Physiology

Lec.2

Movement of Molecules across Cell Membranes

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 تصطدم 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. Thus, if we start with a solution in which a solute is more concentrated in one region than another***, 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***. This movement of molecules from one location to another solely as a result of their random thermal motion is known as **simple diffusion.**

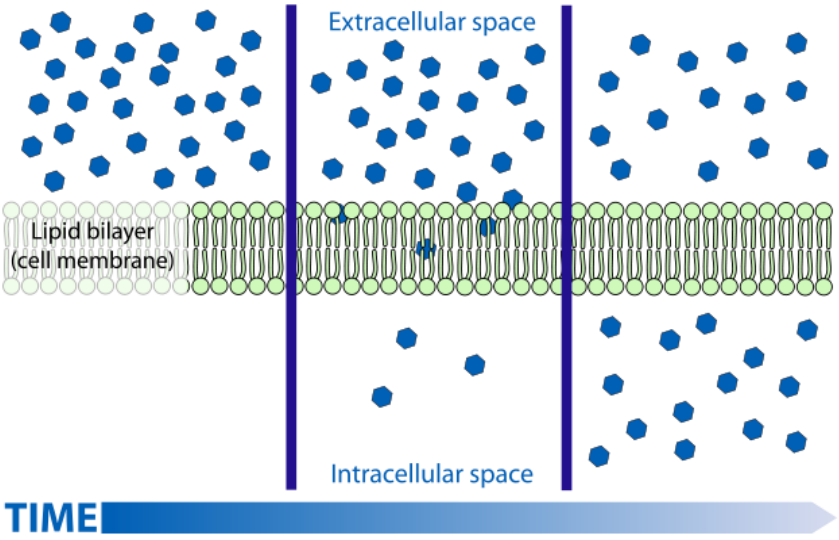
Diffusion through Membranes

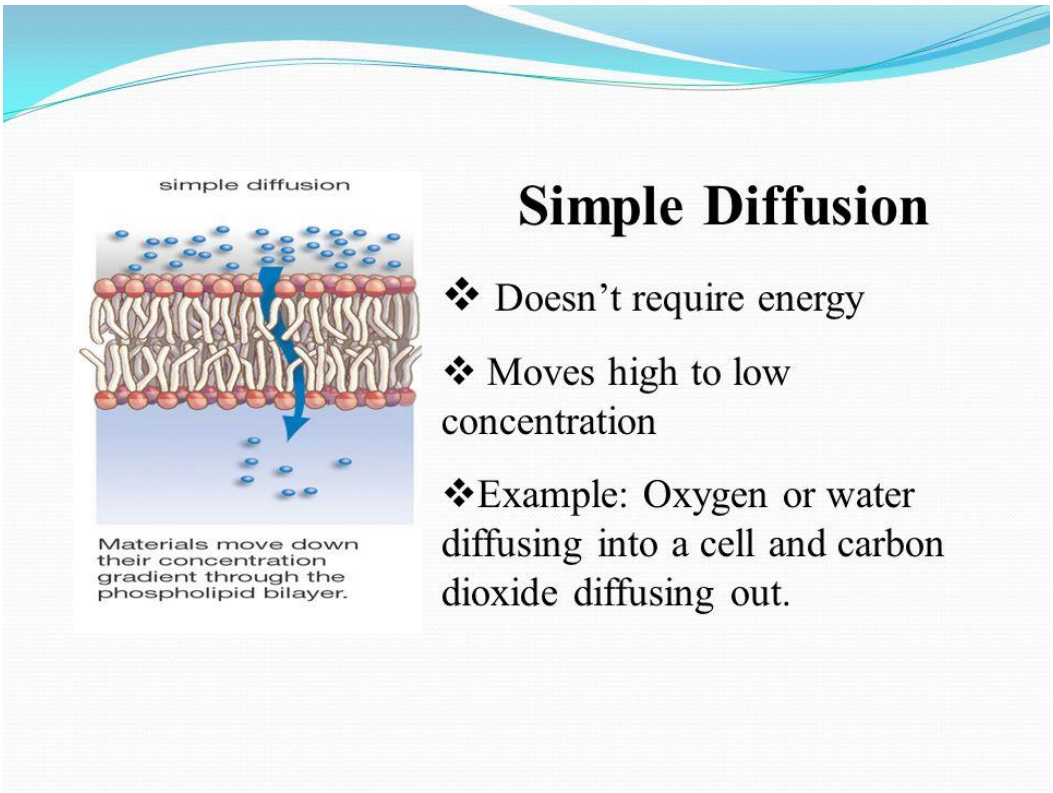
Diffusion through the Lipid Bilayer

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 constants. 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 makeup the intermediate stages of the various metabolic pathways 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 channels.





