosis,* there is mutation in the genes encoding spectrin, resulting in the tendency of the red blood cell (RBC) to become spherical rather than biconcave (see Chapter 21). Membrane proteins can trigger the production of antibodies by the immune system; when the antibody binds to the membrane protein, it alters its function. Autoantibodies to the acetylcholine receptor in skeletal muscle cause *myasthenia gravis.* Ischemia can quickly affect the integrity of various ion channels in membranes. The fragility of red cells is critically dependent on the protein:cholesterol ratio in the RBC membrane.

Membrane Transport

Simple Diffusion

Because simple diffusion involves no expenditure of biologic energy, it can occur only from a region of high solute concentration to a region of low solute concentration. Simple diffusion is the result of the random motion of molecules, and it occurs in both directions across the membrane. However, the diffusion down the concentration gradient is much greater than the diffusion against the gradient. Hence, the ***net diffusion*** is always down the concentration gradient. The rate of simple diffusion is directly proportional to the concentration gradient across the membrane (**Fig. 2.4**) and the permeability of the membrane to the solute. The membrane permeability to a substance depends on the molecule's size, lipid solubility, and electrical charge.

Gases such as oxygen (O_2), carbon dioxide (CO_2), and nitrogen (N_2) and hydrophobic molecules such as steroid hormones and weak organic acids and bases readily diffuse through the cell membrane.

Small uncharged polar molecules like water and urea can diffuse across the lipid bilayer, but not in physiologically sufficient amounts. Much larger amounts of water pass through membrane channels called *aquaporins*, which are present on all cells. Aquaporins do not allow ions to pass through them. The aquaporin molecules are stored in endosomes inside the cells. When suitably stimulated, they are rapidly translocated to the cell membrane. Similarly, urea employs specific transporters for crossing the membrane in larger amounts.

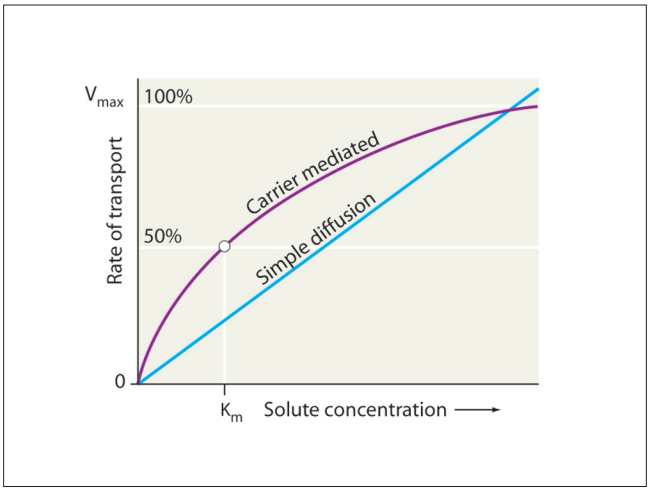

Fig. 2.4 Chemical kinetics of simple diffusion (*blue line*) and carrier-mediated membrane transport (*red line*). Note that although the rate of carrier-mediated transport plateaus at high solute concentration, there is no such limit to simple diffusion.

Large uncharged hydrophilic molecules such as glucose cannot diffuse through the lipid bilayer. Biologic membranes employ carrier-mediated transport for glucose.

Charged particles, whether large (amino acids) or small (Na^+, K^+, Cl^-, and Ca^{2+} ions), cannot diffuse across the lipid bilayer. Amino acids employ membrane transporters to cross the membrane. Ions cross the membranes, often in large amounts, through membrane channels. Ion channels do not allow water to pass through them.

Carrier-mediated Transport

Membrane transport can also occur through carrier-mediated transport, which employs certain integral membrane proteins as carriers or transporters for specific substrates. It may occur without any energy expenditure (facilitated diffusion) or may involve energy expenditure (active transport). When a carrier transports only a single substance, it is called a *uniporter.* When it transports more than one substance in the same direction, it is called a *cotransporter* or *symporter.* When it transports two substances in opposite directions, it is called a *countertransporter* or *antiporter.*

The rate of carrier-mediated transport depends on the concentration gradient across the membrane (**Fig. 2.4**), the number of carriers available (which is the rate-limiting parameter), and the rapidity of bonding and dissociation of the carrier with its substrate. The rate of transport cannot exceed a certain maximum, called the V_{max}. At V_{max}, all substrate-binding sites on the carrier are saturated. The substrate concentration at which the transport is 50% of the maximum is called the binding constant (K_m) of the carrier.

