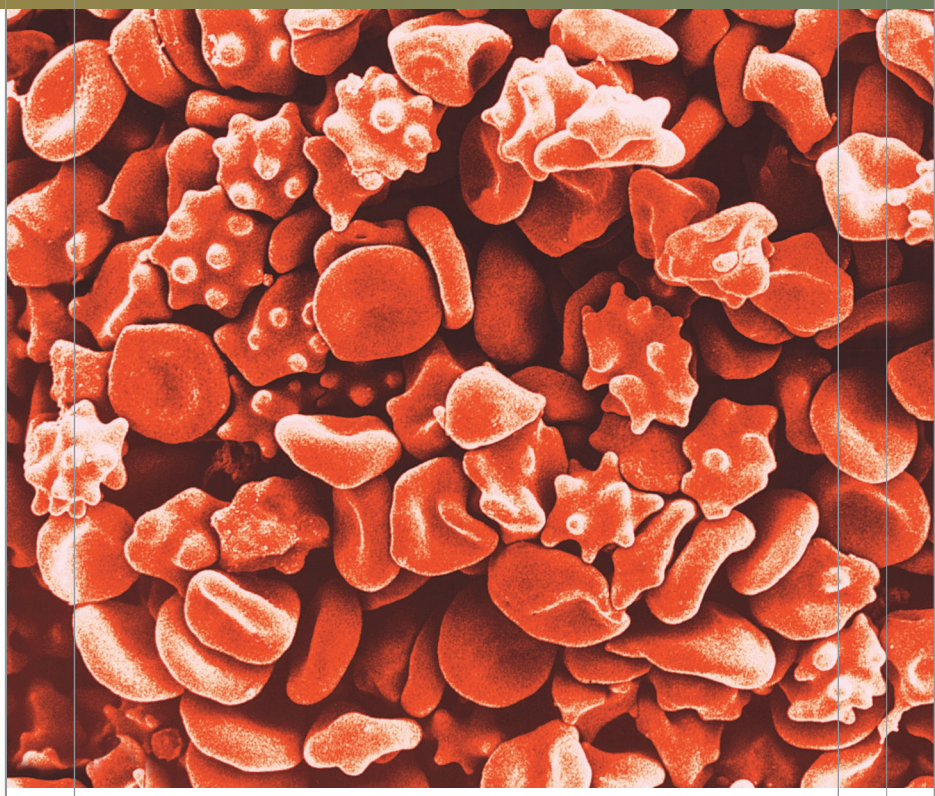
Movement of Solutes and Water Across Cell Membranes

CHAPTER 4



Changes in red blood cell shape due to osmosis; the knobby appearance of some cells is due to water leaving the cell.

You learned in Chapter 3 that the contents of a cell are separated from the surrounding extracellular fluid by a thin bilayer of lipids and protein, which forms the plasma membrane. You also learned that membranes associated with mitochondria, endoplasmic reticulum, lysosomes, the Golgi apparatus, and the nucleus divide the intracellular fluid into several membrane-bound compartments. The movements of molecules and ions between the various cell organelles and the cytosol, and between the cytosol and the extracellular fluid, depend on the properties of these membranes. The rates at which different substances move through membranes vary considerably and in some cases can be controlled—increased or decreased—in response to various signals. This chapter focuses upon the transport functions of membranes, with emphasis on the plasma membrane. The controlled movement of solutes such as ions, glucose, and gases, as well as the movement of water across membranes, is of profound importance in physiology. As just a few examples, such transport mechanisms are essential for cells to maintain their size and shape, energy balance, and their ability to send and respond to electrical or chemical signals from other cells.

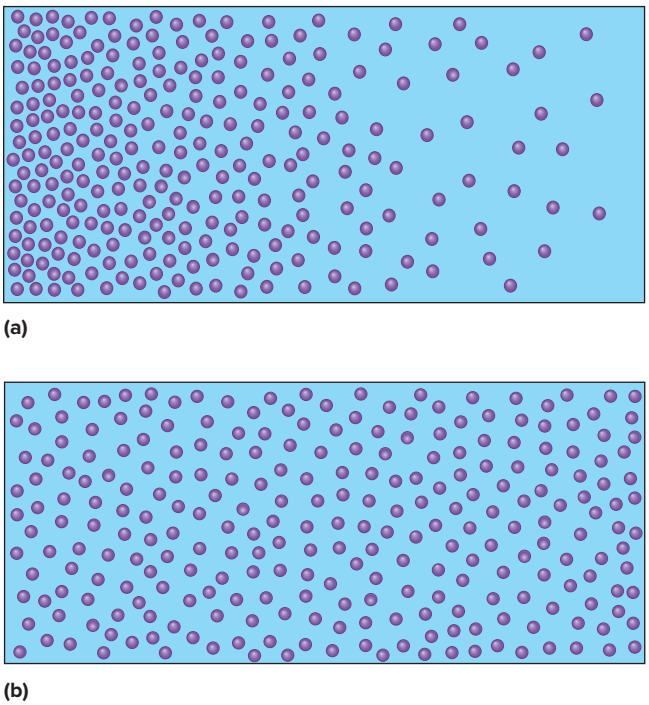
As you read the first section, think how diffusion is a good example of the general principle of physiology introduced in Chapter 1 that physiological processes are dictated by the laws of chemistry and physics. In the subsequent sections, consider how the general physiological principles of homeostasis and of controlled exchange of materials apply.

4.1 Diffusion

One of the fundamental physical features of molecules of any substance, whether solid, liquid, or gas, is that they are in a continuous state of movement or vibration. The energy for this movement comes from heat; the warmer a substance is, the faster its molecules move. In solutions, such rapidly moving molecules cannot travel very far before colliding with other molecules, undergoing millions of collisions every second. Each collision alters the direction of the molecule's movement, so that the path of any one molecule becomes unpredictable. Because a molecule may at any instant be moving in any direction, such movement is random, with no preferred direction of movement.

The random thermal motion of molecules in a liquid or gas will eventually distribute them uniformly throughout a container. This is the second law of thermodynamics, which states that a closed (isolated) system will always tend toward maximum entropy, or disorder. Thus, if we start with a solution in which a solute is more concentrated in one region than another (**Figure 4.1a**), random thermal motion will redistribute the solute from regions of higher concentration to regions of lower concentration until the solute reaches a uniform concentration throughout the solution (**Figure 4.1b**). This movement of molecules from one location to another solely as a result of their random thermal motion is known as **simple diffusion.**

Key to your understanding of this process is recognizing that molecules do not move in a purposeful way; their movement is entirely random. The probability that more molecules will move from the left to the right side of the solution shown in Figure 4.1a is greater than that of the reverse direction, simply because there are initially more molecules on the left side. At equilibrium, the molecules continue to randomly move but do so equally in all directions.



(a)

(b)

AP|R **Figure 4.1** Simple diffusion. (a) Molecules initially concentrated in one region of a solution will, due to random thermal motion, undergo net diffusion from the region of higher concentration to the region of lower concentration. (b) With time, the molecules will become uniformly distributed throughout the solution; that is, the system will achieve maximum entropy.

Many processes in living organisms are closely associated with simple diffusion. For example, oxygen, nutrients, and other molecules enter and leave the smallest blood vessels (capillaries) by simple diffusion, and the movement of many substances across plasma membranes and organelle membranes occurs by simple diffusion. In this way, simple diffusion is one of the key mechanisms by which cells maintain homeostasis. For the remainder of the text, we will often follow convention and refer only to "diffusion" when describing simple diffusion. You will learn later about another type of diffusion called facilitated diffusion.

Magnitude and Direction of Diffusion

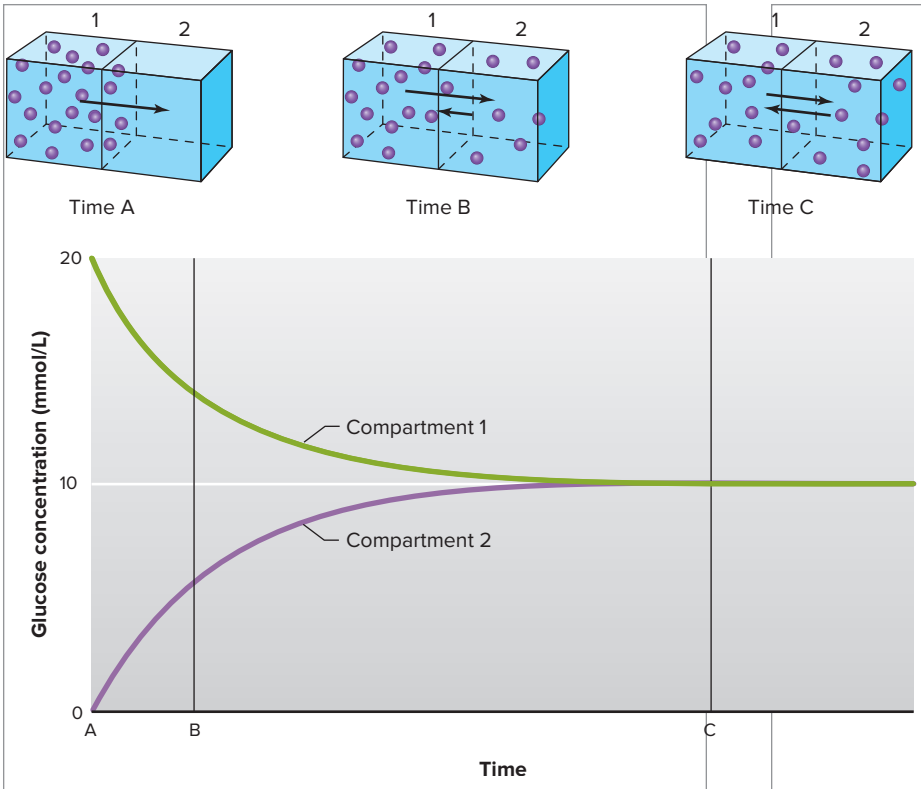
Figure 4.2 illustrates the diffusion of glucose between two compartments of equal volume separated by a permeable barrier. Initially, glucose is present in compartment 1 at a concentration of 20 mmol/L, and there is no glucose in compartment 2. The random movements of the glucose molecules in compartment 1 move some of them into compartment 2. The amount of material crossing a surface in a unit of time is known as a **flux.** This one-way flux of glucose from compartment 1 to compartment 2 depends on the concentration of glucose in compartment 1. If the number of molecules in a unit of volume is doubled, the flux of molecules across the surface of the unit will also be doubled because twice as many molecules will be moving in any direction at a given time.

After a short time, some of the glucose molecules that have entered compartment 2 will randomly move back into compartment 1 (see Figure 4.2, time B). The magnitude of the glucose flux from compartment 2 to compartment 1 depends upon the concentration of glucose in compartment 2 at any time.

The **net flux** of glucose between the two compartments at any instant is the difference between the two one-way fluxes. The net flux determines the net gain of molecules in compartment 2 per unit time and the net loss from compartment 1 per unit time.

Eventually, the concentrations of glucose in the two compartments become equal at 10 mmol/L. Glucose molecules continue to move randomly, and some will find their way from one compartment to the other. However, the two one-way fluxes are now equal in magnitude but opposite in direction; therefore, the *net* flux of glucose is zero (see Figure 4.2, time C). The system has now reached **diffusion equilibrium.** No further change in the glucose concentrations of the two compartments will occur because of the equal rates of diffusion of glucose molecules in both directions between the two compartments.

Several important properties of diffusion can be emphasized using this example. Three fluxes can be identified—the two one-way fluxes occurring in opposite directions from one compartment to the other, and the net flux, which is the difference between them (**Figure 4.3**). The net flux is the most important component in diffusion because it is the net rate of material transfer from one location to another. Although the movement of individual molecules is random, *the net flux is always greater from regions of higher concentration to regions of lower concentration.* For this reason, we often say that substances move "downhill" by diffusion. The greater the difference in concentration between any two regions, the greater the magnitude of the net flux. Therefore,



AP|R **Figure 4.2** Diffusion of glucose between two compartments of equal volume separated by a barrier permeable to glucose. Initially, at time A, compartment 1 contains glucose at a concentration of 20 mmol/L and no glucose is present in compartment 2. At time B, some glucose molecules have moved into compartment 2 and some of these are moving back into compartment 1. The length of the arrows represents the magnitudes of the one-way movements. At time C, diffusion equilibrium has been reached, the concentrations of glucose are equal in the two compartments (10 mmol/L), and the *net* movement is zero. In the graph at the bottom of the figure, the green line represents the concentration in compartment 1, and the purple line represents the concentration in compartment 2. Note that at time C, glucose concentration is 10 mmol/L in both compartments. At that time, diffusion equilibrium has been reached.

PHYSIOLOGICAL INQUIRY

- Imagine that at time C additional glucose could be added to compartment 1 such that its concentration was instantly increased to 15 mmol/L. What would the graph look like following time C? Draw the new graph on the figure and indicate the glucose concentrations in compartments 1 and 2 at diffusion equilibrium. (*Note:* It is not actually possible to instantly change the concentration of a substance in this way because it will immediately begin diffusing to the other compartment as it is added.)

Answer can be found at end of chapter.

the concentration difference determines both the direction and the magnitude of the net flux.

At any concentration difference, however, the magnitude of the net flux depends on several additional factors: (1) temperature—the more elevated the temperature, the greater the speed of molecular movement and the faster the net flux; (2) mass of the molecule—large molecules such as proteins have a greater mass and move more slowly than smaller molecules such as glucose and, consequently, have a slower net flux; (3) surface area—the greater the surface area separating two regions, the greater the space available for diffusion and, therefore, the faster the net flux; and (4) the medium through which the molecules are moving—molecules diffuse more rapidly in air than in water. This is because collisions are less frequent in a gas phase.

Diffusion Rate Versus Distance

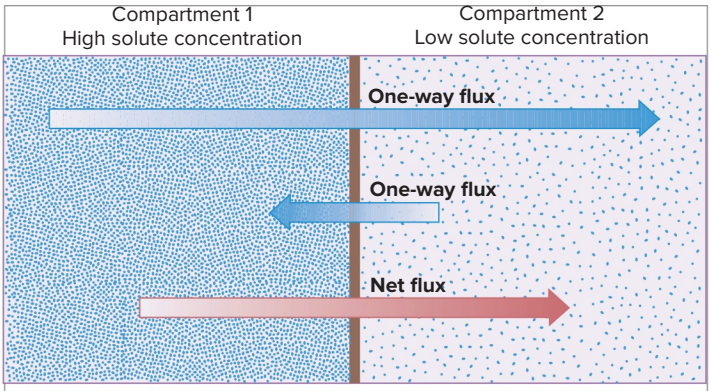
The distance over which molecules diffuse is an important factor in determining the rate at which they can reach a cell from the blood or move throughout the interior of a cell after crossing the plasma membrane. Although individual molecules travel at high speeds, the number of collisions they undergo prevents them from traveling very far in a straight line. Diffusion times increase in proportion to the *square* of the distance over which the molecules diffuse.

Thus, although diffusion equilibrium can be reached rapidly over distances of cellular dimensions, it takes a very long time when distances of a few centimeters or more are involved. For an organism as large as a human being, the diffusion of oxygen and nutrients from the body surface to tissues located only a few centimeters below the surface would be far too slow to provide adequate nourishment. This is overcome by the circulatory system, which provides a mechanism for rapidly moving materials over large distances using a pressure source (the heart). This process, known as bulk flow, is described in Chapter 12. Diffusion, on the other hand, provides movement over the short distances between the blood, interstitial fluid, and intracellular fluid.

Diffusion Through Membranes

Up to now, we have considered general features of diffusion of solutes in water. In living tissue, however, diffusion often occurs across cellular membranes, including between intracellular and extracellular fluid compartments. For example, cellular waste products of metabolism diffuse outward from cells, whereas nutrients diffuse into cells; in both cases, the solutes must cross the plasma membrane. What effects do membranes have on diffusion?