Diffusion of Ions through Protein Channels

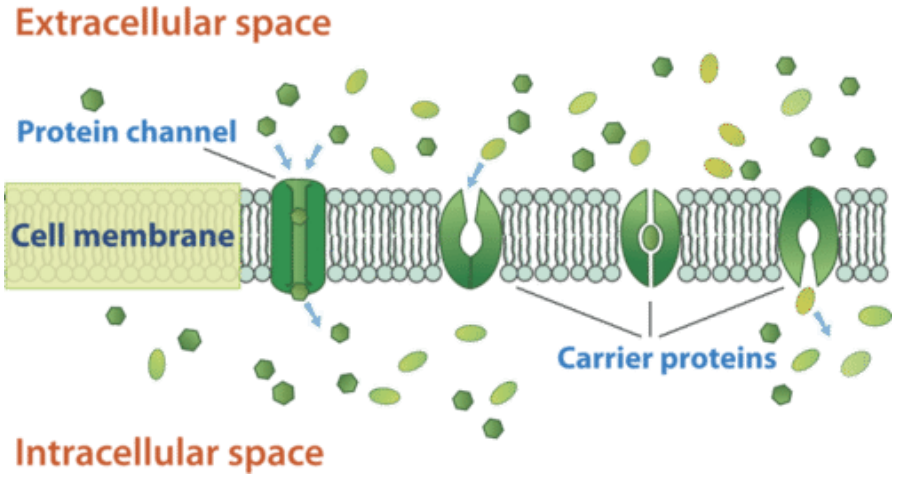
Ions such as Na,K,Cl, and Ca diffuse across plasma membranes at much faster rates than would be predicted from their very **low solubility in membrane lipids**. Also, different cells have quite different permeability to these ions, whereas nonpolar substances have similar permeability in nearly all cells.

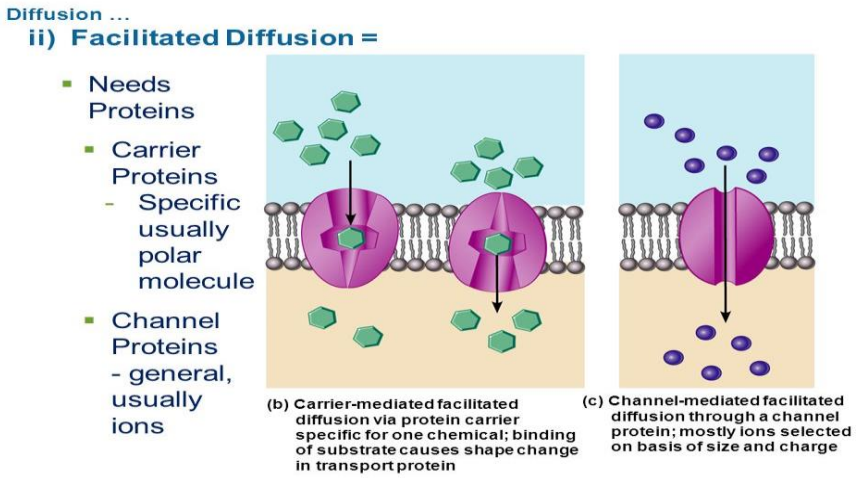
Moreover, artificial lipid bilayers containing no protein are practically impermeable to these ions; this indicates that the protein component of the membrane is responsible for these permeability differences.

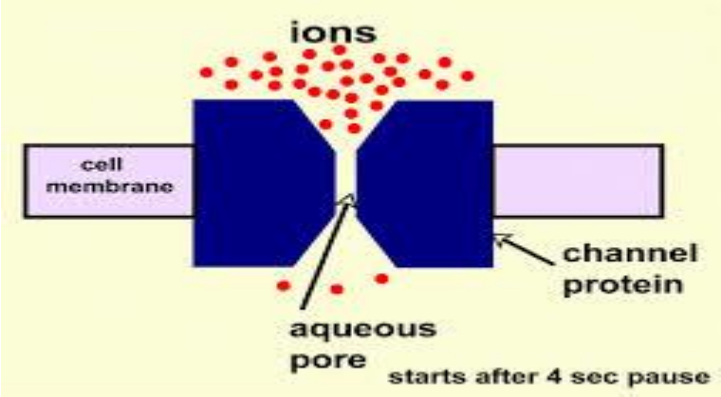
Integral membrane proteins can span تمتدthe lipid bilayer. Some of these proteins form **ion channels** that allow ions to diffuse across the membrane. A single protein may have a conformation resembling that of a doughnutتبرع, with the hole in the middle providing the channel for ion movement. More often, several proteins aggregate,each forming a subunit of the walls of a channel.

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 protein subunits ions**, and **on 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 Na (Na channels). Still others allow diffusion of both Na and K but no other ions.







Role of Electrical Forces on Ion Movement

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 all cells*. This is known as a **membrane potential**

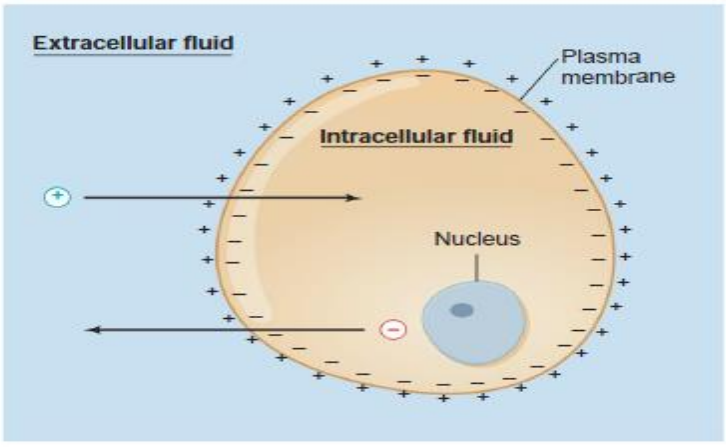


Figure 4.6 The separation of electrical charge across a plasma membrane (the membrane potential) provides the electrical force that drives positive ions (1) into a cell and negative ions (2) out.