Carrier-mediated transport can be blocked by inhibitors that bear structural similarity to the physiologic substrate and compete with the physiologic substrate for a place on the carrier. Once they bind to the carrier, these inhibitors may not dissociate easily, thereby blocking the transport mechanism. For example, the carrier-mediated transport of glucose is blocked by phloridzin.

The inhibitors are often classified as competitive and noncompetitive. If an inhibitor binds irreversibly to the carrier, leaving no chance for the substrate to compete for a place on the carrier, the inhibition is called *noncompetitive.* The carrier in effect gets inactivated. If, however, the inhibitor binds reversibly, the physiologic substrate has a reasonable probability of competing and dislodging the inhibitor from the binding site. The inhibition is then said to be *competitive.*

It is unlikely that the carriers, which are integral membrane proteins, actually move through the thickness of the membrane, carrying their substrate with them. The inside-outside asymmetry of membrane proteins is too stable to permit such movements. Rather, a *ping-pong mechanism* has been proposed (**Fig. 2.5A**). In this model, the carrier protein exists in two principal conformations: ping and pong. In the pong state, it is exposed to high concentrations of solute, and the molecules of the solute bind to specific sites on the carrier protein. Transport occurs when a conformational change to the ping state exposes the carrier to a lower concentration of solute. The transition between the ping and pong states is powered by the bond energy released when the carrier binds to the solute. This is true for all carrier-mediated transport. In active transport (**Fig. 2.5B**), the binding of ATP to the carrier provides the energy needed to move the solute against its electrochemical gradient.

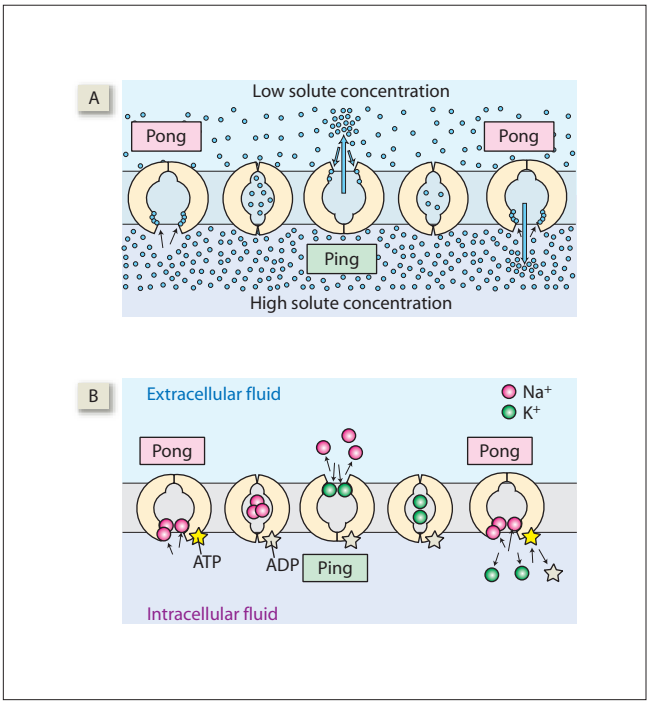

Fig. 2.5 The ping-pong model of carrier-mediated transport. **(A)** Facilitated diffusion. Note that transport of solute occurs in both directions. However, transport is greater from higher to lower solute concentration. **(B)** Active transport. Binding sites for sodium ions ($Na^{+)}$ are present only at the inner side, whereas binding sites for potassium ions (K^+) are present only at the outer side of the membrane carrier. This ensures that Na^+ can only move out, whereas K^+ can only move in. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

While integral membrane proteins employ the ping-pong mechanism for transporting ions, certain microbes synthesize small organic molecules called *ionophores* that transport ions by actually traveling across the membrane. These ionophores contain hydrophilic centers that bind specific ions and a hydrophobic exterior that allows them to dissolve in the membrane and diffuse across it.

Passive carrier-mediated transport, also called *facilitated diffusion*, can transport substrates only from a region of high concentration to a region of low concentration. Like simple diffusion, it is bidirectional—it occurs in both directions. However, when the concentration on one side is higher than the other, the difference in the kinetics of solute–carrier interaction ensures that there is a ***net flux*** of solute movement from high to low concentration.