The rate at which a substance diffuses across a plasma membrane can be measured by monitoring the rate at which its intracellular concentration approaches diffusion equilibrium with its concentration in the extracellular fluid. For simplicity's sake, assume that because the volume of extracellular fluid is large, its solute concentration will remain essentially constant as the substance diffuses into the intracellular fluid (**Figure 4.4**). As with all diffusion processes, the net flux of material across the membrane is from the region of greater concentration (the extracellular solution in this case) to the region of lower concentration (the intracellular fluid). The magnitude of the net flux (that is, the rate of diffusion J) is directly proportional to the difference in concentration across the membrane ($C_o - C_i$, where o and i stand for concentrations outside and inside the cell), the



AP|R **Figure 4.3** The two one-way fluxes occurring during simple diffusion of solute across a boundary and the net flux (the difference between the two one-way fluxes). The net flux always occurs in the direction from higher to lower concentration. Lengths of arrows indicate magnitude of the flux.

surface area of the membrane A, and the membrane permeability coefficient P as described by a modified form of **Fick's first law of diffusion** applied to biological membranes:

$$J = PA(C_o - C_i)$$

The numerical value of the permeability coefficient P is an experimentally determined number for a particular type of molecule at a given temperature; it reflects the ease with which the molecule is able to move through a given membrane. In other words, the greater the permeability coefficient, the faster the net flux across the membrane for any given concentration difference and membrane surface area. Depending on the magnitude of their permeability coefficients, molecules typically diffuse a thousand to a million times slower through membranes than through a water layer of equal thickness. Membranes, therefore, act as barriers that considerably slow the diffusion of molecules across their surfaces. The major factor limiting diffusion across a membrane is its chemical composition, namely the hydrophobic interior of its lipid bilayer, as described next.

Diffusion Through the Lipid Bilayer When the permeability coefficients of different organic molecules are examined in relation to their molecular structures, a correlation emerges. Whereas most polar molecules diffuse into cells very slowly or not at all, nonpolar molecules diffuse much more rapidly across plasma membranes—that is, they have large permeability coefficients. The reason is that nonpolar molecules can dissolve in the nonpolar regions of the membrane occupied by the fatty acid chains of the membrane phospholipids. In contrast, polar molecules have a much lower solubility in the membrane lipids. Increasing the lipid solubility of a substance by decreasing the number of polar or ionized groups it contains will increase the number of molecules dissolved in the membrane lipids. This will increase the flux of the substance across the membrane. Oxygen, carbon dioxide, fatty acids, and steroid hormones are examples of nonpolar molecules that diffuse rapidly through the lipid portions of membranes. Most of the organic molecules that make up the intermediate stages of the various metabolic pathways (Chapter 3) are ionized or polar molecules, often containing an ionized phosphate group; therefore, they have a low solubility in the lipid bilayer. Most of these substances are retained within cells and organelles because they cannot diffuse across the lipid bilayer of membranes, unless the membrane contains special proteins such as ion channels, as we see next. This is an excellent example of the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics.

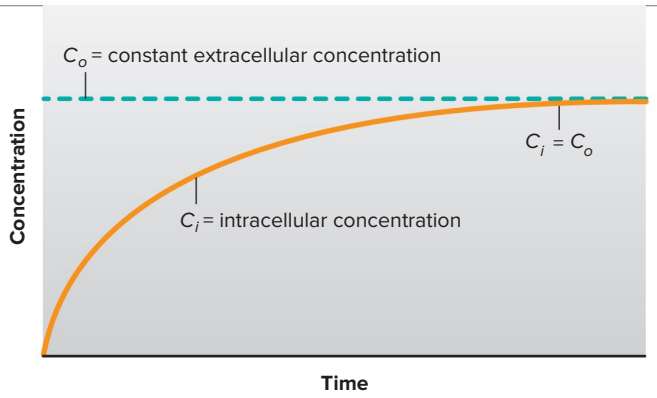


Figure 4.4 The increase in intracellular concentration as a solute diffuses from a constant extracellular concentration until diffusion equilibrium ($C_i = C_o$) is reached across the plasma membrane of a cell.

Diffusion of Ions Through Ion Channels Ions such as Na^+, K^+, Cl^-, and Ca^{2+} diffuse across plasma membranes at much faster rates than would be predicted from their very low solubility in membrane lipids. Also, different cells have quite different permeabilities to these ions, whereas nonpolar substances have similar permeabilities in nearly all cells. Moreover, artificial lipid bilayers containing no protein are practically impermeable to these ions; this indicates that the protein component of the membrane is responsible for these permeability differences.

You learned in Chapter 3 that integral membrane proteins can span the lipid bilayer. Some of these proteins form **ion channels** that allow ions to diffuse across the membrane. A single protein may have a conformation resembling that of a doughnut, with the hole in the middle providing the channel for ion movement. More often, several polypeptides aggregate, each forming a subunit of the borders of a channel (**Figure 4.5**). The diameters of ion channels are very small, only slightly larger than those of the ions that pass through them. The small size of the channels prevents larger molecules from entering or leaving.

An important characteristic of ion channels is that they can show selectivity for the type of ion or ions that can diffuse through them. This selectivity is based on the channel diameter, the charged and polar surfaces of the polypeptide subunits that form the channel walls and electrically attract or repel the ions, and the number of water molecules associated with the ions (so-called waters of hydration). For example, some channels (K^+ channels) allow only potassium ions to pass, whereas others are specific for sodium ions (Na^+ channels). For this reason, two membranes that have the same permeability to K^+ because they have the same number of K^+ channels may nonetheless have quite different permeabilities to Na^+ if they contain different numbers of Na^+ channels.

Ion Movement and Membrane Potential Thus far, we have described the direction and magnitude of solute diffusion across a membrane in terms of the solute's concentration difference across the membrane, its solubility in the membrane lipids, the presence of membrane ion channels, and the area of the membrane. When describing the diffusion of ions, because they are charged, one additional factor must be considered: the presence of electrical forces acting upon the ions.

A separation of electrical charge exists across plasma membranes of most cells. This is known as a **membrane potential** (**Figure 4.6**). The origin of a membrane potential will be described in detail in Chapter 6 in the context of neuronal function. Briefly, it arises from an imbalance in electrical charges (primarily ions) on either side of the plasma membrane, such that a slight excess of negative charge exists within the cell. A fundamental principle of physics is that like charges repel each other, and opposite charges attract each other. The excess negative charges inside the cell attract positive charges outside the cell. The opposite charges tend to align themselves along the surfaces of the plasma membrane. This creates an electrical potential across the membrane, the magnitude of which is measured in units called millivolts.

The membrane potential provides an electrical force that can influence the movement of ions through their channels across a plasma membrane. For example, if the inside of a cell has a net negative charge with respect to the outside, as is generally true, there will be an electrical force attracting positive ions into the cell and repelling negative ions. Consequently, the direction and magnitude of ion fluxes across membranes depend on both the concentration difference *and* the electrical difference (the membrane potential). These two driving forces are considered together as a single, combined **electrochemical gradient** across a membrane. As you will learn in subsequent chapters, the membrane potential is the basis for the regulated flux of ions across membranes, as occurs for example when Ca^{2+} enters the cytosol of a muscle cell and triggers contraction of the cell. It also is the basis for electrical communication between neurons.

The two forces that make up the electrochemical gradient may in some cases oppose each other. For example, the membrane potential may be driving K^+ in one direction across the membrane while the concentration difference for K^+ favors flux of these ions in the opposite direction. The net movement of K^+ in this case would be determined by the relative magnitudes of the two opposing forces—that is, by the electrochemical gradient across the membrane.

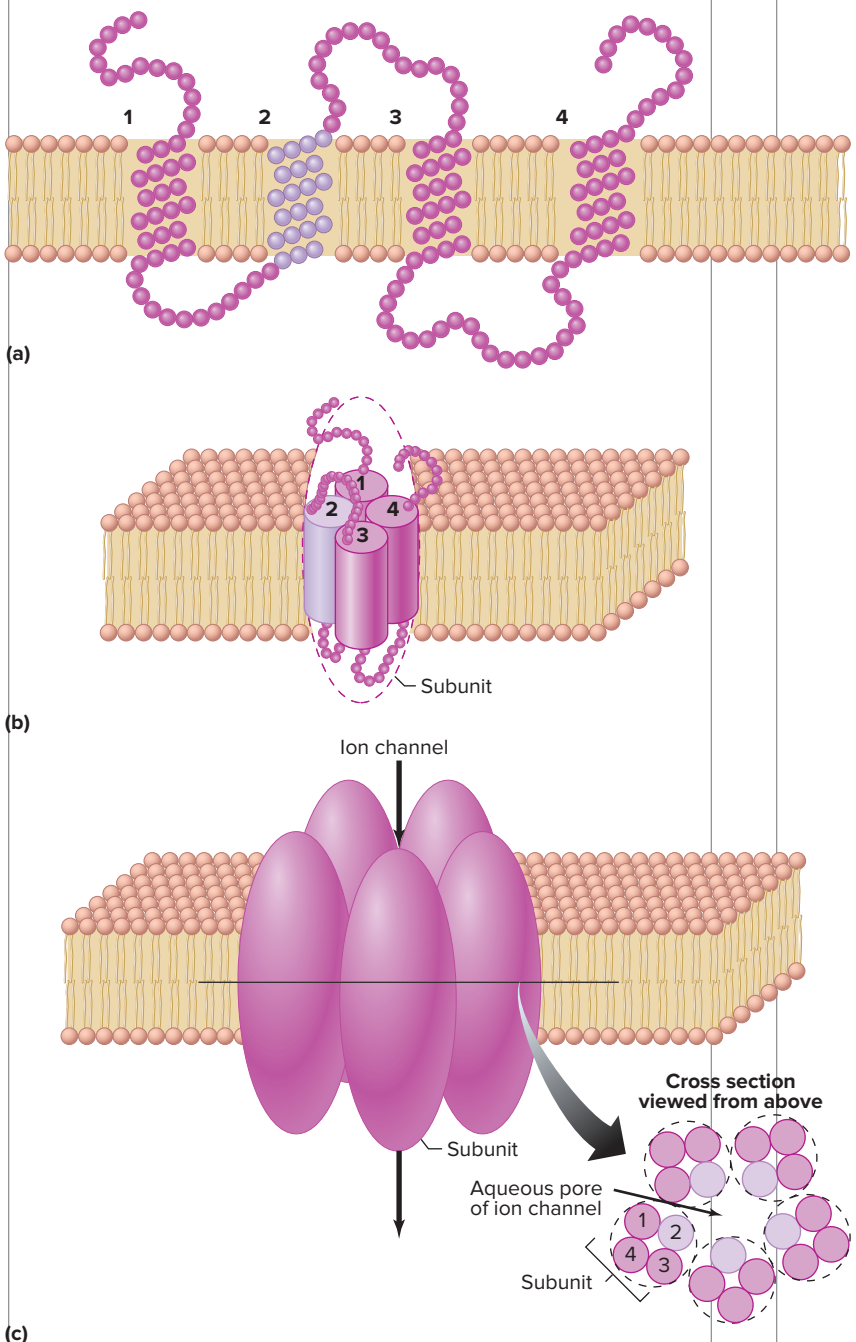


Figure 4.5 Model of an ion channel composed of five polypeptide subunits. Individual amino acids are represented as beads. (a) A channel subunit consisting of an integral membrane protein containing four transmembrane segments (1, 2, 3, and 4), each of which has an alpha-helical configuration within the membrane. Although this model has only four transmembrane segments, some channel proteins have as many as 12. (b) The same subunit as in (a) shown in three dimensions within the membrane, with the four transmembrane helices aggregated together and shown as cylinders. (c) The ion channel consists of five of the subunits illustrated in (b), which form the sides of the channel. As shown in cross section, the helical transmembrane segment 2 (light purple) of each subunit forms each side of the channel opening. The presence of ionized amino acid side chains along this region determines the selectivity of the channel to ions. Although this model shows the five subunits as identical, many ion channels are formed from the aggregation of several different types of subunit polypeptides.

PHYSIOLOGICAL INQUIRY

- In Chapter 2, you learned that proteins have several levels of structure. Which levels of structures are evident in the drawing of the ion channel in this figure?

Answer can be found at end of chapter.

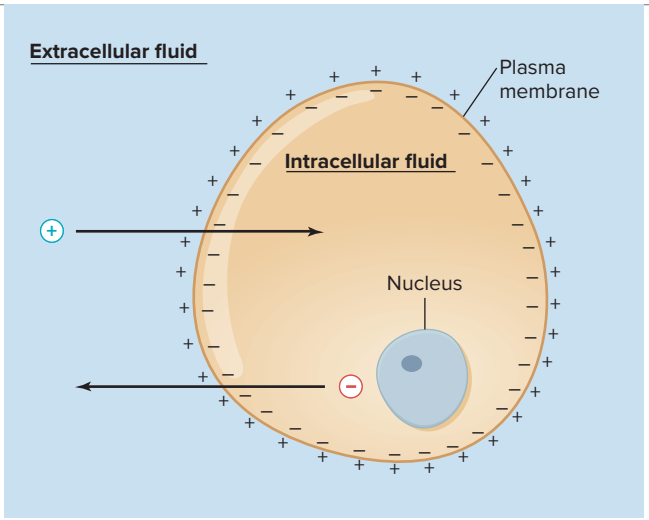


Figure 4.6 The separation of electrical charge across a plasma membrane (the membrane potential) provides the electrical force that tends to drive positive ions (+) into a cell and negative ions (–) out.

Regulation of Diffusion Through Ion Channels Ion channels can exist in an open or closed state (**Figure 4.7**), and changes in a membrane's permeability to ions can occur rapidly as these channels open or close. The process of opening and closing ion channels is known as **channel gating,** like the opening and closing of a gate in a fence. A single ion channel may open and close many times each second, suggesting that the channel protein fluctuates between these conformations. Over an extended period of time, at any given electrochemical gradient, the total number of ions that pass through a channel depends on how often the channel opens and how long it stays open.

Three factors can alter the channel protein conformations, producing changes in how long or how often a channel opens. First, the binding of specific molecules to channel proteins may directly or indirectly produce either an allosteric or covalent change in the shape of the channel protein. A molecule that binds to a protein like this is called a ligand (see Chapter 3). Such channels are therefore termed **ligand-gated ion channels,** and the ligands that influence them are often chemical messengers, such as those released from the ends of neurons onto target cells. Second, changes in the membrane potential can cause movement of certain charged regions on a channel protein, altering its shape—these are **voltage-gated ion channels.** Third, physically deforming (stretching) the membrane may affect the conformation of some channel proteins—these are **mechanically gated ion channels.**

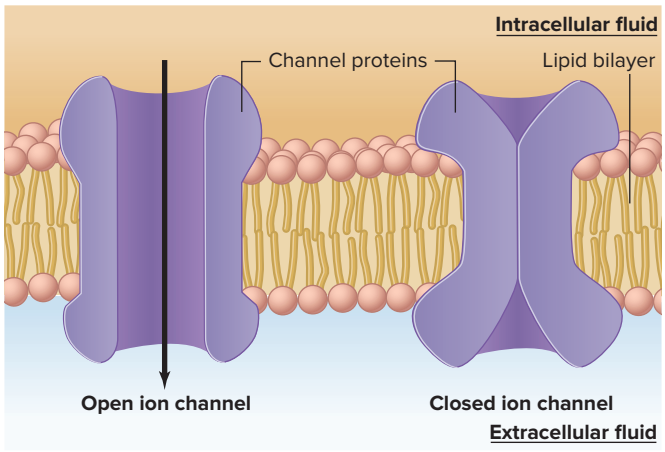


Figure 4.7 As a result of conformational changes in the proteins forming an ion channel, the channel may be open, allowing ions to diffuse across the membrane, or may be closed. The conformational change is grossly exaggerated for illustrative purposes. The actual conformational change is more likely to be just sufficient to allow or prevent an ion to fit through.

A single type of ion may pass through several different types of channels. For example, a membrane may contain ligand-gated K^+ channels, voltage-gated K^+ channels, and mechanically gated K^+ channels. The functions of these gated ion channels in cell communication and electrical activity will be discussed in Chapters 5 through 7, 9, and 12.