The membrane potential provides an *electrical force that influences the movement of ions across the membrane*. A simple principle of physics is that like charges repel each other, whereas opposite charges attract. 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. **Even if no difference in ion concentration existed across the membrane, there would still be a net movement of positive ions into and negative ions out of the cell because of the membrane potential**. Consequently, the direction and magnitude of ion fluxes تدفق across membranes depend on both the **concentration difference***and* the **electrical difference** (the membrane potential).

These two driving forces are collectively known as the **electrochemical gradient** across a membrane.

The two forces that make up the electrochemical gradient may in some cases oppose each other. For example, the membrane potential may be driving potassium ions in one direction across the membrane while the concentration difference for K is driving these ions in the opposite direction.

The net movement of K in this case would be determined by the relative magnitudes حجمof the two opposing forces—that is, by the electrochemical gradient across the membrane.

Regulation of Diffusion through Ion Channels

Ion channels can exist in an **open or closed state**, and changes in a membrane's permeability to ions can occur rapidly as these channels open or close.

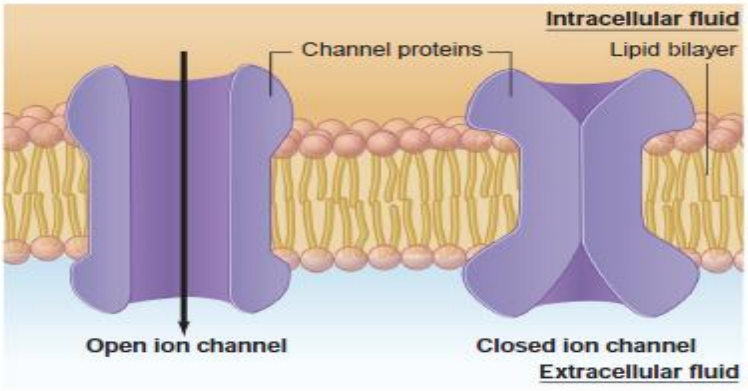


Figure 4.7 As a result of conformational changes in the proteins forming an ion channel, the channel may be open, allowing ions to diffuse across the membrane, or may be closed. The conformational change is grossly exaggerated for illustrative purposes. The actual conformational change is more likely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

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, suggest 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 channelopens) مهمة جدا.

First, the binding of specific molecules to channel proteins may directly or indirectly produce either an allosteric or covalent تساهميchange in the shape of the channel protein. Such channels are termed **ligand-gated channels,**and the ligands that influence them are often chemical messengers.

Second, changes in the membrane potential can cause movement of certain charged regions on a channel protein, altering its shape—these are **voltage-gated channels.**

Third, physically deforming(stretching) the membrane may affect the conformation of some channel proteins—these are **mechanically gated channels.**

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. Moreover, the same membrane may have several types of voltage-gated K channels, each responding to a different range of membrane voltage, or several types of ligand-gated K channels, each responding to a different chemical messenger.

Mediated-Transport Systems

A general principle of physiology is that controlled exchange of materials occurs between compartment sand across cellular membranes. Although diffusion through gated channels accounts for some of the controlled trans-membrane 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 non-diffusional movements of ions are mediated by integral membrane proteins known as **transporters** (or carriers).

The movement of substances through a membrane by 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, a site exposed to the solute on one surface of the membrane.

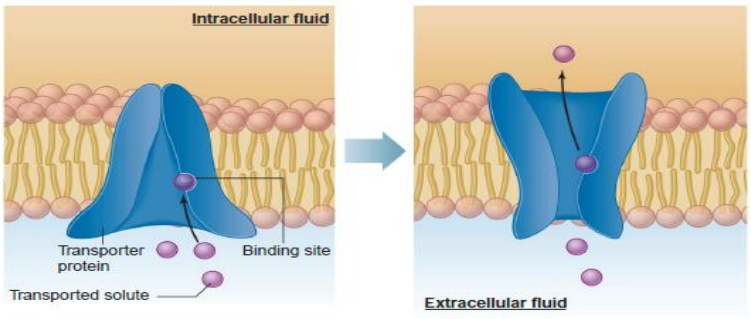


Figure 4.8 AP R Model of mediated transport. A change in the conformation of the transporter exposes the transporter binding site first to one surface of the membrane then to the other, thereby transferring the bound solute from one side of the membrane to the other. This model shows net mediated transport 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.

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. The diagram of the transporter is only a model, because the specific conformational changes of any transport protein are still uncertain.

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 do transporters*.(why???) 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.

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 both 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.

Three factors determine the magnitude of solute flux through a mediated-transport system.