Glucose and other large uncharged hydrophilic molecules have extremely slow rates of simple diffusion across the lipid bilayer. They cross the membrane much faster through facilitated diffusion. Examples of facilitated diffusion are the cotransport of Na^+ with monosaccharides or amino acids in renal tubular cells (see Chapter 55) and intestinal mucosal cells (see Chapter 70). An example of facilitated countertransport is the Cl^--HCO_3^- antiporter found in renal tubular cells and gastric parietal cells.

Facilitated diffusion is faster than simple diffusion, but the amount transported by facilitated diffusion is limited by the availability of the carrier. Hormones can regulate facilitated diffusion by changing the number of carriers available. For example, insulin increases glucose transport into cells by moving glucose transporters from an intracellular reservoir into the membrane.

Primary-active carrier-mediated transport involves energy expenditure. The energy comes mostly from ATP that is hydrolyzed by the carrier protein itself, which also acts as an ATPase. Unlike passive transport, active transport can transport substrates against a concentration gradient. The best-known example of a carrier ATPase is the Na^+–K^+ ATPase. It has binding sites for both ATP and Na^+ on the cytoplasmic side of the membrane, but the K^+ binding site is located on the extracellular side of the membrane (**Fig. 2.5B**). This asymmetry of location of the binding sites explains why, unlike facilitated diffusion, primary-active transport can occur only in one direction. Ouabain or digitalis inhibits this ATPase by binding to the extracellular site on the transporter.

Secondary-active carrier-mediated transport represents a combination of primary-active transport and facilitated diffusion. It is exemplified by glucose transport across renal tubular cells and intestinal mucosal cells (**Fig. 2.6**). The basolateral border of the cell lowers the intracellular Na^+ concentration through primary active transport of Na^+ ions to the exterior. The low intracellular Na^+ concentration provides the necessary concentration gradient for Na^+ to diffuse in passively at the luminal border through facilitated cotransport with glucose. Thus, the Na^+–K^+ ATPase indirectly powers the movement of glucose into the cell, and glucose can move in against a concentration gradient so long as Na^+ diffuses in along a concentration gradient.

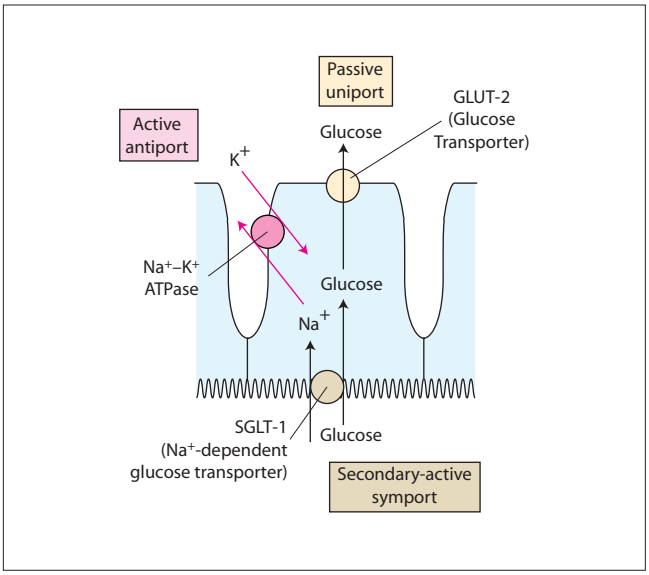

Fig. 2.6 Passive, active, and secondary-active transport. Sodium-dependent glucose transporter-1 (SGLT-1) transports glucose against its concentration gradient. The energy for this uphill transport is derived from the favorable concentration gradient for sodium ion (Na^+) with which it is cotransported. The Na^+ concentration gradient is created by the Na^+–K^+ adenosine triphosphatase (ATPase).

Endocytosis

Endocytosis is the process by which cells take up macromolecules and large particles from the extracellular environment. The process requires ATPase, Ca^{2+}, and microfilaments. Endocytosis occurs by invagination of the plasma membrane so as to enclose a small droplet of extracellular fluid and its contents. The invagination gets pinched off at its neck to form an endocytotic vesicle. The vesicle then transports its contents to other organelles by fusing with their membranes.