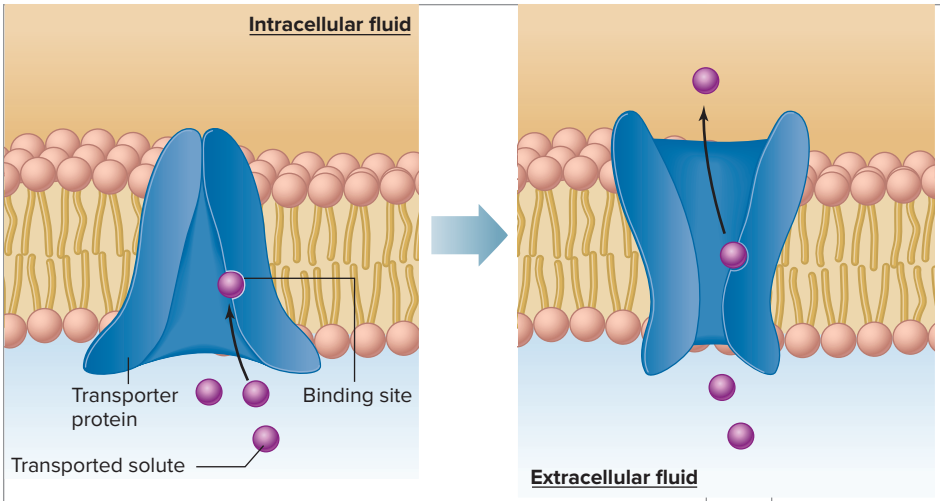
4.2 Mediated-Transport Systems

A general principle of physiology is that controlled exchange of materials occurs between compartments and across cellular membranes. Although diffusion through gated ion channels accounts for some of the controlled transmembrane movement of ions, it does not account for all of it. Moreover, a number of other molecules, including amino acids and glucose, are able to cross membranes yet are too polar to diffuse through the lipid bilayer and too large to diffuse through channels. The passage of these molecules and the nondiffusional movements of ions are mediated by integral membrane proteins known as **transporters.** The movement of substances through a membrane by any of these mechanisms is called **mediated transport,** which depends on conformational changes in these transporters.

The transported solute must first bind to a specific site on a transporter protein, a site exposed to the solute on one surface of the membrane (**Figure 4.8**). A portion of the transporter then undergoes a change in shape, exposing this same binding site to the solution on the opposite side of the membrane. The dissociation of the substance from the transporter binding site completes the process of moving the material through the membrane. Using this mechanism, molecules can move in either direction, getting on the transporter on one side and off at the other.

Many of the characteristics of transporters and ion channels are similar. Both involve membrane proteins and show chemical specificity. They do, however, differ in the number of molecules or ions crossing the membrane by way of these membrane proteins. Ion channels typically move several thousand times more ions per unit time than molecules moved by transporters. In part, this is because a transporter must change its shape for each molecule transported across the membrane, whereas an open ion channel can support a continuous flow of ions without a change in conformation. Imagine, for example, how many more cars can move over a bridge than can be shuttled back and forth by a ferry boat.

Many types of transporters are present in membranes, each type having binding sites that are specific for a particular substance or a specific class of related substances. For example, although amino acids and sugars undergo mediated transport, a protein that transports amino acids does not transport sugars, and vice versa. Just as with ion channels, the plasma membranes of different cells contain different types and numbers of transporters; consequently, they exhibit differences in the types of substances transported and in their rates of transport.



AP|R **Figure 4.8** Highly schematic model of mediated transport. A change in the conformation of the transporter exposes the transporter binding site first to one surface of the membrane then to the other, thereby transferring the bound solute from one side of the membrane to the other. This model shows net mediated transport from the extracellular fluid to the inside of the cell. In many cases, the net transport is in the opposite direction. The size of the conformational change is exaggerated for illustrative purposes in this and subsequent figures.

Four factors determine the magnitude of solute flux through a mediated-transport system: (1) the solute concentration, (2) the affinity of the transporters for the solute, (3) the number of transporters in the membrane, and (4) the rate at which the conformational change in the transport protein occurs. The flux through a mediated-transport system can be altered by changing any of these four factors.

For any transported solute, a finite number of specific transporters reside in a given membrane at any particular moment. As with any binding site, as the concentration of the solute to be transported is increased, the number of occupied binding sites increases until the transporters become saturated—that is, until all the binding sites are occupied. When the transporter binding sites are saturated, the maximal flux across the membrane has been reached and no further increase in solute flux will occur with increases in solute concentration. Contrast the solute flux resulting from mediated transport with the flux produced by diffusion through the lipid portion of a membrane (**Figure 4.9**). The flux due to diffusion increases in direct proportion to the increase in extracellular concentration, and there is no limit because diffusion does not involve binding to a fixed number of sites. (At very high ion concentrations, however, diffusion through ion channels may approach a limiting value because of the fixed number of channels available, just as an upper limit determines the rate at which cars can move over a bridge.)

When transporters are saturated, however, the maximal transport flux depends upon the rate at which the conformational changes in the transporters can transfer their binding sites from one surface to the other. This rate is much slower than the rate of ion diffusion through ion channels.

Thus far, we have described mediated transport as though all transporters had similar properties. In fact, two types of mediated transport exist—facilitated diffusion and active transport.

Facilitated Diffusion

As in simple diffusion, in **facilitated diffusion** the net flux of a molecule across a membrane always proceeds from higher to lower concentration, or "downhill" across a membrane. The key difference between these two processes is that facilitated diffusion uses a transporter to move solute, as in Figure 4.8. Net facilitated diffusion continues until the concentrations of the solute on the two sides of the membrane become equal. At this point, equal numbers of molecules are binding to the transporter at the outer surface of the cell and moving into the cell as are binding at the inner surface and moving out. Neither simple diffusion nor facilitated diffusion is directly coupled to energy (ATP) derived from metabolism. For this reason, they are incapable of producing a net flux of solute from a lower to a higher concentration across a membrane.

Among the most important facilitated-diffusion systems in the body are those that mediate the transport of glucose across plasma membranes. Without such glucose transporters, or GLUTs as they are abbreviated, cells would be virtually impermeable to glucose, which is a polar molecule. It might be expected that as a result of facilitated diffusion the glucose concentration inside cells would become equal to the extracellular concentration. This

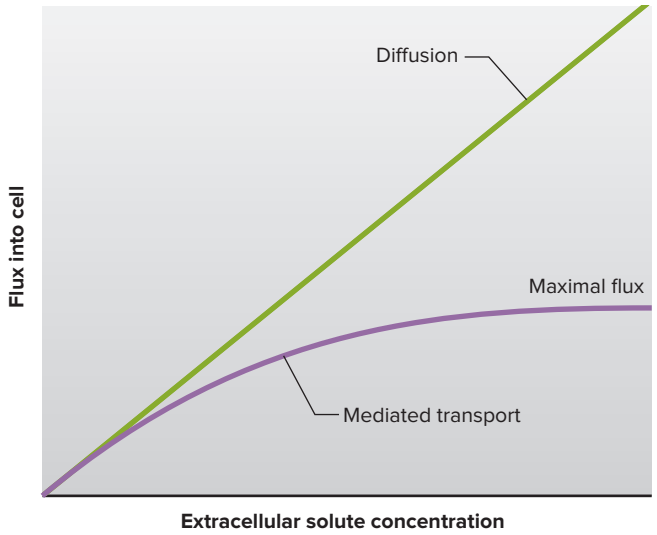


Figure 4.9 The flux of molecules diffusing into a cell across the lipid bilayer of a plasma membrane (green line) increases continuously in proportion to the extracellular concentration, whereas the flux of molecules through a mediated-transport system (purple line) reaches a maximal value.

PHYSIOLOGICAL INQUIRY

- What might determine the value for maximal flux of a mediated-transport system as shown here?

Answer can be found at end of chapter.

does not occur in most cells, however, because glucose is metabolized in the cytosol to glucose 6-phosphate almost as quickly as it enters (refer back to Figure 3.42). Consequently, the intracellular glucose concentration remains lower than the extracellular concentration, and there is a continuous net flux of glucose into cells. In later chapters, you will learn that the number of GLUT molecules in the plasma membranes of many cells can be regulated by the endocrine system. In this way, facilitated diffusion contributes significantly to metabolic homeostasis.

Active Transport

Active transport differs from facilitated diffusion in that it uses energy to move a substance *uphill* across a membrane—that is, against the substance's concentration gradient (**Figure 4.10**). As with facilitated diffusion, active transport requires a substance to bind to the transporter in the membrane. Because these transporters move the substance *uphill,* they are often referred to as pumps. As with facilitated-diffusion transporters, active-transport transporters exhibit specificity and saturation—that is, the flux via the transporter is maximal when all transporter binding sites are occupied.

The net movement of solute from lower to higher concentration and the maintenance of a higher steady-state concentration on one side of a membrane is counter to the second law of thermodynamics because it creates less disorder. It can be achieved only with continuous input of energy into the active-transport process. Two means of coupling energy to transporters are known: (1) the direct use of ATP in **primary active transport,** and (2) the use of an electrochemical gradient across a membrane to drive the process in **secondary active transport.**

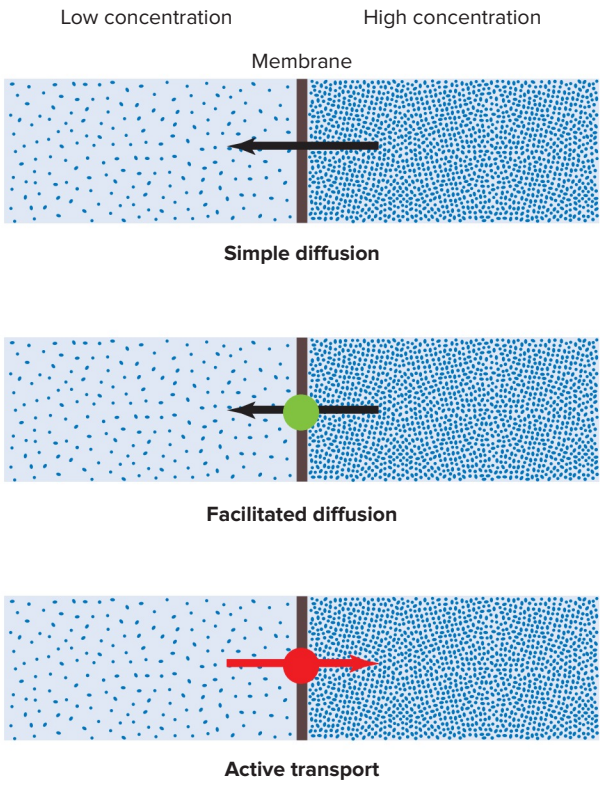


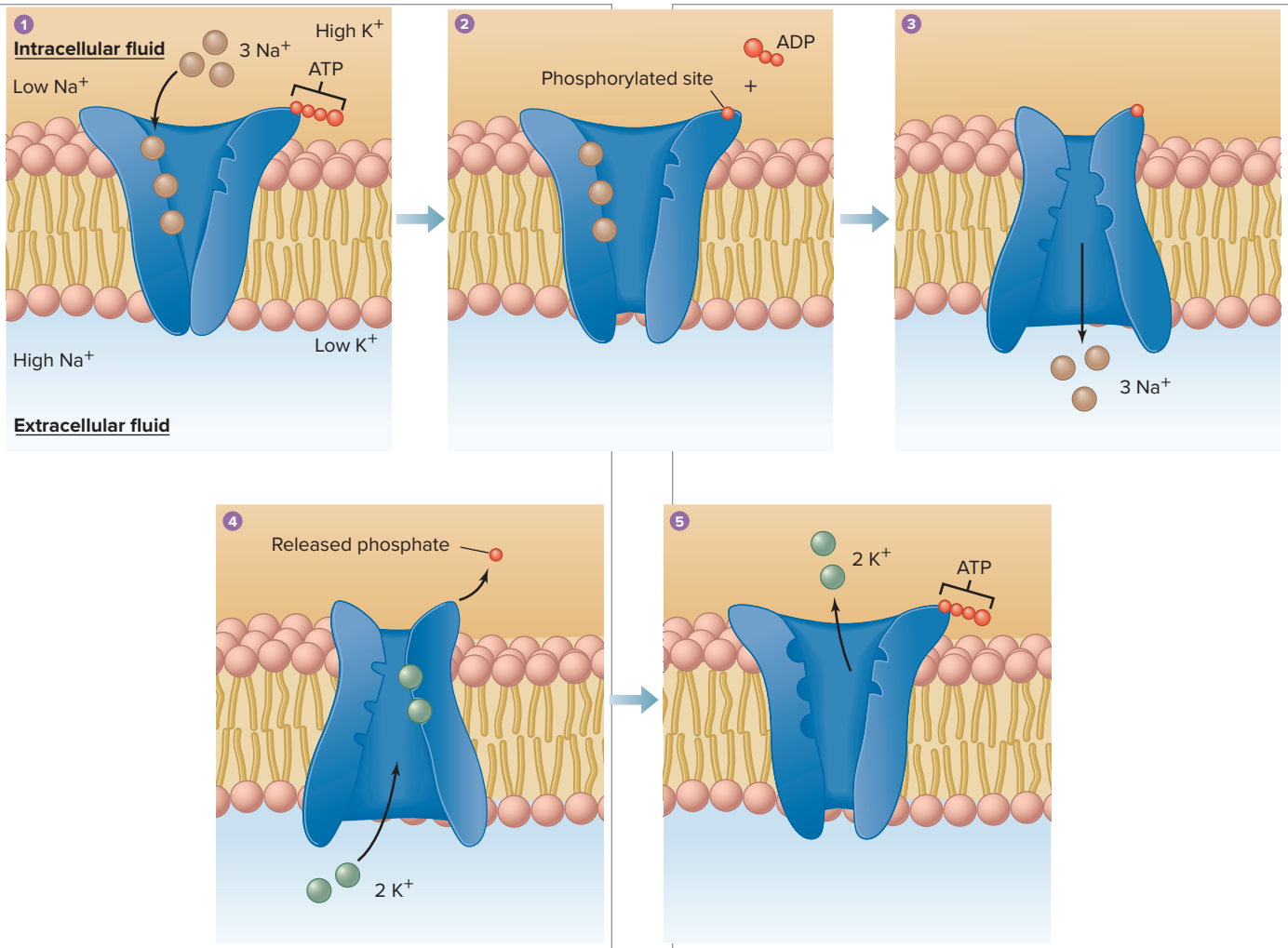
Figure 4.10 Direction of net solute flux crossing a membrane by simple diffusion (high to low concentration), facilitated diffusion (high to low concentration), and active transport (low to high concentration). The colored circles represent transporter molecules.

Primary Active Transport The hydrolysis of ATP by a transporter provides the energy for primary active transport. The transporter itself is an enzyme called *ATPase* that catalyzes the breakdown of ATP and, in the process, phosphorylates itself. Phosphorylation of the transporter protein is a type of covalent modulation that changes the conformation of the transporter and the affinity of the transporter's solute binding site.

One of the best-studied examples of primary active transport is the movement of sodium and potassium ions across plasma membranes by the **Na^+/K^+-ATPase pump.** This transporter, which is present in all cells, moves Na^+ from intracellular to extracellular fluid, and K^+ in the opposite direction. In both cases, the movements of the ions are against their respective concentration gradients. **Figure 4.11** illustrates the sequence the Na^+/K^+-ATPase pump is believed to use to transport these two ions in opposite directions. (1) Initially, the transporter, with an associated molecule of ATP, binds three sodium ions at high-affinity sites on the intracellular surface of the protein. Two binding sites also exist for K^+, but at this stage they are in a low-affinity state and therefore do not bind intracellular K^+. (2) Binding of Na^+ results in activation of an inherent ATPase activity of the transporter protein, causing phosphorylation of the cytosolic surface of the transporter and releasing a molecule of ADP. (3) Phosphorylation results in a conformational change of the transporter, exposing the bound Na^+ to the extracellular fluid and, at the same time, reducing the affinity of the binding sites for Na^+. The Na^+ is released from its binding sites. (4) The new conformation of the transporter results in an increased affinity of the two binding sites for K^+, allowing two K^+ to bind to the transporter on the extracellular surface. (5) Binding of K^+ results in dephosphorylation of the transporter. This returns the transporter to its original conformation, resulting in reduced affinity of the K^+ binding sites and increased affinity of the Na^+ binding sites. K^+ is therefore released into the intracellular fluid, allowing additional Na^+ (and ATP) to be bound at the intracellular surface.