- The first of these is the extent, to which the transporter binding sites are saturated, which depends on both the solute concentration and the affinity of the transporters for the solute.
- Second, the number of transporters in the membrane determines the flux at any level of saturation.
- The third factor is 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 three 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.

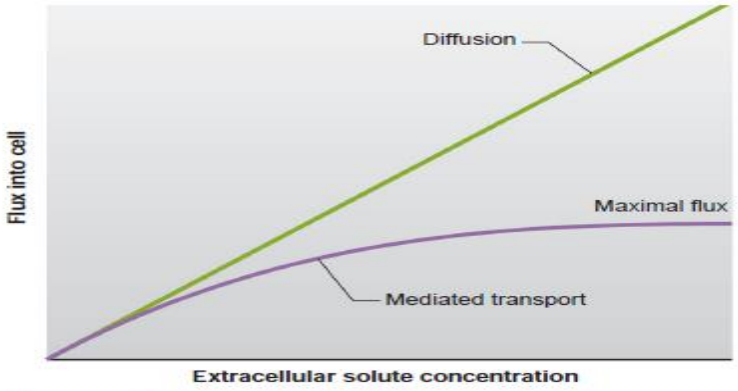


Figure 4.9 The flux of molecules diffusing into a cell across the lipid bilayer of a plasma membrane (green line) increases continuously in proportion to the extracellular concentration, whereas the flux of molecules through a mediated-transport system (purple line) reaches a maximal value.

The flux due to diffusion increases indirect 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.

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 processes is that **facilitated diffusion uses a transporter to move solute**.

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 extra cellular oncentration. This does not occur in most cells,however, because glucose is metabolized in the cytosol to glucose6-phosphate almost as quickly as it enters. Consequently, the intracellular glucose concentration remains lower than the extracellular concentration,and there is a continuous net flux of glucose into cells.

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.

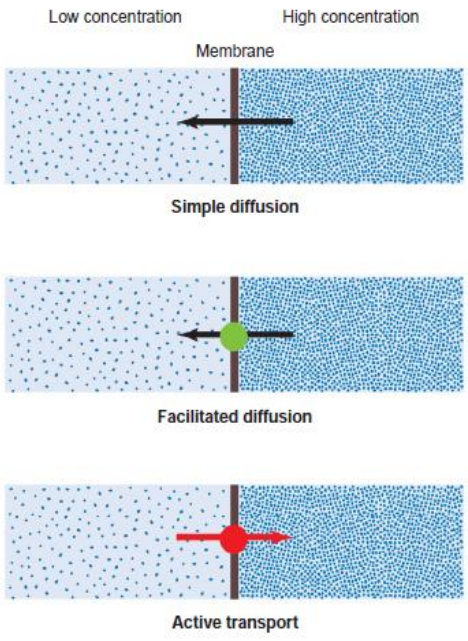


Figure 4.10 Direction of net solute flux crossing a membrane by simple diffusion (high to low concentration), facilitated diffusion (high to low concentration), and active transport (low to high concentration). The colored circles represent transporter molecules.

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 from lower to higher concentrations and the maintenance of a higher steady-state concentration on one side of a membrane can be achieved only by the 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.**

(2) The use of an electro chemical gradient across a membrane to drive the process in **secondary active transport.**

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 ATPand, in the process, phosphorylates itself. Phosphorylation ofthe 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 sodium ions fromintracellular to extracellular fluid, and potassium ions in theopposite direction. In both cases, the movements of the ions areagainst their respective concentration gradients.