Alternatively, it can fuse back with the plasma membrane. Depending on what is endocytosed, endocytosis is called phagocytosis or pinocytosis. Endocytosis of cells, bacteria, viruses, or debris is called *phagocytosis*. Endocytic vesicles containing these particles fuse with primary lysosomes to form secondary lysosomes, where the ingested particles are digested. Endocytosis of water, nutrient molecules, and parts of the cell membrane is called *pinocytosis*.

Fluid-phase pinocytosis is a nonselective process in which the cell takes up fluid and all its solutes indiscriminately. Vigorous fluid-phase pinocytosis is associated with internalization of considerable amounts of the plasma membrane. To avoid reduction in the surface area of the membrane, the membrane is replaced simultaneously by exocytosis of vesicles. In this way, the plasma membrane is constantly recycled.

Absorptive pinocytosis is also called *receptor-mediated pinocytosis*. It is responsible for the uptake of selected macromolecules for which the cell membrane bears specific receptors. Such uptake minimizes the indiscriminate uptake of fluid or other soluble macromolecules. The vesicles formed during absorptive pinocytosis are derived from invaginations (pits)

that are coated on the cytoplasmic side with a filamentous material called *clathrin*, a peripheral membrane protein. Such pits are called *coated pits*.

An example of absorptive pinocytosis is provided by the endocytosis of low-density lipoprotein (LDL) molecules. The molecules bind with their receptor on the plasma membrane, and the receptor-LDL complexes are internalized by means of coated pits. The endocytotic vesicles fuse with lysosomes in the cell. The receptor is released and recycled back to the cell surface membrane, but the LDL is metabolized.

Endocytosed hormone receptors can trigger intracellular events after being endocytosed. Following pinocytosis, these hormone receptors form *receptosomes*, vesicles that avoid lysosomes and deliver their contents to other intracellular sites, such as the Golgi body.

Receptor-mediated endocytosis can at times be self-defeating. Viruses causing hepatitis, poliomyelitis, and acquired immunodeficiency syndrome (AIDS) gain access into the cell through this mechanism. Iron toxicity also begins with excessive uptake of iron through endocytosis.

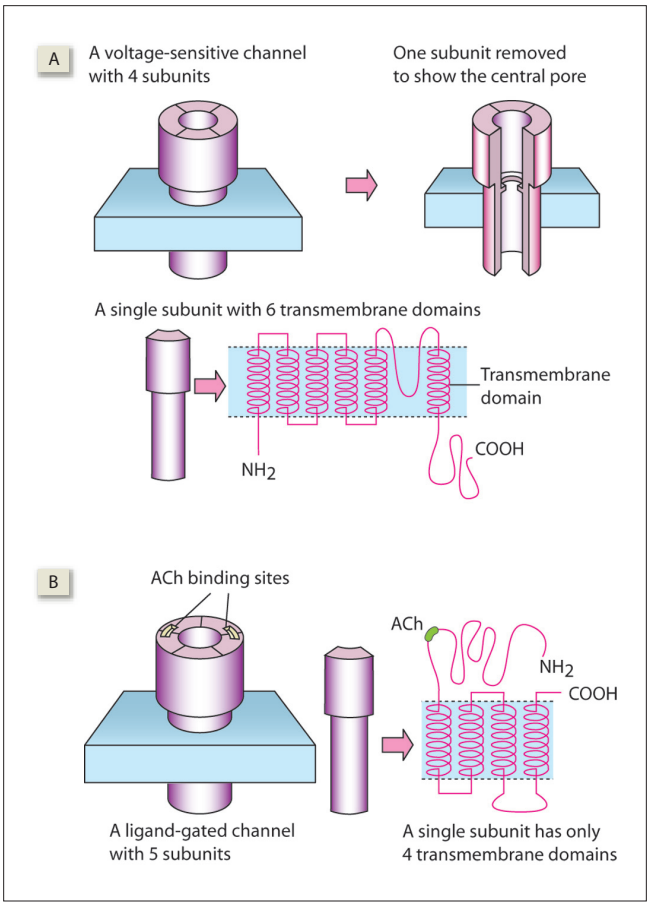

Fig. 2.7 **(A)** Structure of a voltage-gated channel. It is made of four subunits, with each subunit made of six transmembrane domains. The subunits enclose a central pore. **(B)** Structure of a ligand-gated cation channel. It is made of five subunits, each with four transmembrane domains. The subunits enclose a central pore. The binding sites for acetylcholine (ACh) are present on the exterior at the junctions between two adjacent subunits.