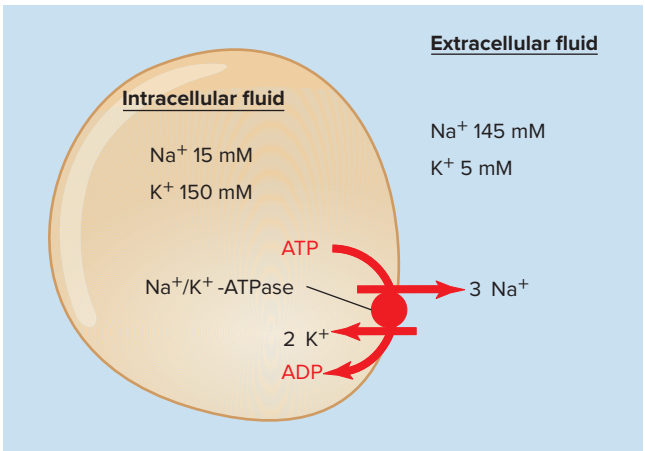
The pumping activity of the Na^+/K^+-ATPase primary active transporter establishes and maintains the characteristic distribution of high intracellular K^+ and low intracellular Na^+ relative to their respective extracellular concentrations (**Figure 4.12**). For each molecule of ATP hydrolyzed, this transporter moves three sodium ions out of a cell and two potassium ions into a cell. This results in a net transfer of positive charge to the outside of the cell; therefore, this transport process is not electrically neutral and as such plays a small role in the establishment of a cell's membrane potential (see Figure 4.6).

In addition to the Na^+/K^+-ATPase transporter, the major primary active-transport proteins found in most cells are (1) Ca^{2+}-ATPase; (2) H^+-ATPase; and (3) H^+/K^+-ATPase. Together, the activities of these and other active-transport systems account for a significant share of the total energy usage of the human body. Ca^{2+}-ATPase is found in the plasma membrane and several organelle membranes, including the membranes of the endoplasmic reticulum. In the plasma membrane, the direction of active Ca^{2+} transport is from cytosol to extracellular fluid. In organelle membranes, it is from cytosol into the organelle lumen. Thus, active transport of Ca^{2+} out of the cytosol, via Ca^{2+}-ATPase, is one reason that the cytosol of most cells has a very low Ca^{2+} concentration, about 10^{-7} mol/L, compared with an extracellular Ca^{2+} concentration of 10^{-3} mol/L, 10,000 times greater. These transport mechanisms help ensure intracellular Ca^{2+} homeostasis, an important function



AP|R **Figure 4.11** Active transport of Na^+ and K^+ mediated by the Na^+/K^+-ATPase pump. See text for the numbered sequence of events occurring during transport.

because of the many physiological activities in cells that are regulated by changes in Ca^{2+} concentration (for example, release of cell secretions from storage vesicles into the extracellular fluid).

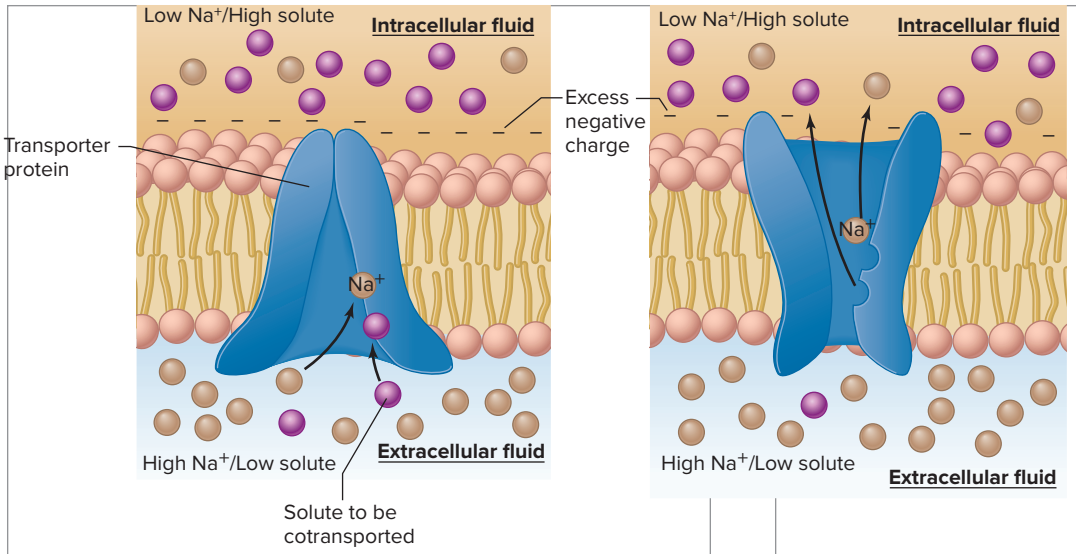


AP|R **Figure 4.12** The primary active transport of sodium and potassium ions in opposite directions by the Na^+/K^+-ATPase in plasma membranes is responsible for the low Na^+ and high K^+ intracellular concentrations. For each ATP hydrolyzed, three Na^+ move out of a cell and two K^+ move in.

H^+-ATPase is in the plasma membrane and several organelle membranes, including the inner mitochondrial and lysosomal membranes. In the plasma membrane, H^+-ATPase moves H^+ produced by metabolism out of cells and in this way helps maintain cellular pH. All enzymes in the body require a narrow range of pH for optimal activity; consequently, this active-transport process is vital for cell metabolism and survival.

H^+/K^+-ATPase is in the plasma membranes of numerous cells, such as the acid-secreting cells in the stomach, where it pumps one H^+ out of the cell and moves one K^+ in for each molecule of ATP hydrolyzed. The hydrogen ions enter the stomach lumen where they have an important function in the digestion of proteins.

Secondary Active Transport In secondary active transport, the movement of an ion down its electrochemical gradient is coupled to the transport of another molecule, often an organic nutrient like glucose or an amino acid. Thus, transporters that mediate secondary active transport have two binding sites, one for an ion—typically but not always Na^+—and another for a second substance. An example of such transport is shown in **Figure 4.13**. In this example, the electrochemical gradient for Na^+ is directed into the cell because of the higher concentration of Na^+ in the extracellular fluid and the excess negative charges inside the cell. The other solute to be transported, however, must move *against* its



AP|R **Figure 4.13** Secondary active-transport model. In this example, the binding of a sodium ion to the transporter produces an allosteric increase in the affinity of the solute binding site at the extracellular surface of the membrane. Binding of Na^+ and solute causes a conformational change in the transporter that exposes the binding sites to the intracellular fluid. Na^+ diffuses down its electrochemical gradient into the cell, which returns the solute binding site to a low-affinity state.

PHYSIOLOGICAL INQUIRY

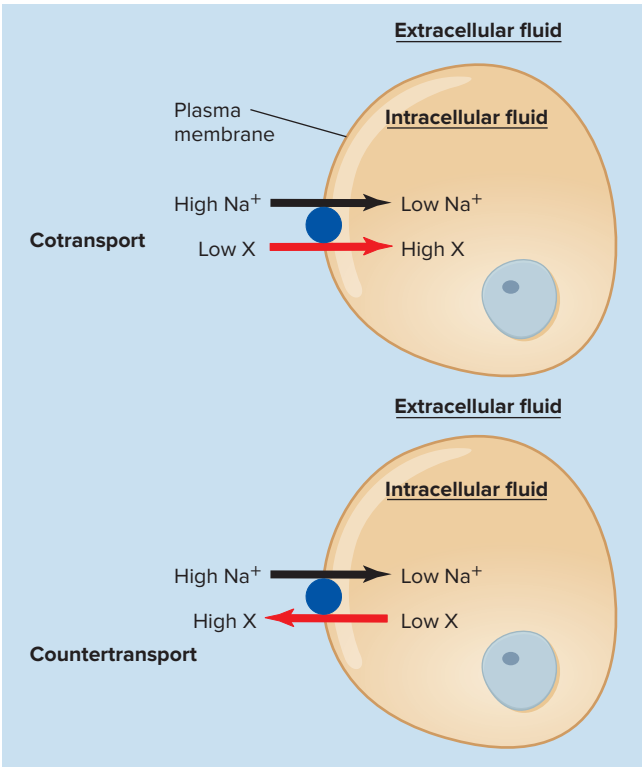
- Is ATP hydrolyzed in the process of transporting solutes with secondary active transport?

Answer can be found at end of chapter.

concentration gradient, uphill into the cell. High-affinity binding sites for Na^+ exist on the extracellular surface of the transporter. Binding of Na^+ increases the affinity of the binding site for the transported solute. The transporter then undergoes a conformational change, which exposes both binding sites to the intracellular side of the membrane. When the transporter changes conformation, its affinity for Na^+ decreases, and Na^+ moves into the intracellular fluid by simple diffusion down its electrochemical gradient. At the same time, the affinity of the solute binding site decreases, which releases the solute into the intracellular fluid. Once the transporter releases both molecules, the protein assumes its original conformation. The Na^+ is then actively transported back out of the cell by primary active transport, so that the electrochemical gradient for Na^+ is maintained. The secondarily transported solute remains in the cell. The most important distinction, therefore, between primary and secondary active transport is that secondary active transport uses the stored energy of an electrochemical gradient to move both an ion and a second solute across a plasma membrane. The creation and maintenance of the electrochemical gradient, however, depend on the action of primary active transporters.

The creation of a Na^+ concentration gradient across the plasma membrane by the primary active transport of Na^+ is a means of indirectly "storing" energy that can then be used to drive secondary active-transport pumps linked to Na^+. Ultimately, however, the energy for secondary active transport is derived from metabolism in the form of the ATP that is used by the Na^+/K^+-ATPase to create the Na^+ concentration gradient. If the production of ATP were inhibited, the primary active transport of Na^+ would cease and the cell would no longer be able to maintain a Na^+ concentration gradient across the membrane. This, in turn, would lead to a failure of the secondary active-transport systems that depend on the Na^+ concentration gradient for their source of energy.

As noted earlier, the net movement of Na^+ by a secondary active-transport protein is always from high extracellular concentration into the cell, where the concentration of Na^+ is lower. Therefore, in secondary active transport, the movement of Na^+ is always *downhill,* whereas the net movement of the actively transported solute on the same transport protein is *uphill,* moving from lower to higher concentration. The movement of the actively transported solute can be either into the cell (in the same direction as Na^+), in which case it is known as **cotransport,** or out of the cell (opposite the direction of Na^+ movement), which is called **countertransport** (**Figure 4.14**). The terms *symport* and *antiport* are



AP|R **Figure 4.14** Cotransport and countertransport during secondary active transport driven by Na^+. Sodium ions always move *down* their concentration gradient into a cell, and the transported solute always moves *up* its gradient. Both Na^+ and the transported solute X move in the same direction during cotransport, but in opposite directions during countertransport.

also used to refer to the processes of cotransport and countertransport, respectively.

In summary, the distribution of substances between the intracellular and extracellular fluid is often unequal (**Table 4.1**)

TABLE 4.1 Composition of Extracellular and Intracellular Fluids

	Extracellular Concentration (mM)	Intracellular Concentration (mM)*
Na^+	145	15
K^+	5	150
Ca^{2+}	1	0.0001
Mg^{2+}	1.5	12
Cl^-	100	7
HCO_3^-	24	10
P_i	2	40
Amino acids	2	8
Glucose	5.5	1
ATP	0	4
Protein	0.2	4

*The intracellular concentrations differ slightly from one tissue to another, depending on the expression of plasma membrane ion channels and transporters. The intracellular concentrations shown in the table are typical of most cells. For Ca^{2+}, values represent free concentrations. Total calcium levels, including the portion sequestered by proteins or in organelles, approach 2.5 mM (extracellular) and 1.5 mM (intracellular).

due to the presence in the plasma membrane of primary and secondary active transporters, ion channels, and the membrane potential. **Table 4.2** provides a summary of the major characteristics of the different pathways by which substances move through cell membranes, whereas **Figure 4.15** illustrates the variety of commonly encountered channels and transporters associated with the movement of substances across a typical plasma membrane.

Not included in Table 4.2 is the mechanism by which water moves across membranes. The special case whereby this polar molecule moves between body fluid compartments is covered next.

4.3 Osmosis

Water is a polar molecule and yet it diffuses across the plasma membranes of most cells very rapidly. This process is mediated by a family of membrane proteins known as **aquaporins** that form channels through which water can diffuse. The type and number of these water channels differ in different membranes. Consequently, some cells are more permeable to water than others. Furthermore, in some cells, the number of aquaporin channels—and, therefore, the permeability of the membrane to water—can be altered in response to various signals. This is especially important in the epithelial cells that line certain ducts in the kidneys. As you will learn in Chapter 14, one of the major functions of the kidneys is to regulate the amount of water that gets excreted in the urine; this helps keep the total amount of water in the body fluid compartments homeostatic. The epithelial cells of the kidney ducts contain numerous aquaporins that can be increased or decreased in number depending on the water balance of the body at any time. For example, in an individual who is dehydrated, the numbers of aquaporins in the membranes of the kidney epithelial cells will increase; this will permit additional water to move from the urine that is being formed in the kidney ducts back into the blood. That is why the volume of urine decreases whenever an individual becomes dehydrated.

TABLE 4.2 Major Characteristics of Pathways by Which Substances Cross Membranes

	Diffusion		*Mediated Transport*		
	Through Lipid Bilayer	**Through Protein Channel**	**Facilitated Diffusion**	**Primary Active Transport**	**Secondary Active Transport**
Direction of net flux	High to low concentration	High to low concentration	High to low concentration	Low to high concentration	Low to high concentration
Equilibrium or steady state	$C_o = C_i$	$C_o = C_i$*	$C_o = C_i$	$C_o \neq C_i$	$C_o \neq C_i$
Use of integral membrane protein	No	Yes	Yes	Yes	Yes
Maximal flux at high concentration (saturation)	No	No	Yes	Yes	Yes
Chemical specificity	No	Yes	Yes	Yes	Yes
Use of energy and source	No	No	No	Yes: ATP	Yes: ion gradient (often Na^+)
Typical molecules using pathway	Nonpolar: O_2, CO_2, fatty acids	Ions: Na^+, K^+, Ca^{2+}	Polar: glucose	Ions: Na^+, K^+, Ca^{2+}, H^+	Polar: amino acids, glucose, some ions

*In the presence of a membrane potential, the intracellular and extracellular ion concentrations will not be equal at steady state.

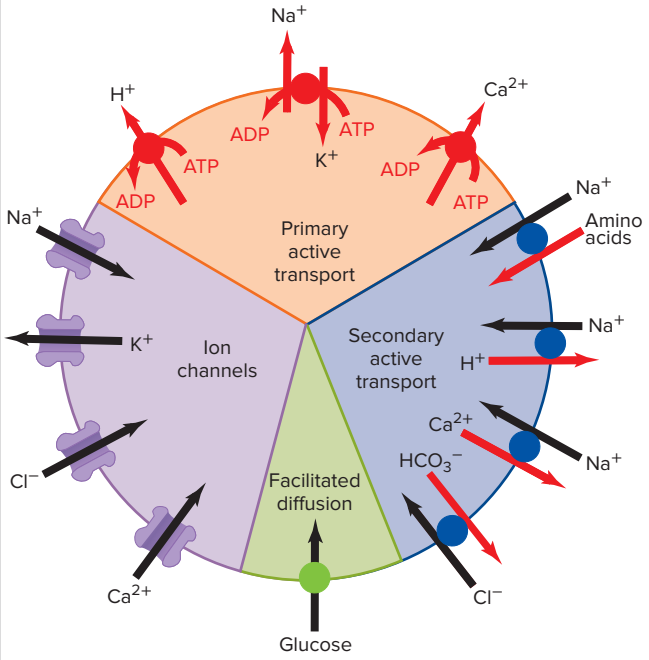


Figure 4.15 Movement of solutes across a typical plasma membrane involving membrane proteins. A specialized cell may contain additional transporters and channels not shown in this figure. Many of these membrane proteins can be modulated by various signals, leading to a controlled increase or decrease in specific solute fluxes across the membrane. The stoichiometry of cotransporters is not shown.