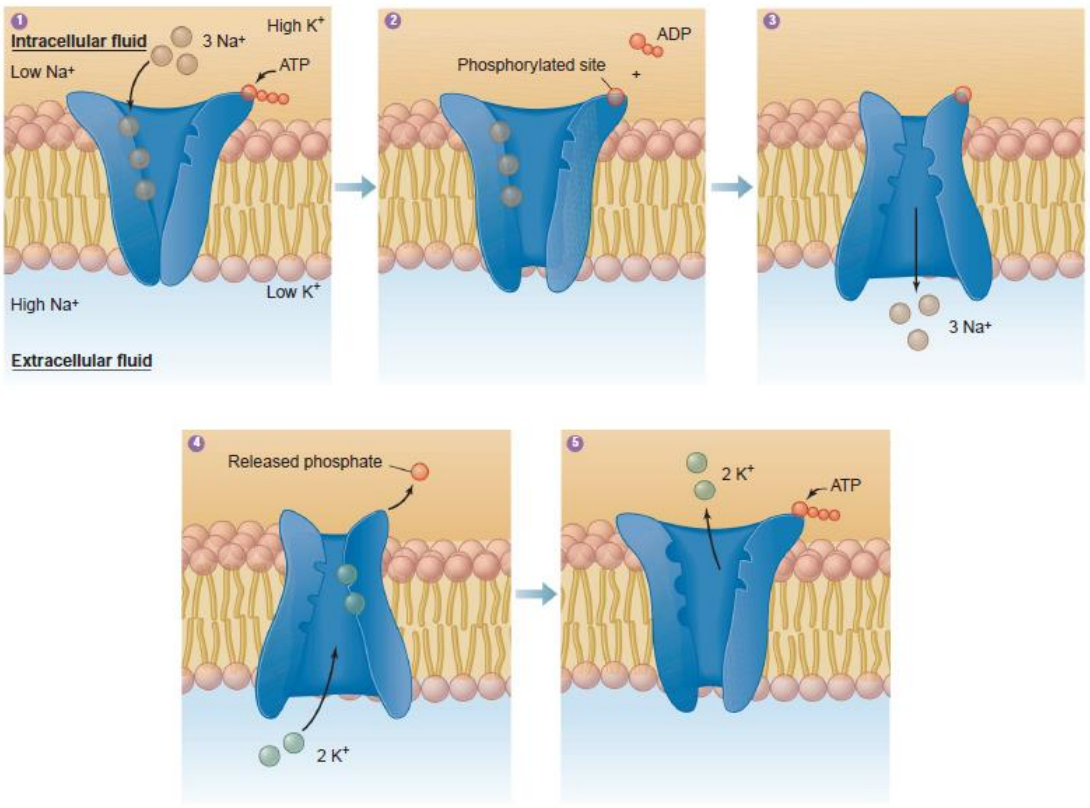


Figure 4.11 AP|R Active transport of Na^1 and K^1 mediated by the Na^1/K^1-ATPase pump. See text for the numbered sequence of events occurring during transport.

(1)Initially, the transporter, with an associated molecule of ATP,binds three sodium ions at high-affinity sites on the intracellularsurface 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 transporterand releasing a molecule of ADP.

(3) Phosphorylation results in a conformational change of the transporter, exposing the bound sodium ions to the extracellular fluid and, at the same time, reducing the affinity of the binding sites for Na. The sodium ions are released from their binding sites.

(4) The new conformation of the transporter results in an increased affinity of the two binding sites for K, allowing two molecules of K to bind to the transporter on the extracellular surface.

(5) Binding of K results in de-phosphorylation of the transporter. This returns the transporter to its original conformation, resulting in reduced affinity of the K 1 binding sites and increased affinity of the Na binding sites. K is therefore released into the intracellular fluid, allowing new molecules of 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

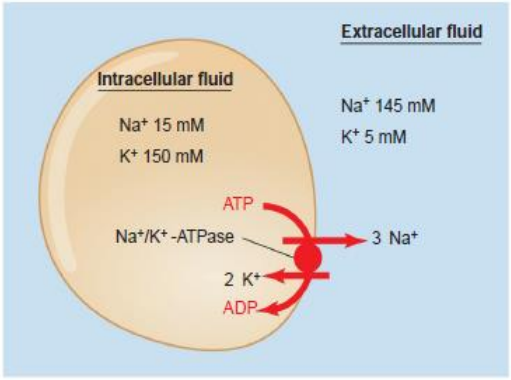


Figure 4.12 AP|R The primary active transport of sodium and potassium ions in opposite directions by the Na^1/K^1-ATPase in plasma membranes is responsible for the low Na^1 and high K^1 intracellular concentrations. For each ATP hydrolyzed, three sodium ions move out of a cell and two potassium ions move in.

For each molecule of ATP hydrolyzed these transporter moves three sodium ions out of a cell and two potassium ions into a cell. This result in a net transfer of positive charge to the outside of the cell; therefore, this stransport process is not electrically neutral

TheNa /K -ATPase primary active transporter is found in every cell and helps establish and maintain the membrane potential of the cell. Addition to the Na /K -ATPase transporter, the major primary active-transport proteins found in most cells are

(1) Ca -ATPase;

(2) H -ATPase;

(3) H /K -ATPase.

Secondary Active Transport

In secondary active transport, the movement of an ion down its **electrochemical gradient** is coupled to the transport of another molecule, such as a 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 the co-transported molecule**.