Exocytosis

Exocytosis is the process for release of macromolecules formed in the cell to the exterior. Exocytosis is associated with an increase in the area of the plasma membrane. Working in tandem with fluid-filled endocytosis, this process is involved in remodeling of the membrane. Exocytosed molecules are of three types. Some attach to the cell surface and become peripheral proteins, for example, antigens. Some become part of the extracellular matrix, such as collagen and glycosaminoglycans. Some enter the extracellular fluid and serve as hormones or neurotransmitters. These are exocytosed only when the cell is stimulated.

Membrane Channels

Ion channels are integral membrane proteins that enclose a central pore. They traverse the entire thickness of the cell membrane, projecting a little at both the outer and inner membrane surfaces.

The structural characteristics of some ionic channels are shown in **Fig. 2.7** and are summarized in **Table 2.1**. A voltage-sensitive Na^+ ion channel, for example, is made of four subunits designated as α, β, γ, and δ. Each subunit in turn is made of six coiled transmembrane segments designated S1–S6. In general, channels have variable numbers of subunits and transmembrane domains having different designations.

Ion Channel Specificity

Ion channels are highly specific for certain ions. Although it is understandable that a larger ion cannot pass through a smaller channel, it requires some explanation as to why smaller ions do not pass through larger channels. This is explained by the *closest-fit hypothesis*. The hydration of ions is an important consideration in this hypothesis.

The smaller an ion, the more highly localized is its charge, and the stronger is its electric field. Smaller ions, such as Na^+ (crystal radius of 0.095 nm), have stronger effective electric fields than larger ions, such as K^+ (crystal radius of 0.133 nm). As a result, smaller ions attract water more strongly. Thus, the strong electrostatic attraction for water causes Na^+ to have a larger water shell.

Table 2.1 **Structural Characteristics of Ionic Channels**

	Number of Subunits	Number of Transmembrane Domains per Subunit
Voltage-gated Na^+ and K^+ channels	4 subunits. All are α-type and are designated I, II, III, and IV	6 (S1, S2, S3, S4, S5, and S6)
Ligand-gated cation channel	5 subunits. 2 are α-type, 1 each are β, γ, and δ	4 (M1, M2, M3, and M4)

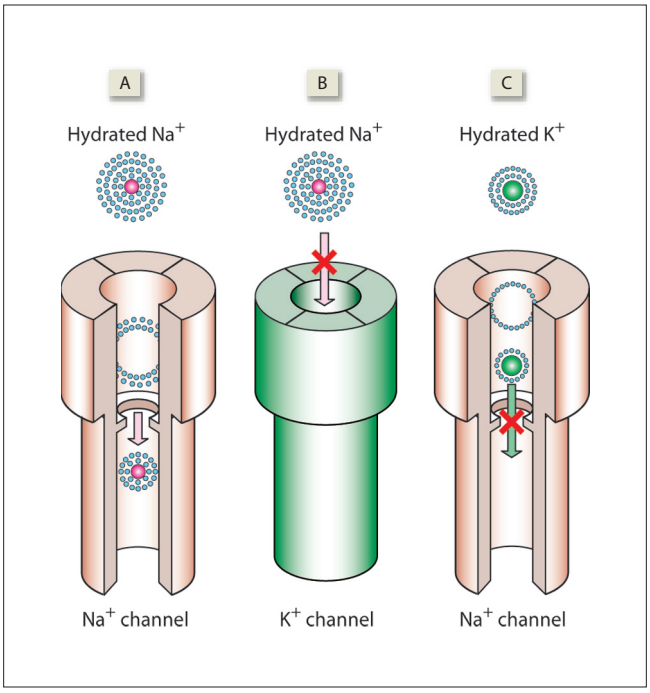

Fig. 2.8 The closest-fit theory of ion channel specificity. **(A)** A sodium ion (Na^+) passes through the outer and inner pores. **(B)** A hydrated sodium ion is unable to pass through the outer pore of a potassium ion (K^+) channel. **(C)** A hydrated K^+ is unable to pass through the inner pore.