PHYSIOLOGICAL INQUIRY

- This figure summarizes several of the many types of transporters in the cells of the human body. List a few ways in which the variety of transport mechanisms shown here relate to the general principle of physiology that homeostasis is essential for health and survival.

Answer can be found at end of chapter.

The net diffusion of water across a membrane is called **osmosis.** As with any diffusion process, a concentration difference must be present in order to produce a net flux. How can a difference in water concentration be established across a membrane?

The addition of a solute to water decreases the concentration of water in the solution compared to the concentration of pure water. For example, if a solute such as glucose is dissolved in water, the concentration of water in the resulting solution is less than that of pure water. A given volume of a glucose solution contains fewer water molecules than an equal volume of pure water because each glucose molecule occupies space formerly occupied by a water molecule (**Figure 4.16**). In quantitative terms, a liter of pure water weighs about 1000 g, and the molecular weight of water is 18. Thus, the concentration of water molecules in pure water is 1000/18 = 55.5 M. The decrease in water concentration in a solution is approximately equal to the concentration of added solute. In other words, one solute molecule will displace one water molecule. The water concentration in a 1 M glucose solution is therefore approximately 54.5 M rather than 55.5 M. Just as adding water to a solution will dilute the solute, adding solute to water will "dilute" the water. The greater the solute concentration, the lower the water concentration.

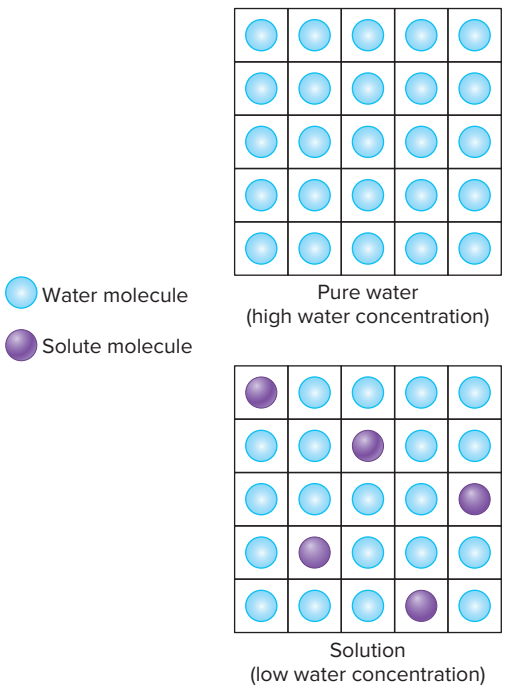


Figure 4.16 The addition of solute molecules to pure water lowers the water concentration in the solution.

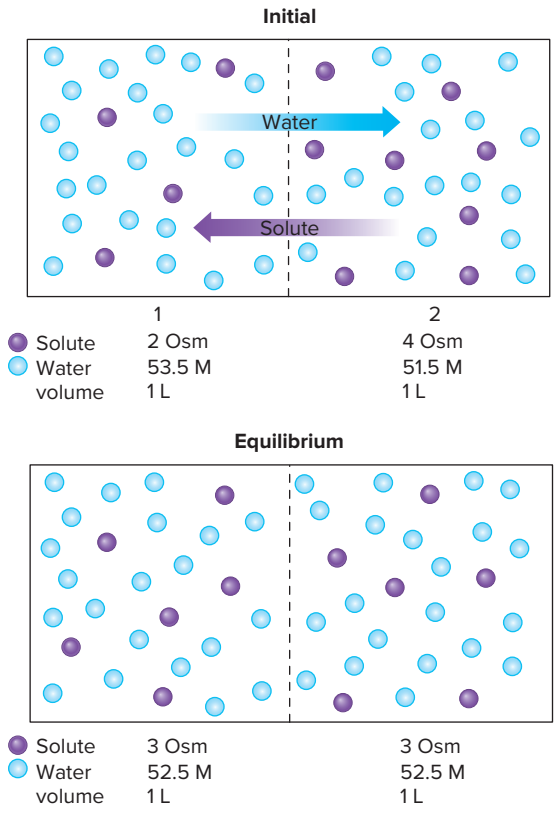
The degree to which the water concentration is decreased by the addition of solute depends upon the *number* of particles (molecules or ions) of solute in solution (the solute concentration) and not upon the *chemical nature* of the solute. For example, 1 mol of glucose in 1 L of solution decreases the water concentration to the same extent as does 1 mol of an amino acid, or 1 mol of urea, or 1 mol of any other molecule that exists as a single particle in solution. On the other hand, a molecule that ionizes in solution decreases the water concentration in proportion to the number of ions formed. For example, many simple salts dissociate nearly completely in water. For simplicity's sake, we will assume the dissociation is 100% at body temperature and at concentrations found in the blood. Therefore, 1 mol of sodium chloride in solution gives rise to 1 mol of sodium ions and 1 mol of chloride ions, producing 2 mol of solute particles. This decreases the water concentration twice as much as 1 mol of glucose. By the same reasoning, if a 1 M $MgCl_2$ solution were to dissociate completely, it would decrease the water concentration three times as much as would a 1 M glucose solution.

Because the water concentration in a solution depends upon the number of solute particles, it is useful to have a concentration term that refers to the total concentration of solute particles in a solution, regardless of their chemical composition. The total solute concentration of a solution is known as its **osmolarity.** One **osmol** is equal to 1 mol of solute particles. Therefore, a 1 M solution of glucose has a concentration of 1 Osm (1 osmol per liter), whereas a 1 M solution of NaCl contains 2 osmol of solute per liter of solution. A liter of solution containing 1 mol of glucose and 1 mol of NaCl has an osmolarity of 3 Osm. A solution with an osmolarity of 3 Osm may contain

1 mol of glucose and 1 mol of NaCl, or 3 mol of glucose, or 1.5 mol of NaCl, or any other combination of solutes as long as the total solute concentration is equal to 3 Osm. (For reference, most physiological solutions such as blood are usually in the milliosmolar range.)

Although *osmolarity* refers to the concentration of solute particles, it also determines the water concentration in the solution because the higher the osmolarity, the lower the water concentration. The concentration of water in any two solutions having the same osmolarity is the same because the total number of solute particles per unit volume is the same.

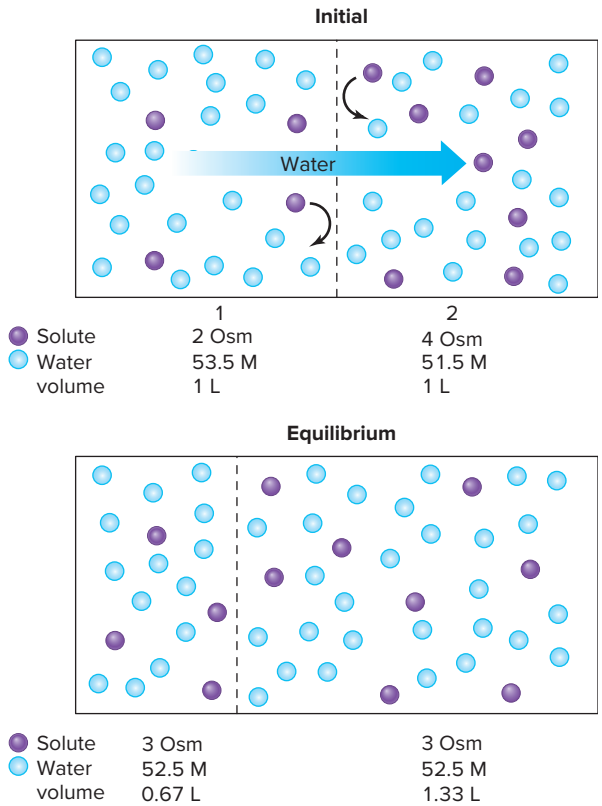
Let us now apply these principles governing water concentration to osmosis of water across membranes. **Figure 4.17** shows two 1 L compartments separated by a membrane permeable to *both* solute and water. Initially, the concentration of solute is 2 Osm in compartment 1 and 4 Osm in compartment 2. This difference in solute concentration means there is also a difference in water concentration across the membrane: 53.5 M in compartment 1 and 51.5 M in compartment 2. Therefore, a net diffusion of water from the higher concentration in compartment 1 to the lower concentration in compartment 2 will take place, and a net diffusion of solute in the opposite direction, from 2 to 1. When diffusion equilibrium is reached, the two compartments will have identical solute and water concentrations, 3 Osm and 52.5 M, respectively. One mol of water will have diffused from compartment 1 to compartment 2, and 1 mol of solute will have diffused from 2 to 1. Because 1 mol of solute has replaced 1 mol of water in compartment 1, and vice versa in compartment 2, no change in the volume occurs for either compartment.



AP|R **Figure 4.17** Between two compartments of equal volume, the net diffusion of water and solute across a membrane permeable to both leads to diffusion equilibrium of both, with no change in the volume of either compartment. (For clarity, not all water molecules are shown here or in Figure 4.18.)

If the membrane is now replaced by one *permeable to water but impermeable to solute* (**Figure 4.18**), the same *concentrations* of water and solute will be reached at equilibrium as before, but a change in the *volumes* of the compartments will also occur. Water will diffuse from 1 to 2, but there will be no solute diffusion in the opposite direction because the membrane is impermeable to solute. Water will continue to diffuse into compartment 2, therefore, until the water concentrations on the two sides become equal. The solute concentration in compartment 2 decreases as it is diluted by the incoming water, and the solute in compartment 1 becomes more concentrated as water moves out. When the water reaches diffusion equilibrium, the osmolarities of the compartments will be equal; therefore, the solute concentrations must also be equal. To reach this state of equilibrium, enough water must pass from compartment 1 to 2 to increase the volume of compartment 2 by one-third and decrease the volume of compartment 1 by an equal amount. Note that it is the presence of a membrane impermeable to solute that leads to the volume changes associated with osmosis.

The two compartments in our example were treated as if they were infinitely expandable, so the net transfer of water did not create a pressure difference across the membrane. In contrast, if the walls of compartment 2 in Figure 4.18 had only a limited capacity to expand, as occurs across plasma membranes, the movement of water into compartment 2 would increase the pressure in compartment 2, which would oppose further net water entry. Thus, the movement



AP|R **Figure 4.18** The movement of water across a membrane that is permeable to water but not to solute leads to an equilibrium state involving a change in the volumes of the two compartments. In this case, a net diffusion of water (0.33 L) occurs from compartment 1 to 2. (We will assume that the membrane in this example stretches as the volume of compartment 2 increases so that no significant change in compartment pressure occurs.)

of water into compartment 2 can be prevented by the application of pressure to compartment 2. This leads to an important definition. When a solution containing solutes is separated from pure water by a **semipermeable membrane** (a membrane permeable to water but not to solutes), the pressure that must be applied to the solution to prevent the net flow of water into it is known as the **osmotic pressure** of the solution. The greater the osmolarity of a solution, the greater the osmotic pressure. It is important to recognize that osmotic pressure does not push water molecules into a solution. Rather, it represents the amount of pressure that would have to be applied to a solution to *prevent* the net flow of water into the solution by osmosis. Like osmolarity, the osmotic pressure associated with a solution is a measure of the solution's water concentration—the lower the water concentration, the higher the osmotic pressure.

Extracellular Osmolarity and Cell Volume

We can now apply the principles learned about osmosis to cells, which meet all the criteria necessary to produce an osmotic flow of water across a membrane. Both the intracellular and extracellular fluids contain water, and cells are encased by a membrane that is very permeable to water but impermeable to many substances. Substances that cannot cross the plasma membrane are called **nonpenetrating solutes;** that is, they do not penetrate through the lipid bilayer.

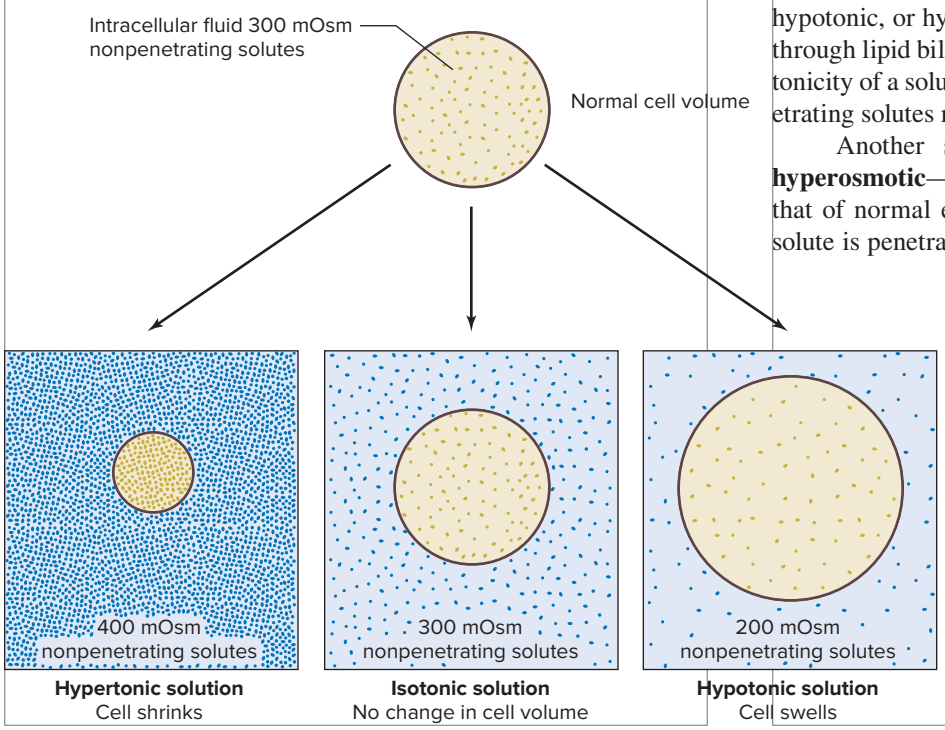
Most of the extracellular solute particles are sodium and chloride ions, which can diffuse into the cell through ion channels in the plasma membrane or enter the cell during secondary active transport. As we have seen, however, the plasma membrane contains Na^+/K^+-ATPase pumps that actively move Na^+ out of the cell. Therefore, Na^+ moves into cells and is pumped back out, behaving as if it never entered in the first place. For this reason, extracellular Na^+ behaves as a nonpenetrating solute. Any chloride ions that enter cells are also removed as quickly as they enter, due to the electrical repulsion generated by the membrane potential and the action of various transporters. Like Na^+, therefore, extracellular chloride ions behave as if they were nonpenetrating solutes.

Inside the cell, the major solute particles are K^+ and a number of organic solutes. Most of the latter are large polar molecules unable to diffuse through the plasma membrane. Although K^+ can diffuse out of a cell through K^+ channels, it is actively transported back by the Na^+/K^+-ATPase pump. The net effect, as with extracellular Na^+ and Cl^-, is that K^+ behaves as if it were a nonpenetrating solute, but in this case one confined to the intracellular fluid. Therefore, Na^+ and Cl^- outside the cell and K^+ and organic solutes inside the cell behave as nonpenetrating solutes on the two sides of the plasma membrane.

The osmolarity of the extracellular fluid is normally in the range of 285–300 mOsm (we will round off to a value of 300 for the rest of this text unless otherwise noted). Because water can diffuse across plasma membranes, water in the intracellular and extracellular fluids will come to diffusion equilibrium. At equilibrium, therefore, the osmolarities of the intracellular and extracellular fluids are the same—approximately 300 mOsm. Changes in extracellular osmolarity can cause cells, such as the red blood cells shown in the chapter-opening photo, to shrink or swell as water molecules move across the plasma membrane.