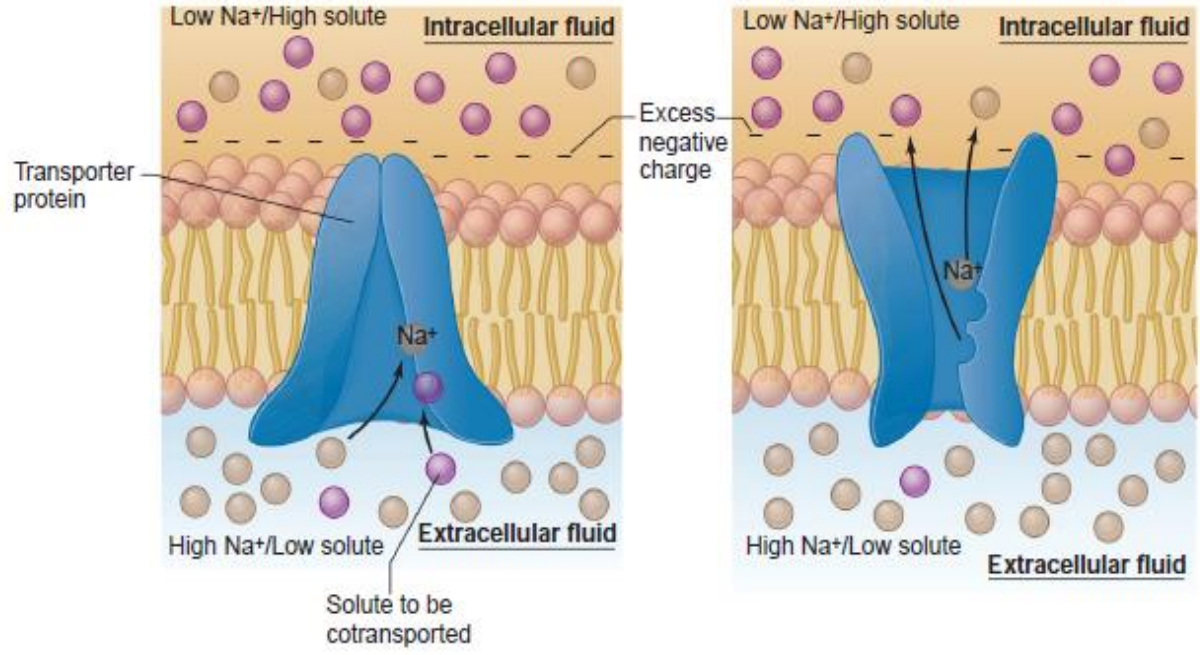


Figure 4.13 AP|R Secondary active-transport model. In this example, the binding of a sodium ion to the transporter produces an allosteric increase in the affinity of the solute binding site at the extracellular surface of the membrane. Binding of Na^1 and solute causes a conformational change in the transporter that exposes the binding sites to the intracellular fluid. Na^1 diffuses down its electrochemical gradient into the cell, which returns the solute binding site to a low-affinity state.

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 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, Na moves into the intracellularfluid 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. The solute can be thought of as entering the

cellby “piggyback” with the sodium ion. Once the transporterreleases both molecules, the protein assumes its originalconformation.

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 ions 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 Na concentration gradient across the membrane.This, in turn, would lead to a failure of the

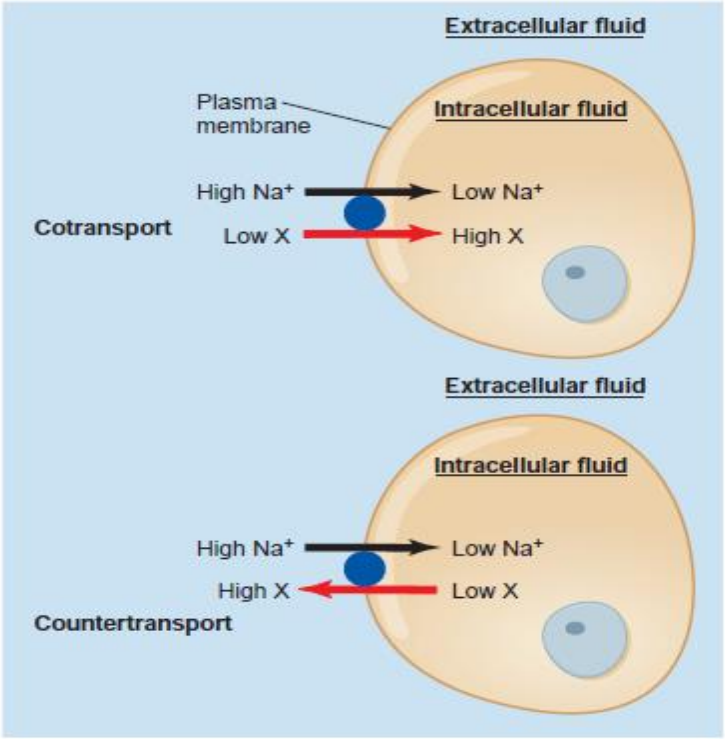


Figure 4.14 AP|R Cotransport and countertransport during secondary active transport driven by Na^1. Sodium ions always move *down* their concentration gradient into a cell, and the transported solute always moves *up* its gradient. Both Na^1 and the transported solute X move in the same direction during cotransport, but in opposite directions during countertransport.

secondary active transport driven by Na1. Sodium ions always move*down* their concentration gradient into a cell, and the transportedsolute always moves *up* its gradient. Both Na1 and the transportedsolute X move in the same direction during co-transport, but inopposite directions during countertransport.

TABLE 4.1 Composition of Extracellular and Intracellular Fluids

	Extracellular Concentration (mM)	Intracellular Concentration (mM)*
Na^{1}	145	15
K^{1}	5	150
Ca^{21}	1	0.0001
Mg^{21}	1.5	12
Cl^{2}	100	7
HCO_3^{2}	24	10
P_i	2	40
Amino acids	2	8
Glucose	5.6	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^{21}, 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).

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 movementof Na is always *downhill*, whereas the net movement ofthe actively transported solute on the same transport protein is*uphill*, moving from lower to higher concentration. The movementof the actively transported solute can be either into thecell (in the same direction as Na), in which case it is known as**co-transport ,**or out of the cell (opposite the direction of Na movement), which is called **countertransport** (**Figure 4.14**).