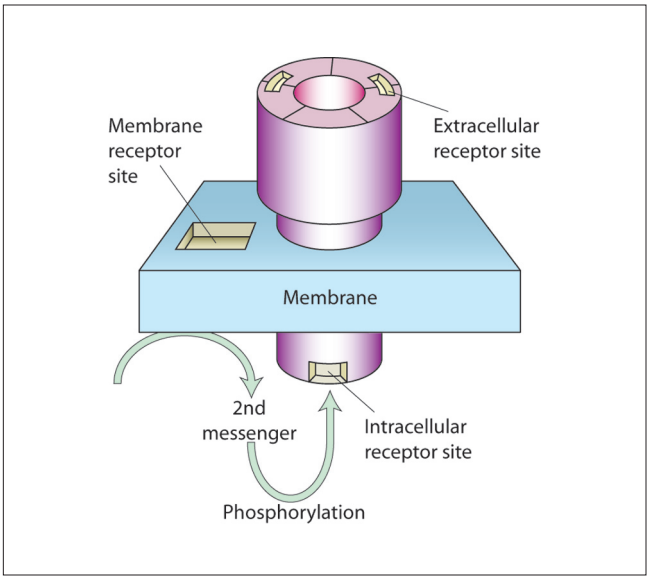

Fig. 2.9 Ligand-binding sites may be located on the outer membrane surface, or they may be present on the outer or inner parts of a membrane channel.

For passing completely through a channel, an ion has to negotiate two barriers: an *outer pore* and another pore called the *selectivity filter* located midway inside the channel (**Fig. 2.8**). The ion enters the outer pore with its complete water of hydration. Once it arrives at the inner selectivity filter, the ion sheds most of its water shell and forms a weak electrostatic bond with the polar (carboxyl) residues of the amino acids that line the channel wall. This electrostatic bond must release adequate energy for stripping the ion of its water shell. The energy released is maximum when the unhydrated ion fits closely in the channel and is less if it floats loosely within the channel.

The hydrated Na^+ ion is larger than the hydrated K^+ ion, and as would be expected, a Na^+ channel has a larger diameter than a K^+ channel. A hydrated Na^+ ion is a little too large to pass through the outer pore of a K^+ channel. The hydrated K^+ ion is slightly less in diameter than the Na^+ channel, yet it is unable to pass through the Na^+ channel because the selectivity filter of the Na^+ channel is oversized for a K^+ ion bereft of its water shell. Hence, the energy released due to the electrostatic attraction between the K^+ ion and the wall of the Na^+ selectivity filter is inadequate for stripping the K^+ ion of its water shell. With its shell intact, the K^+ is unable to negotiate the selectivity filter of the Na^+ channel.

Types of Channels

What makes channels unique as compared with other mechanisms of membrane transport is that they can be gated (opened or closed) precisely. Depending on the factors that produce their opening and closing (gating), ion channels are classified into four types.

Voltage-gated channels are gated by changes in membrane potential. Examples are voltage-gated Na^+, K^+, and Ca^{2+} channels.

Ligand-gated channels are regulated by chemicals that bind to them (ligands). The ligand affects channel permeability in different ways (**Fig. 2.9**). (1) It can bind to the receptor channel protein at an extracellular site (e.g., in acetylcholine receptors). (2) It can bind to the channel at an intracellular site (e.g., pronase, local anesthetics). (3) It can bind to membrane receptors and activate a second messenger cascade, leading to phosphorylation of channel protein.

Mechanically gated channels have pores that respond to mechanical stimuli like the stretch of the membrane.

Resting channels are not gated at all. Resting channels make a substantial contribution to the membrane potential.

Apart from these physiologic channels, membrane pores may be created in pathologic situations. Diphtheria toxin and activated serum complement components like the C5b-C6-C7-C8-C9 fragment can produce large pores in cellular membranes and thereby provide macromolecules with direct access to the cell interior.

Summary

- **The cell membrane controls the movement of solutes into and out of the cell.**
- **The cell membrane is a lipid bilayer in which are embedded a large number of different proteins that serve different functions.**

- Transport of solutes across the membrane occurs by four different processes: passive diffusion (down a gradient), carrier-mediated transport (also down a gradient), primary-active transport (against a gradient), and secondary-active transport (also against a gradient).

- Channels are membrane-spanning proteins (some always open, others gated by different stimuli) through which solutes can diffuse down a gradient.