If cells with an intracellular osmolarity of 300 mOsm are placed in a solution of nonpenetrating solutes having an osmolarity of 300 mOsm, they will neither swell nor shrink because the water concentrations in the intracellular and extracellular fluids are the same, and the solutes cannot leave or enter. Such solutions are said to be **isotonic** (**Figure 4.19**), meaning any solution that does not cause a change in cell size. Isotonic solutions have the same concentration of *nonpenetrating* solutes as normal extracellular fluid. By contrast, **hypotonic** solutions have a nonpenetrating solute concentration lower than that found in cells; therefore, water moves by osmosis into the cells, causing them to swell. Similarly, solutions containing greater than 300 mOsm of nonpenetrating solutes (**hypertonic** solutions) cause cells to shrink as water diffuses out of the cell into the fluid with the lower water concentration. The concentration of *nonpenetrating* solutes in a solution, not the total osmolarity, determines its tonicity—isotonic, hypotonic, or hypertonic. By contrast, solutes that readily diffuse through lipid bilayers (penetrating solutes) do not contribute to the tonicity of a solution. This is so because the concentrations of penetrating solutes rapidly equilibrate across the membrane.

Another set of terms—**isoosmotic, hypoosmotic,** and **hyperosmotic**—denotes the osmolarity of a solution relative to that of normal extracellular fluid without regard to whether the solute is penetrating or nonpenetrating. The two sets of terms are



AP|R **Figure 4.19** Changes in cell volume produced by hypertonic, isotonic, and hypotonic solutions.

PHYSIOLOGICAL INQUIRY

- Blood volume must be restored in a person who has lost large amounts of blood due to serious injury. This is often accomplished by infusing isotonic NaCl solution into the blood. Why is this more effective than infusing an isoosmotic solution of a penetrating solute, such as urea?

Answer can be found at end of chapter.

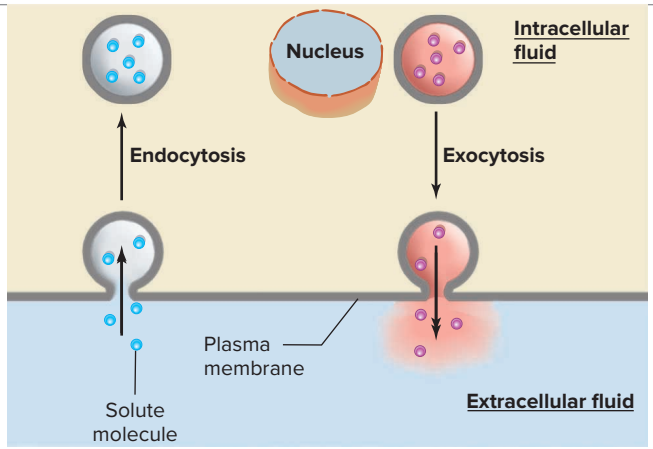
TABLE 4.3	Terms Referring to the Osmolarity and Tonicity of Solutions*
Isotonic	A solution that does not cause a change in cell volume; one that contains 300 mOsmol/L of nonpenetrating solutes, regardless of the concentration of membrane-penetrating solutes present
Hypertonic	A solution that causes cells to shrink; one that contains greater than 300 mOsmol/L of nonpenetrating solutes, regardless of the concentration of membrane-penetrating solutes present
Hypotonic	A solution that causes cells to swell; one that contains less than 300 mOsmol/L of nonpenetrating solutes, regardless of the concentration of membrane-penetrating solutes present
Isoosmotic	A solution containing 300 mOsmol/L of solute, regardless of its composition of membrane-penetrating and nonpenetrating solutes
Hyperosmotic	A solution containing greater than 300 mOsmol/L of solutes, regardless of its composition of membrane-penetrating and nonpenetrating solutes
Hypoosmotic	A solution containing less than 300 mOsmol/L of solutes, regardless of its composition of membrane-penetrating and nonpenetrating solutes

*These terms are defined using an intracellular osmolarity of 300 mOsm as a reference, which is within the range for human cells but not an absolute fixed number.

therefore not synonymous. For example, a 1 L solution containing 150 mOsm each of nonpenetrating Na^+ and Cl^- and 100 mOsm of urea, which can rapidly cross plasma membranes, would have a total osmolarity of 400 mOsm and would be hyperosmotic relative to a typical cell. It would, however, also be an isotonic solution, producing no change in the equilibrium volume of cells immersed in it. Initially, cells placed in this solution would shrink as water moved into the extracellular fluid. However, urea, as a penetrating solute, would quickly diffuse into the cells and reach the same concentration as the urea in the extracellular solution; consequently, both the intracellular and extracellular solutions would soon reach the same osmolarity. Therefore, at equilibrium, there would be no difference in the water concentration across the membrane and thus no change in final cell volume; this would be the case even though the extracellular fluid would remain hyperosmotic relative to the normal value of 300 mOsm. Table 4.3 provides a comparison of the various terms used to describe the osmolarity and tonicity of solutions.

4.4 Endocytosis and Exocytosis

In addition to diffusion and mediated transport, there is another pathway by which substances can enter or leave cells, one that does not require the molecules to pass through the structural



AP|R **Figure 4.20** Endocytosis and exocytosis.

matrix of the plasma membrane. When sections of cells are observed under an electron microscope, regions of the plasma membrane can often be seen to have folded into the cell, forming small pockets that pinch off to produce intracellular, membrane-bound vesicles that enclose a small volume of extracellular fluid. This process is known as **endocytosis** (Figure 4.20). The reverse process, **exocytosis,** occurs when membrane-bound vesicles in the cytoplasm fuse with the plasma membrane and release their contents to the outside of the cell (see Figure 4.20).

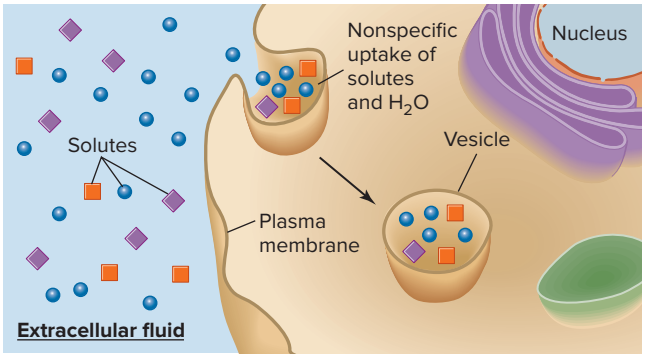
Endocytosis

Three common types of endocytosis may occur in a cell. These are pinocytosis ("cell drinking"), phagocytosis ("cell eating"), and receptor-mediated endocytosis (Figure 4.21).

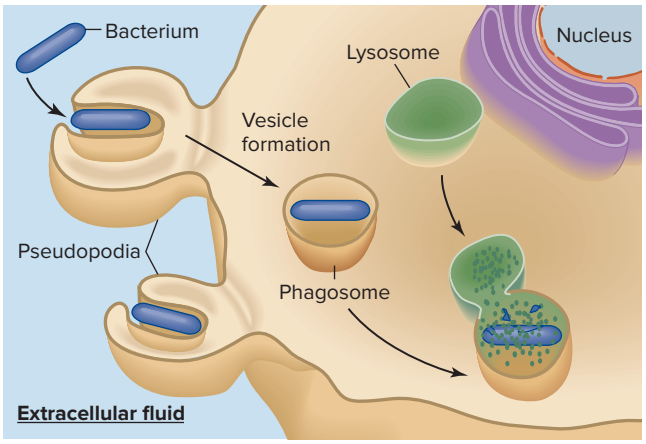
Pinocytosis In **pinocytosis,** also known as **fluid endocytosis,** an endocytotic vesicle encloses a small volume of extracellular fluid. This process is nonspecific because the vesicle simply engulfs the water in the extracellular fluid along with whatever solutes are present. These solutes may include ions, nutrients, or any other small extracellular molecule. Large macromolecules, other cells, and cell debris do not normally enter a cell via this process.

Phagocytosis In **phagocytosis,** cells engulf bacteria or large particles such as cell debris from damaged tissues. In this form of endocytosis, extensions of the plasma membrane called pseudopodia fold around the surface of the particle, engulfing it entirely. The pseudopodia, with their engulfed contents, then fuse into large vesicles called **phagosomes** that are internalized into the cell. Phagosomes migrate to and fuse with lysosomes in the cytoplasm, and the contents of the phagosomes are then destroyed by lysosomal enzymes and other molecules. Whereas most cells undergo pinocytosis, only a few special types of cells, such as those of the immune system (Chapter 18), carry out phagocytosis.

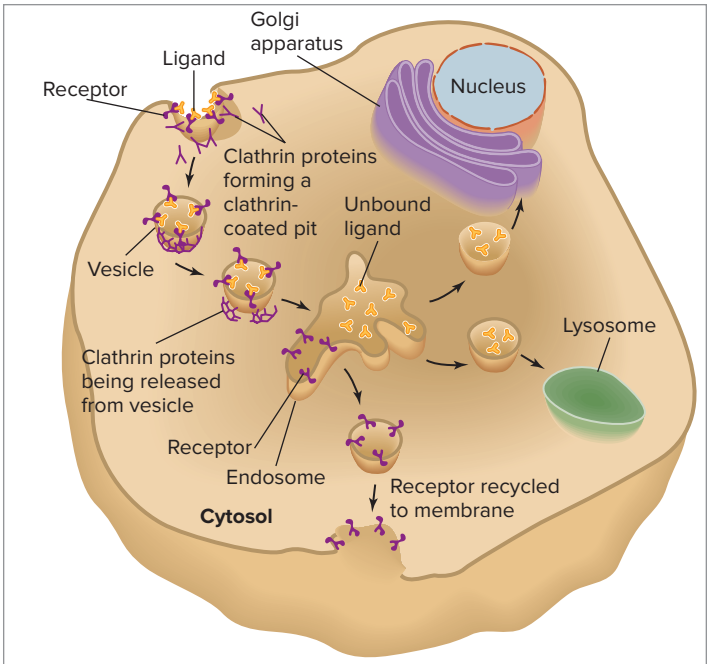
Receptor-Mediated Endocytosis In contrast to pinocytosis and phagocytosis, most cells have the capacity to *specifically* take up molecules that are important for cellular function or structure. In **receptor-mediated endocytosis,** certain molecules in the extracellular fluid bind to specific proteins on the outer surface of the plasma membrane. These proteins are called **receptors,** and



(a) Pinocytosis (fluid endocytosis)



(b) Phagocytosis



(c) Receptor-mediated endocytosis

AP|R **Figure 4.21** Pinocytosis, phagocytosis, and receptor-mediated endocytosis. (a) In pinocytosis, solutes and water are nonspecifically brought into the cell from the extracellular fluid via endocytotic vesicles. (b) In phagocytosis, specialized cells form extensions of the plasma membrane called pseudopodia, which engulf bacteria or other large objects such as cell debris. The vesicles that form fuse with lysosomes, which contain enzymes and other molecules that destroy the vesicle contents. (c) In receptor-mediated endocytosis, a cell recognizes a specific extracellular ligand that binds to a plasma membrane receptor. The binding triggers endocytosis. In the example shown here, the ligand-receptor complexes are internalized via clathrin-coated vesicles, which merge with endosomes (for simplicity, adapter proteins are not shown). Ligands may be routed to the Golgi apparatus for further processing, or to lysosomes. The receptors are typically recycled to the plasma membrane.

each one recognizes one ligand with high affinity (see Section C of Chapter 3 for a discussion of ligand–protein interactions). In one form of receptor-mediated endocytosis, the receptor undergoes a conformational change when it binds a ligand. Through a series of steps, a cytosolic protein called **clathrin** is recruited to the plasma membrane. A class of proteins called adaptor proteins links the ligand-receptor complex to clathrin. The entire complex then forms a cagelike structure that leads to the aggregation of ligand-bound receptors into a localized region of membrane, forming a depression, or **clathrin-coated pit,** which then invaginates and pinches off to form a clathrin-coated vesicle. By localizing ligand-receptor complexes to discrete patches of plasma membrane prior to endocytosis, cells may obtain concentrated amounts of ligands without having to engulf large amounts of extracellular fluid from many different sites along the membrane. Receptor-mediated endocytosis, therefore, leads to a selective concentration in the endocytotic vesicle of a specific ligand bound to one type of receptor.

Once an endocytotic vesicle pinches off from the plasma membrane in receptor-mediated endocytosis, the clathrin coat is removed and clathrin proteins are recycled back to the membrane. The vesicles then have several possible fates, depending upon the cell type and the ligand that was engulfed. Some vesicles fuse with the membrane of an intracellular organelle, adding the contents of the vesicle to the lumen of that organelle. Other endocytotic vesicles pass through the cytoplasm and fuse with the plasma membrane on the opposite side of the cell, releasing their contents to the extracellular space. This provides a pathway for the transfer of large molecules, such as proteins, across the layers of cells that separate two fluid compartments in the body (for example, the blood and interstitial fluid). A similar process allows small amounts of macromolecules to move across the intestinal epithelium.

Most endocytotic vesicles fuse with a series of intracellular vesicles and tubular elements known as endosomes (Chapter 3), which lie between the plasma membrane and the Golgi apparatus. Like the Golgi apparatus, the endosomes perform a sorting function, distributing the contents of the vesicle and its membrane to various locations. Some of the contents of endocytotic vesicles are passed from the endosomes to the Golgi apparatus, where the ligands are modified and processed. Other vesicles fuse with lysosomes, organelles that contain digestive enzymes that break down large molecules such as proteins, polysaccharides, and nucleic acids. The fusion of endosomal vesicles with the lysosomal membrane exposes the contents of the vesicle to these digestive enzymes. Finally, in many cases, the receptors that were internalized with the vesicle get recycled back to the plasma membrane.

Potocytosis Another fate of endocytotic vesicles is seen in a special type of receptor-mediated endocytosis called potocytosis. **Potocytosis** is similar to other types of receptor-mediated endocytosis in that an extracellular ligand typically binds to a plasma membrane receptor, initiating formation of an intracellular vesicle. In potocytosis, however, the ligands appear to be primarily restricted to low-molecular-weight molecules such as certain vitamins, but have also been found to include the lipoprotein complexes just described. Potocytosis differs from clathrin-dependent, receptor-mediated endocytosis in the fate of the endocytotic vesicle. In potocytosis, tiny vesicles called **caveolae** (singular, *caveola,* "little cave") pinch off from the plasma membrane and deliver their contents directly to the cell cytosol rather than merging with lysosomes or other organelles. The small molecules within the caveolae may diffuse into the cytosol via channels or be transported by carriers. Although their functions are still being actively investigated, caveolae have been implicated in a variety of important cellular functions, including cell signaling, transcellular transport, and cholesterol homeostasis.

Each episode of endocytosis removes a small portion of the membrane from the cell surface. In cells that have a great deal of endocytotic activity, more than 100% of the plasma membrane may be internalized in an hour, yet the membrane surface area remains constant. This is because the membrane is replaced at about the same rate by vesicle membrane that fuses with the plasma membrane during *exocytosis.* Some of the plasma membrane proteins taken into the cell during endocytosis are stored in the membranes of endosomes and, upon receiving the appropriate signal, can be returned to fuse with the plasma membrane during exocytosis.

Exocytosis

Exocytosis performs two functions for cells: (1) It provides a way to replace portions of the plasma membrane that endocytosis has removed and, in the process, a way to add new membrane components as well; and (2) it provides a route by which membrane-impermeable molecules (such as protein hormones) that the cell synthesizes can be secreted into the extracellular fluid.

How does the cell package substances that are to be secreted by exocytosis into vesicles? Chapter 3 described the entry of newly formed proteins into the lumen of the endoplasmic reticulum and the protein's processing through the Golgi apparatus. From the Golgi apparatus, the proteins to be secreted travel to the plasma membrane in vesicles from which they can be released into the extracellular fluid by exocytosis. In some cases, substances enter vesicles via mediated transporters in the vesicle membrane.

The secretion of substances by exocytosis is triggered in most cells by stimuli that lead to an increase in cytosolic Ca^{2+} concentration in the cell. As will be described in Chapters 5 and 6, these stimuli open Ca^{2+} channels in the plasma membrane and/or the membranes of intracellular organelles. The resulting increase in cytosolic Ca^{2+} concentration activates proteins required for the vesicle membrane to fuse with the plasma membrane and release the vesicle contents into the extracellular fluid. Material stored in secretory vesicles is available for rapid secretion in response to a stimulus, without delays that might occur if the material had to be synthesized after the stimulus arrived. Exocytosis is the mechanism by which most neurons communicate with each other through the release of neurotransmitters stored in secretory vesicles that merge with the plasma membrane. It is also a major way in which many types of hormones are released from endocrine cells into the extracellular fluid.