The terms *symport* and *antiport* are also used to refer to theprocesses of co-transport and countertransport, respectively. In summary, the distribution of substances between the intracellular and extracellular fluid is often unequal(**Table 4.1**) 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 themajor characteristics of the different pathways by which substancesmove through cell membranes,

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^1)
Typical molecules using pathway	Nonpolar: O_2, CO_2, fatty acids	Ions: Na^1, K^1, Ca^{21}	Polar: glucose	Ions: Na^1, K^1, Ca^{21}, H^1	Polar: amino acids, glucose, some ions

illustrates the variety of commonly encountered channelsand transporters associated with the movement of substancesacross a typical plasma membrane.

Osmosis

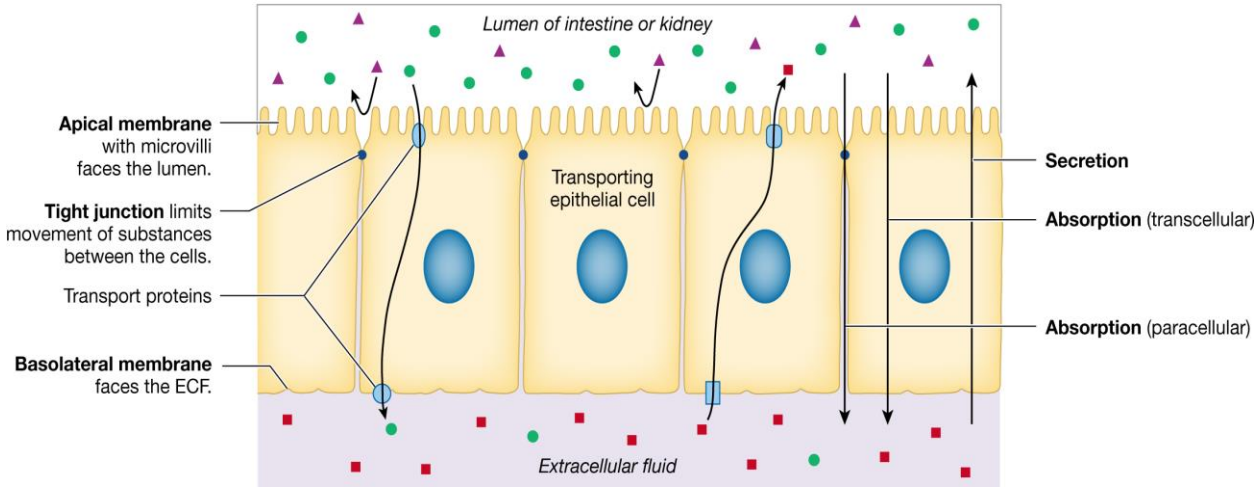
Water is a polar molecule and yet it diffuses across the plasmamembranes of most cells very rapidly. This process is mediated bya family of membrane proteins known as **aqua-porins** that form channels through which water can diffuse. The **type and number of these water channels** differ in different membranes. Consequently, some cells are more permeable to water than others.

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.

Epithelial Transport

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 تجويفor fluid-filled chamber, and the plasma membrane on this side is referred to as the **apical membrane** (also known as the luminal or mucosal membrane) of the epithelium. The plasma membrane on the opposite surface, which is usually adjacent to a network of blood vessels, is referred to as the **basolateral membrane**(also known as the serosal membrane).

The apical membrane and the basolateral membrane are the two poles of the cell. Polarized epithelia have different transport proteins on apical and basolateral membranes. This allows selective directional transport across the epithelium. Transport from lumen to ECF is called **absorption.** Transport from ECF to lumen is called **secretion.**



The two pathways by which a substance can cross a layer of epithelial cells are

(1) The **paracellularpathway,**in which diffusion occurs *between* the adjacent cells of the epithelium

(2) The **transcellularpathway,**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.

Diffusion through the paracellular pathwayis limited by the presence of tight junctions between adjacent cells, because these junctions form a seal around the

apical endof the epithelial cells. Although small ions and water can diffuse to some degree through tight junctions, the amountof 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 moleculesthrough the plasma membranes of epithelial cells occurs via the pathways (diffusion and mediated transport)already described for movement across membranes. However,the transport and permeability characteristics of the apicaland basolateral membranes are not the same. These two membranes often contain different ion channels and differenttransporters for mediated transport. As a result of these differences,substances can undergo a net movement from a lowconcentration on one side of an epithelium to a higher concentrationon the other side. Examples include the absorptionof material from the gastrointestinal tract into the blood, themovement of substances between the kidney tubules and theblood during urine formation, and the secretion of salts andwater by glands such as sweat glands.

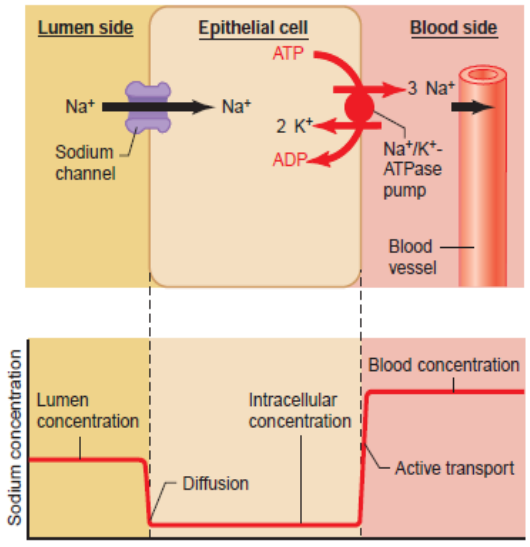


Figure 4.22 Active transport of Na^1 across an epithelial cell. The transepithelial transport of Na^1 always involves primary active transport out of the cell across one of the plasma membranes, typically via an Na^1/K^1-ATPase pump as shown here. The movement of Na^1 into the cell across the plasma membrane on the opposite side is always downhill. Sometimes, as in this example, it is by diffusion through Na^1 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.

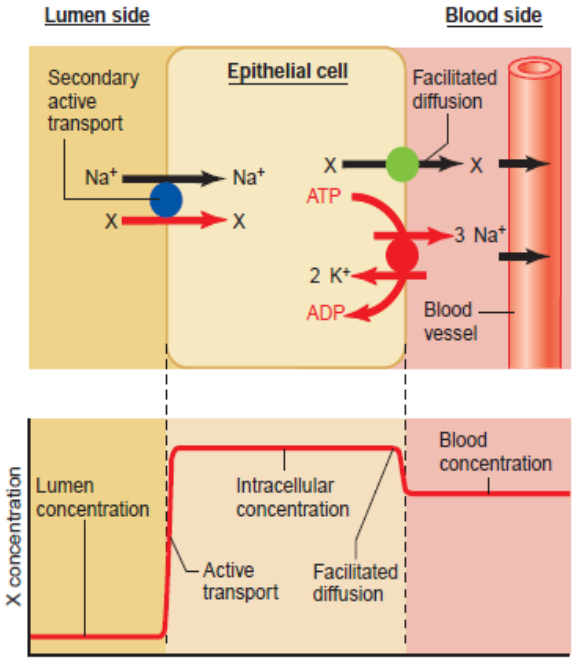


Figure 4.23 The transepithelial transport of most organic solutes (X) involves their movement into a cell through a secondary active transport driven by the downhill flow of Na^1. The organic substance then moves out of the cell at the blood side down a concentration gradient by means of facilitated diffusion. Shown below the cell is the concentration profile of the transported solute across the epithelium.

Na 1 is actively transportedacross most epithelia from lumen to blood side inabsorptive processes, and from blood side to lumen duringsecretion. In our example, the movement of Na fromthe lumen into the epithelial cell occurs by diffusion through Na channels in the apical membrane (see Figure 4.22).

Na diffusesinto the cell because the intracellular concentration ofNa is kept low by the active transport of Na back out ofthe cell across the basolateral membrane on the opposite side,where all of the Na /K -ATPase pumps are located. In otherwords, Na moves downhill into the cell and then uphill outof it. The net result is that Na can be moved from lower tohigher concentration across the epithelium.

Figure 4.23 illustrates the active absorption of organicmolecules across an epithelium. In this case, the entry of anorganic molecule X across the luminal plasma membraneoccurs via a secondary active transporter linked to the

downhillmovement of Na into the cell. In the process, X movesfrom a lower concentration in the luminal fluid to a higherconcentration in the cell. The substance exits across the basolateralmembrane by facilitated diffusion, which moves thematerial from its higher concentration in the cell to a lowerconcentration in the extracellular fluid on the blood side. Theconcentration of the substance may be considerably higher onthe blood side than in the lumen because the blood-side concentrationcan approach equilibrium with the high intracellularconcentration created by the apical membrane entry step.

Although water is not actively transported across cellmembranes, net movement of water across an epithelium canoccur by osmosis as a result of the active transport of solutes,notably Na, across the epithelium. The active transport ofNa, as previously described, results in a decrease in the Na concentration on one side of an epithelial layer (the luminalside in our example) and an increase on the other. Thesechanges in solute concentration are accompanied by changesin the water concentration on the two sides because a changein solute concentration, as we have seen, produces a change inwater concentration. The water concentration difference willcause water to move by osmosis from the low-Na side to theHigh-Na side of the epithelium.

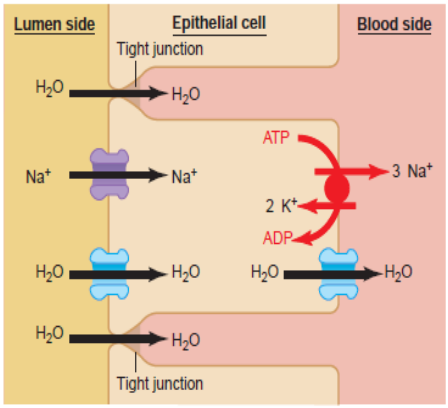


Figure 4.24 Net movements of water across an epithelium are dependent on net solute movements. The active transport of Na^1 across the cells and into the surrounding interstitial spaces produces an elevated osmolarity in this region and a decreased osmolarity in the lumen. This leads to the osmotic flow of water across the epithelium in the same direction as the net solute movement. The water diffuses through water channels in the membrane and across the tight junctions between the epithelial cells.

Therefore, netmovement of solute across an epithelium is accompanied by aflow of water in the same direction. If the epithelial cells arehighly permeable to water, large net movements of water canoccur with very small differences in osmolarity.