Cells that actively undergo exocytosis recover bits of membrane via a process called compensatory endocytosis. This process, the mechanisms of which are still uncertain but that may involve both clathrin- and non-clathrin-mediated events, restores membrane material to the cytoplasm that can be made available for the formation of new secretory vesicles. It also helps prevent the plasma membrane's unchecked expansion.

4.5 Epithelial Transport

As described in Chapter 1, epithelial cells line hollow organs or tubes and regulate the absorption or secretion of substances across these surfaces. One surface of an epithelial cell generally faces a hollow or fluid-filled tube or chamber, and the plasma membrane on this side is referred to as the **apical membrane** (also known as the luminal membrane) (refer back to Figures 1.2 and 3.9). The plasma membrane on the opposite surface rests upon a basement membrane and is usually adjacent to a network of blood vessels; it is referred to as the **basolateral membrane** (also known as the serosal membrane).

The two pathways by which a substance can cross a layer of epithelial cells are (1) the **paracellular pathway,** in which diffusion occurs *between* the adjacent cells of the epithelium; and (2) the **transcellular pathway,** in which a substance moves *into* an epithelial cell across either the apical or basolateral membrane, diffuses through the cytosol, and exits across the opposite membrane (**Figure 4.22**). Diffusion through the paracellular pathway is limited by the presence of tight junctions between adjacent cells, because these junctions form a seal around the apical end of the epithelial cells (Chapter 3). Although small ions and water can diffuse to some degree through tight junctions, the amount of paracellular diffusion is limited by the tightness of the junctional seal and the relatively small area available for diffusion.

During transcellular transport, the movement of molecules through the plasma membranes of epithelial cells occurs via the pathways (diffusion and mediated transport) already described for movement across membranes. However, the transport and

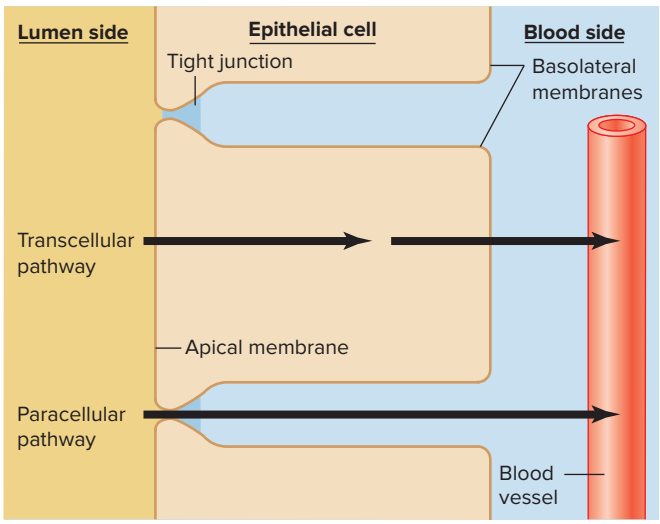


Figure 4.22 The two major routes by which water and solutes move across an epithelium, shown here as moving from the lumen of a tube or hollow chamber into the blood.

permeability characteristics of the apical and basolateral membranes are not the same. These two membranes often contain different ion channels and different transporters for mediated transport. As a result of these differences, substances can undergo a net movement from a low concentration on one side of an epithelium to a higher concentration on the other side. Examples include the absorption of material from the gastrointestinal tract into the blood, the movement of substances between the kidney tubules and the blood during urine formation, and the secretion of ions and water by glands such as sweat glands.

Figure 4.23 and **Figure 4.24** illustrate two examples of active transport across an epithelium. Na^+ is actively transported across most epithelia from lumen to blood side. In our example, the movement of Na^+ from the lumen into the epithelial cell occurs by diffusion through Na^+ channels in the apical membrane (see Figure 4.23). Na^+ diffuses into the cell because the intracellular concentration of Na^+ is kept low by the active transport of Na^+ back out of the cell across the basolateral membrane on the opposite side, where all of the Na^+/K^+-ATPase pumps are located. In other words, Na^+ moves downhill into the cell and then uphill out of it. The net result is that Na^+ can be moved via the transcellular pathway from lower to higher concentration across the epithelium.

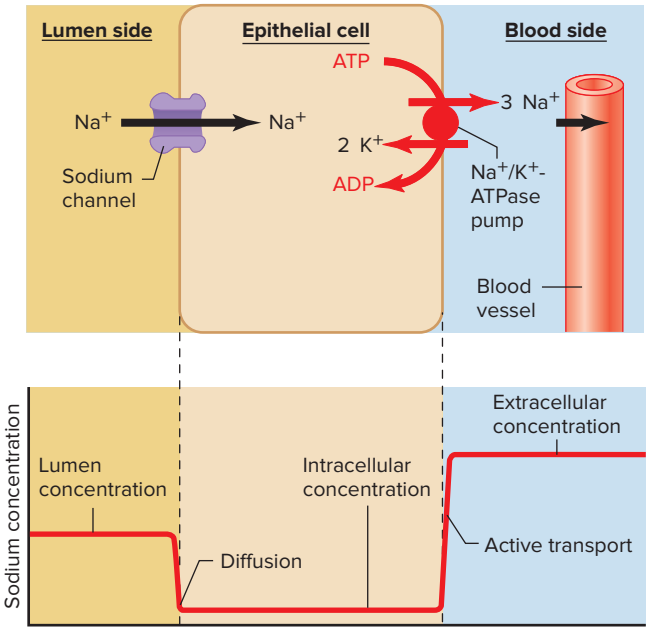


Figure 4.23 Active transport of Na^+ across an epithelial cell. The transepithelial transport of Na^+ always involves primary active transport out of the cell across one of the plasma membranes, typically via an Na^+/K^+-ATPase pump as shown here. The movement of Na^+ into the cell across the plasma membrane on the opposite side is always downhill. Sometimes, as in this example, it is by diffusion through Na^+ channels, whereas in other epithelia this downhill movement occurs through a secondary active transporter. Shown below the cell is the concentration profile of the transported solute across the epithelium.

PHYSIOLOGICAL INQUIRY

- What would happen in this situation if the cell's ATP supply decreased significantly?

Answer can be found at end of chapter.

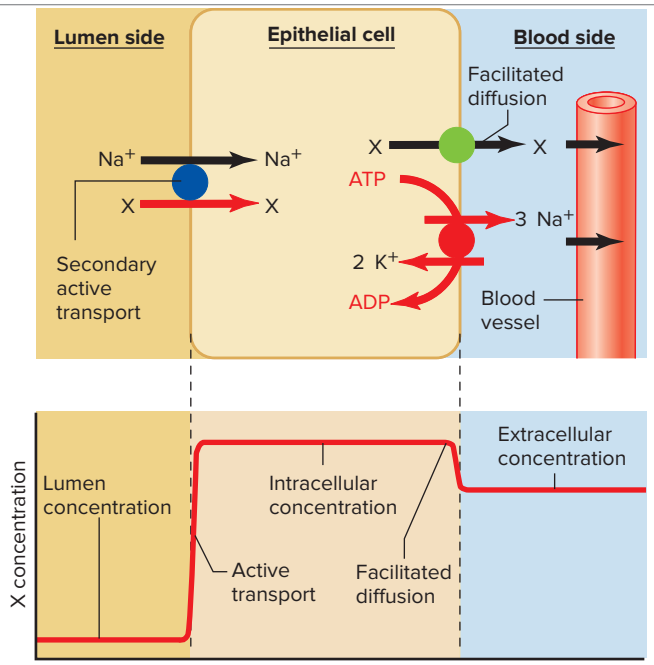


Figure 4.24 The transepithelial transport of most organic solutes (X) involves their movement into a cell through a secondary active transport driven by the downhill flow of Na^+. The organic substance then moves out of the cell at the blood side down a concentration gradient by means of facilitated diffusion. Shown below the cell is the concentration profile of the transported solute across the epithelium.

Figure 4.24 illustrates the active absorption of organic molecules across an epithelium, again by a transcellular pathway. In this case, the entry of an organic molecule X across the apical plasma membrane occurs via a secondary active transporter linked to the downhill movement of Na^+ into the cell. In the process, X moves from a lower concentration in the luminal fluid to a higher concentration in the cell. The substance exits across the basolateral membrane by facilitated diffusion, which moves the material from its higher concentration in the cell to a lower concentration in the extracellular fluid on the blood side. The concentration of the substance may be considerably higher on the blood side than in the lumen because the blood-side concentration can approach equilibrium with the high intracellular concentration created by the apical membrane entry step.

Although water is not actively transported across cell membranes, net movement of water across an epithelium can occur by osmosis as a result of the active transport of solutes, notably Na^+, across the epithelium. The active transport of Na^+, as previously described, results in a decrease in the Na^+ concentration on one side of an epithelial layer (the luminal side in our example) and an increase on the other. These changes in solute concentration are accompanied by changes in the water concentration on the two sides because a change in solute concentration, as we have seen, produces a change in water concentration. The water concentration difference will cause water to move by osmosis from the low-Na^+ side to the high-Na^+ side of the epithelium (**Figure 4.25**). Therefore, net movement of solute across an epithelium is accompanied by a flow of water in the same direction. As you will learn in Chapter 14, this is a major way in which epithelial cells of the kidney absorb water from the urine back into the blood. It is also the major way in which water is absorbed from the intestines into the blood (Chapter 15).

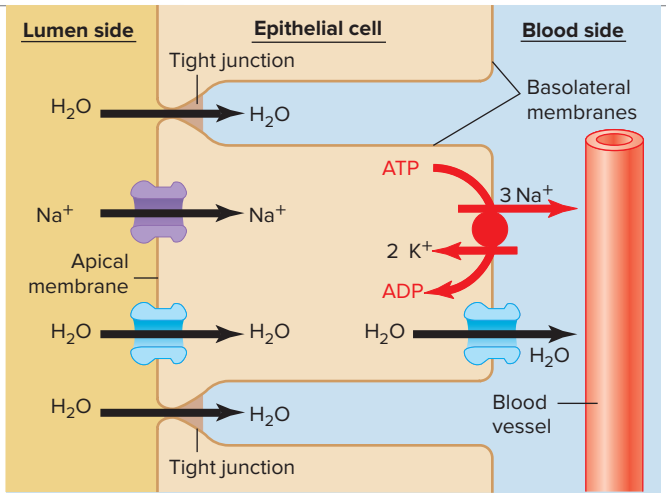


Figure 4.25 Net movements of water across an epithelium are dependent on net solute movements. The active transport of Na^+ across the cells and into the surrounding interstitial spaces produces an elevated osmolarity in this region and a decreased osmolarity in the lumen. This leads to the osmotic flow of water across the epithelium in the same direction as the net solute movement. The water diffuses through aquaporins in the membrane (transcellular pathway) and across the tight junctions between the epithelial cells (paracellular pathway).

PHYSIOLOGICAL INQUIRY

- A general principle of physiology is that structure is a determinant of—and has coevolved with—function. What features of epithelial cells shown in this figure lend support to that principle?

Answer can be found at end of chapter.

SUMMARY

Diffusion

I. Simple diffusion is the movement of molecules from one location to another by random thermal motion.
   a. The net flux between two compartments always proceeds from higher to lower concentrations.
   b. Diffusion equilibrium is reached when the concentrations of the diffusing substance in the two compartments become equal.

II. The magnitude of the net flux J across a membrane is directly proportional to the concentration difference across the membrane $C_o - C_i$, the surface area of the membrane A, and the membrane permeability coefficient P.

III. Nonpolar molecules diffuse through the hydrophobic portions of membranes much more rapidly than do polar or ionized molecules because nonpolar molecules can dissolve in the fatty acyl tails in the lipid bilayer.

IV. Ions diffuse across membranes by passing through ion channels formed by integral membrane proteins.
   a. The diffusion of ions across a membrane depends on both the concentration gradient and the membrane potential.
   b. The flux of ions across a membrane can be altered by opening or closing ion channels.

Mediated-Transport Systems

I. The mediated transport of molecules or ions across a membrane involves binding the transported solute to a transporter protein in the membrane. Changes in the conformation of the transporter move the binding site to the opposite side of the membrane, where the solute dissociates from the protein.
   a. The binding sites on transporters exhibit chemical specificity, affinity, and saturation.
   b. The magnitude of the flux through a mediated-transport system depends on the degree of transporter saturation, the number of transporters in the membrane, and the rate at which the conformational change in the transporter occurs.

II. Facilitated diffusion is a mediated-transport process that moves molecules from higher to lower concentrations across a membrane by means of a transporter until the two concentrations become equal. Metabolic energy is not required for this process.

III. Active transport is a mediated-transport process that moves molecules against an electrochemical gradient across a membrane by means of a transporter and an input of energy.
   a. Primary active transport uses the phosphorylation of the transporter by ATP to drive the transport process.
   b. Secondary active transport uses the binding of ions (often Na^+) to the transporter to drive the secondary-transport process.
   c. In secondary active transport, the downhill flow of an ion is linked to the uphill movement of a second solute either in the same direction as the ion (cotransport) or in the opposite direction of the ion (countertransport).

Osmosis

I. Water crosses membranes by (a) diffusing through the lipid bilayer, and (b) diffusing through protein channels in the membrane.

II. Osmosis is the diffusion of water across a membrane from a region of higher water concentration to a region of lower water concentration. The osmolarity—total solute concentration in a solution—determines the water concentration: The higher the osmolarity of a solution, the lower the water concentration.

III. Osmosis across a membrane that is permeable to water but impermeable to solute leads to an increase in the volume of the compartment on the side that initially had the higher osmolarity, and a decrease in the volume on the side that initially had the lower osmolarity.

IV. Application of sufficient pressure to a solution will prevent the osmotic flow of water into the solution from a compartment of pure water. This pressure is called the osmotic pressure. The greater the osmolarity of a solution, the greater its osmotic pressure. Net water movement occurs from a region of lower osmotic pressure to one of higher osmotic pressure.

V. The osmolarity of the extracellular fluid is about 300 mOsm. Because water comes to diffusion equilibrium across cell membranes, the intracellular fluid has an osmolarity equal to that of the extracellular fluid.
   a. Na^+ and Cl^- are the major effectively nonpenetrating solutes in the extracellular fluid; K^+ and various organic solutes are the major effectively nonpenetrating solutes in the intracellular fluid.
   b. Table 4.3 lists the terms used to describe the osmolarity and tonicity of solutions containing different compositions of penetrating and nonpenetrating solutes.

Endocytosis and Exocytosis

I. During endocytosis, regions of the plasma membrane invaginate and pinch off to form vesicles that enclose a small volume of extracellular material.
   a. The three classes of endocytosis are (i) fluid endocytosis, (ii) phagocytosis, and (iii) receptor-mediated endocytosis.
   b. Most endocytotic vesicles fuse with endosomes, which in turn transfer the vesicle contents to lysosomes for digestion by lysosomal enzymes.
   c. Potocytosis is a special type of receptor-mediated endocytosis in which vesicles called caveolae deliver their contents directly to the cytosol.

II. Exocytosis, which occurs when intracellular vesicles fuse with the plasma membrane, provides a means of adding components to the

plasma membrane and a route by which membrane-impermeable molecules, such as proteins the cell synthesizes, can be released into the extracellular fluid.

Epithelial Transport

I. Molecules can cross an epithelial layer of cells by two pathways: (a) through the extracellular spaces between the cells—the paracellular pathway; and (b) through the cell, across both the apical and basolateral membranes as well as the cell's cytoplasm—the transcellular pathway.
II. In epithelial cells, the permeability and transport characteristics of the apical and basolateral plasma membranes differ, resulting in the ability of cells to actively transport a substance between the fluid on one side of the cell and the fluid on the opposite side.
III. The active transport of Na^+ through an epithelium increases the osmolarity on one side of the cell and decreases it on the other, causing water to move by osmosis in the same direction as the transported Na^+.

REVIEW QUESTIONS

1. What determines the direction in which net diffusion of a nonpolar molecule will occur?
2. In what ways can the net solute flux between two compartments separated by a permeable membrane be increased?
3. Why are membranes more permeable to nonpolar molecules than to most polar and ionized molecules?
4. Ions diffuse across cell membranes by what pathway?
5. When considering the diffusion of ions across a membrane, what driving force, in addition to the ion concentration gradient, must be considered?
6. Describe the mechanism by which a transporter of a mediated-transport system moves a solute from one side of a membrane to the other.
7. What determines the magnitude of flux across a membrane in a mediated-transport system?
8. What characteristics distinguish simple diffusion from facilitated diffusion?
9. What characteristics distinguish facilitated diffusion from active transport?
10. Describe the direction in which sodium ions and a solute transported by secondary active transport move during cotransport and countertransport.
11. How can the concentration of water in a solution be decreased?
12. If two solutions with different osmolarities are separated by a water-permeable membrane, why will a change occur in the volumes of the two compartments if the membrane is impermeable to the solutes, but no change in volume will occur if the membrane is permeable to solutes?
13. Why do sodium and chloride ions in the extracellular fluid and potassium ions in the intracellular fluid behave as though they were nonpenetrating solutes?
14. What is the approximate osmolarity of the extracellular fluid? Of the intracellular fluid?
15. What change in cell volume will occur when a cell is placed in a hypotonic solution? In a hypertonic solution?
16. Under what conditions will a hyperosmotic solution be isotonic?
17. How do the mechanisms for actively transporting glucose and Na^+ across an epithelium differ?
18. By what mechanism does the active transport of Na^+ lead to the osmotic flow of water across an epithelium?

KEY TERMS

4.1 Diffusion

channel gating
diffusion equilibrium
electrochemical gradient
Fick's first law of diffusion
flux
ion channels
ligand-gated ion channels
mechanically gated ion channels
membrane potential
net flux
simple diffusion
voltage-gated ion channels

4.2 Mediated-Transport Systems

active transport
cotransport
countertransport
facilitated diffusion
mediated transport
Na^+/K^+-ATPase pump
primary active transport
secondary active transport
transporters

4.3 Osmosis

aquaporins
hyperosmotic
hypertonic
hypoosmotic
hypotonic
isoosmotic
isotonic
nonpenetrating solutes
osmol
osmolarity
osmosis
osmotic pressure
semipermeable membrane

4.4 Endocytosis and Exocytosis

caveolae
clathrin
clathrin-coated pit
endocytosis
exocytosis
fluid endocytosis
phagocytosis
phagosomes
pinocytosis
potocytosis
receptor-mediated endocytosis
receptors

4.5 Epithelial Transport

apical membrane
basolateral membrane
paracellular pathway
transcellular pathway

CHAPTER 4

Clinical Case Study: A Novice Marathoner Collapses After a Race

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A 22-year-old, 102-pound (46.4 kg) woman who had occasionally competed in short-distance races, decided to compete in her first marathon. She was in good health but was completely inexperienced in long-distance runs. During the hour before the race, she drank 1.2 liters of water (about two 20-ounce bottles) in anticipation of the water loss she expected to occur due to perspiration over the next few hours. The race took place on an unseasonably cool day in April. As she ran, she was careful to drink a cup of water (about 200 mL) at each water station, roughly each mile along the course. Being a newcomer to competing in marathons, she had already been running for 3 hours at the 20-mile mark and was beginning to feel extremely fatigued. Soon after, her leg muscles began cramping. Thinking she was losing too much fluid, she stopped for a moment at a water station and drank several cups of water, then continued on. After another

2 miles, she consumed a full 0.6 L bottle of water; a mile later, she began to feel confused and disoriented and developed a headache. At that point, she became panicked that she would not finish the race; even though she did not feel thirsty, she finished yet another bottle of water. Twenty minutes later, she collapsed, lost consciousness, and was taken by ambulance to a local hospital. She was diagnosed with **exercise-associated hyponatremia** (EAH), a condition in which the concentration of Na^+ in the blood decreases to dangerously low levels (in her case, to 115 mM; see Table 4.1 for comparison).

Reflect and Review #1

- How much total water did the woman consume before and during the race? How does that volume compare to an estimate of the total extracellular fluid volume in a 102-pound woman? (See Figure 1.3 for help.)

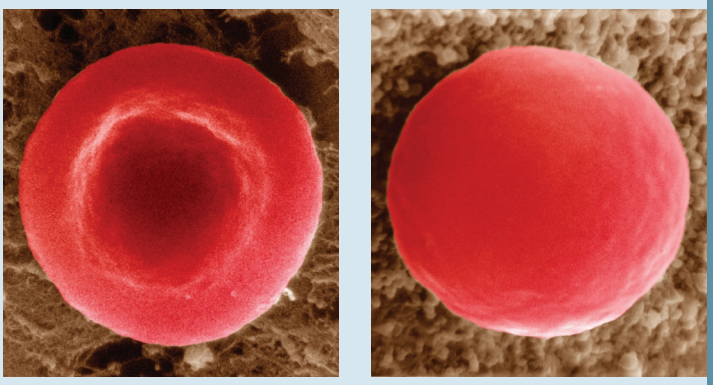
It was clear to her physicians what caused the EAH. When we exercise, perspiration helps cool us down. Sweat is a dilute solution of several ions, particularly Na^+ (the other major ones being Cl^- and K^+). The result of excessive sweating is that the total amount of water and Na^+ in the body becomes depleted. Our subject was exercising very hard and for a very long time but was not losing as much fluid as she had anticipated because of the cool weather. She was wise to be aware of the potential for fluid loss, but she was not aware that drinking pure water in such quantities could significantly dilute her body fluids.

Reflect and Review #2

- What effect might a change in extracellular osmolarity have on the movement of water across cell membranes (you can assume that plasma and interstitial fluid osmolarities are the same)?

As the concentration of Na^+ in her extracellular fluid decreased, the electrochemical gradient for Na^+ across her cells—including her muscle and brain cells—also decreased as a consequence. As you will learn in detail in Chapters 6 and 9, the electrochemical gradient for Na^+ is part of what regulates the function of skeletal muscle and brain cells. As a result of disrupting this gradient, our subject's muscles and neurons began to malfunction, accounting in part for the cramps and mental confusion.

In addition, however, recall from Figure 4.19 what happens to cells when the concentrations of nonpenetrating solutes across the cell membrane are changed. As our subject's extracellular fluid became more dilute than her intracellular fluid, water moved by osmosis into her cells. Many types of cells, including those of the brain, are seriously damaged when they swell due to water influx (Figure 4.26). It is even worse in the brain than elsewhere because there is no room for the brain to expand within the skull.



Normal cell | Swollen cell

Figure 4.26 A normal red blood cell (left) and one that has swelled due to osmotic movement of water into the cell. Compare the appearance of this cell with the ones in the chapter-opening image, which have lost water due to osmosis. ©David M. Phillips/Science Source

As brain cells swell, the fluid pressure in the brain increases, compressing blood vessels and restricting blood flow. When blood flow is reduced, oxygen and nutrient levels decrease and metabolic waste products build up, further contributing to brain cell malfunction. Thus, the combination of water influx, increased pressure, and changes in the electrochemical gradient for Na^+ all contributed to the mental disturbances and subsequent loss of consciousness in our subject.

What do you think would be an appropriate way to treat EAH? Remember, the person is not dehydrated. In fact, one of the best predictors of EAH in subjects like ours is weight *gain* during a marathon; such individuals actually weigh more at the end of a race than at the beginning because of all the water they drink! The treatment is an intravenous infusion of an isotonic solution of NaCl to bring the total levels of Na^+ in the body fluids back toward normal. At the same time, however, the extracellular fluid volume is reduced with a diuretic (a medication that increases the amount of water excreted in the urine). In addition, patients may also receive medications to prevent or stop seizures. As you will learn in Chapters 6 and 8, a seizure is uncontrolled, unregulated electrical activity of the neurons in the brain; one potential cause of a seizure is a large imbalance in extracellular ion concentrations in the brain. In our subject, gradual restoration of a normal Na^+ concentration was sufficient to save her life, but careful monitoring of her progress over the course of a 24-hour hospital stay was required.

Clinical term: exercise-associated hyponatremia

See Chapter 19 for complete, integrative case studies.

CHAPTER 4 TEST QUESTIONS *Recall and Comprehend*

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. Which properties are characteristic of ion channels?
   a. They are usually lipids.
   b. They exist on one side of the plasma membrane, usually the intracellular side.
   c. They can open and close depending on the presence of any of three types of "gates."
   d. They permit movement of ions against electrochemical gradients.
   e. They mediate facilitated diffusion.

2. Which of the following does *not* directly or indirectly require an energy source?
   a. primary active transport
   b. operation of the Na^+/K^+-ATPase pump
   c. the mechanism used by cells to produce a calcium ion gradient across the plasma membrane
   d. facilitated transport of glucose across a plasma membrane
   e. secondary active transport
3. If a small amount of urea were added to an isoosmotic saline solution containing cells, what would be the result?
   a. The cells would shrink and remain that way.
   b. The cells would first shrink but then be restored to normal volume after a brief period of time.
   c. The cells would swell and remain that way.
   d. The cells would first swell but then be restored to normal volume after a brief period of time.
   e. The urea would have no effect, even transiently.
4. Which is/are true of epithelial cells?
   a. They can only move uncharged molecules across their surfaces.
   b. They may have segregated functions on apical (luminal) and basolateral surfaces.
   c. They cannot form tight junctions.
   d. They depend upon the activity of Na^+/K^+-ATPase pumps for much of their transport functions.
   e. Both b and d are correct.
5. Which is *incorrect*?
   a. Diffusion of a solute through a membrane is considerably quicker than diffusion of the same solute through a water layer of equal thickness.
   b. A single ion, such as K^+, can diffuse through more than one type of channel.
   c. Lipid-soluble solutes diffuse more readily through the phospholipid bilayer of a plasma membrane than do water-soluble ones.
   d. The rate of facilitated diffusion of a solute is limited by the number of transporters in the membrane at any given time.
   e. A common example of cotransport is that of an ion and an organic molecule.
6. In considering diffusion of ions through an ion channel, which driving force/forces must be considered?
   a. the ion concentration gradient
   b. the electrical gradient
   c. osmosis
   d. facilitated diffusion
   e. both a and b
7. The difference between the fluxes of a solute moving in two opposite directions is the _____.
8. In _____, membrane-bound vesicles in the cytosol of a cell fuse with the plasma membrane and release their contents to the extracellular fluid.
9. The channels through which water moves across plasma membranes are called _____.
10. _____ is the name of the process by which glucose moves across a plasma membrane.

CHAPTER 4 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. In two cases (A and B), the concentrations of solute X in two 1 L compartments separated by a membrane through which X can diffuse are

Concentration of X (mM)

Case	Compartment 1	Compartment 2
A	3	5
B	32	30

   a. In what direction will the net flux of X take place in case A and in case B?
   b. When diffusion equilibrium is reached, what will the concentration of solute in each compartment be in case A and in case B?
   c. Will A reach diffusion equilibrium faster, slower, or at the same rate as B? *Hint:* See Figures 4.1–4.3.
2. If a transporter that mediates active transport of a substance has a lower affinity for the transported substance on the extracellular surface of the plasma membrane than on the intracellular surface, in what direction will there be a net transport of the substance across the membrane? *Hint:* See Figure 4.11 and assume that the rate of transporter conformational change is the same in both directions.
3. Why will inhibition of ATP synthesis by a cell lead eventually to a decrease and, ultimately, cessation in secondary active transport? *Hint:* See Figure 4.13, and refer to Figure 4.11 for a reminder about primary active transport.
4. Given the following solutions, which has the lowest water concentration? Which two have the same osmolarity? *Hint:* Refer to Figures 4.16 and 4.17 for help.

Solute Concentration (mM)

Solution	Glucose	Urea	NaCl	$CaCl_2$
A	20	30	150	10
B	10	100	20	50
C	100	200	10	20
D	30	10	60	100

5. Assume that a membrane separating two compartments is permeable to urea but not permeable to NaCl. If compartment 1 contains 200 mmol/L of NaCl and 100 mmol/L of urea, and compartment 2 contains 100 mmol/L of NaCl and 300 mmol/L of urea, which compartment will have increased in volume when osmotic equilibrium is reached? *Hint:* See Figure 4.19 and Table 4.3.
6. What will happen to cell volume if a cell is placed in each of the following solutions? *Hint:* See Figure 4.19 and Table 4.3.

Concentration of X, mM

Solution	NaCl (Nonpenetrating)	Urea (Penetrating)
A	150	100
B	100	150
C	200	100
D	100	50

7. Characterize each of the solutions in question 6 as isotonic, hypotonic, hypertonic, isoosmotic, hypoosmotic, or hyperosmotic. *Hint:* Refer to Table 4.3.
8. By what mechanism might an increase in intracellular Na^+ concentration lead to an increase in exocytosis? *Hint:* See Figure 4.15 for help.

CHAPTER 4 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. How does the information presented in Figures 4.8–4.10 and 4.17 illustrate the general principle that *homeostasis is essential for health and survival*?
2. Give two examples from this chapter that illustrate the general principle that *controlled exchange of materials occurs between compartments and across cellular membranes.*
3. Another general principle states that *physiological processes are dictated by the laws of chemistry and physics.* How does this relate to the movement of solutes through lipid bilayers and its dependence on electrochemical gradients? How is heat related to solute movement?

CHAPTER 4 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 4.2 As shown in the accompanying graph, there would be a net flux of glucose from compartment 1 to compartment 2, with diffusion equilibrium occurring at 12.5 mmol/L.

Figure 4.5 The primary structure of the protein is represented by the beads—the amino acid sequence shown in (a). The secondary structure includes all the helical regions in the lipid bilayer, shown in (a) and (b). The tertiary structure is the folded conformation shown in (b). The quaternary structure is the association of the five subunit polypeptides into one protein, shown in (c).

Figure 4.9 Maximal flux depends on the number of transporter molecules in the membrane and their inherent rate of conformational change when binding solute. If we assume that the rate of conformational change stays constant, then the greater the number of transporters, the greater the maximal flux that can occur.

Figure 4.13 ATP is not hydrolyzed when a solute moves across a membrane by secondary active transport. However, ATP *is* hydrolyzed by an ion pump (typically the Na^+/K^+-ATPase primary active transporter) to establish the ion concentration gradient that is used during secondary active transport. Therefore, secondary active transport *indirectly* requires ATP.

Figure 4.15 Transport of ions and organic compounds between fluid compartments is a critical feature of homeostasis. Among many examples, movement of glucose into cells is essential for energy production. Transport of H^+ regulates the pH of body fluids which, in turn, regulates all enzymatic processes in the body. Ca^{2+} transport controls such processes as muscle contraction and the release of stored secretory products from certain types of cells. The transcellular movement of numerous ions contributes to the membrane potential of cells. Finally, the transport of amino acids into cells is necessary for the synthesis of proteins, without which cells cannot survive and therefore homeostasis would not be possible. There are many diseases you will learn about in later chapters that result from functional problems with transporters. Also, there are drugs used to treat disease that alter the function of these transporters.

Figure 4.19 Because it is a nonpenetrating solute, infusion of isotonic NaCl restores blood volume without causing a redistribution of water between body fluid compartments due to osmosis. An isoosmotic solution of a penetrating solute, however, would only partially restore blood volume because some water would enter the intracellular fluid by osmosis as the solute enters cells. This could also result in damage to cells as their volume expands beyond normal.

Figure 4.23 Active transport of Na^+ across the basolateral (blood side) membrane would decrease, resulting in an increased intracellular concentration of Na^+. This would reduce the rate of Na^+ diffusion into the cell through the Na^+ channel on the lumen side because the diffusion gradient would be smaller.

Figure 4.25 The structure of an epithelium is characterized by tight junctions along the apical membranes of the epithelial cells. These junctions provide epithelial cells with one of their major functions, namely acting as a barrier to the movement of most solutes across the epithelium. In addition, the structure of individual epithelial cells also determines the function of the entire epithelium. Note in the figure (and refer back to Figures 4.23 and 4.24) that different transport proteins or ion channels are localized to either the apical or basolateral membranes of the epithelial cells. Because of this cellular structure, the epithelium can selectively transport different solutes in one or the other direction. This allows the precise control of the intracellular concentrations of solutes that are critical for normal function.

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