Contents

Section 8: Endocrine Physiology, 676

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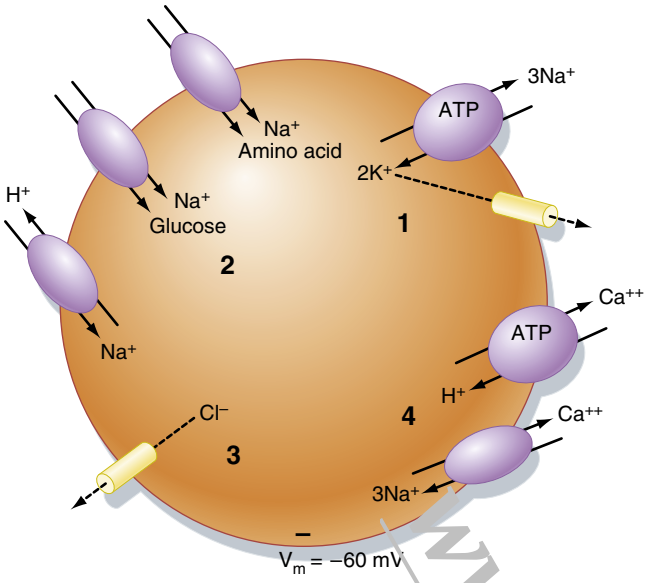


• **Fig. 2.3** Cell model depicting how cellular gradients and the membrane potential (V_m) are established. (1) The Na^+,K^+-ATPase decreases the intracellular $[Na^+]$ and increases the intracellular $[K^+]$. Some K^+ exits the cell via K^+-selective channels and generates the V_m (cell's interior is electrically negative). (2) The energy in the Na^+ electrochemical gradient drives the transport of other ions and molecules through the use of various solute carriers. (3) The V_m drives Cl^- out of the cell via Cl^--selective channels. (4) The Ca^{++}-ATPase and the $3Na^+$-Ca^{++} antiporters maintain the low intracellular $[Ca^{++}]$. *ATP*, Adenosine triphosphate.

The Na^+,K^+-ATPase–generated ion and electrical gradients are used to drive the transport of other ions and molecules into or out of the cell (Fig. 2.3). For example, as described in Chapter 1, a number of solute carriers couple the transport of Na^+ to that of other ions or molecules. The Na^+-glucose and Na^+–amino acid symporters use the energy in the Na^+ electrochemical gradient, directed to bring Na^+ into the cell, to drive the secondary active cellular uptake of glucose and amino acids. Similarly, the inwardly directed Na^+ gradient drives the secondary active extrusion of H^+ from the cell and thus contributes to the maintenance of intracellular pH. The $3Na^+$-Ca^{++} antiporter, along with the plasma membrane Ca^{++}-ATPase, extrudes Ca^{++} from the cell and thus contributes to the maintenance of a low intracellular $[Ca^{++}]$.[f] In addition, the membrane voltage drives Cl^- out of the cell through Cl^--selective channels, thus lowering the intracellular concentration below that of the ECF.

Membrane Potential

As described previously, the Na^+,K^+-ATPase and K^+-selective channels in the plasma membrane are important determinants of the membrane potential (V_m) of the cell. For all cells within the body, the resting V_m is oriented with the interior of the cell electrically negative in relation to the ECF. However, the magnitude of the V_m can vary widely.

To understand what determines the magnitude of the V_m, it is important to recognize that any transporter that transfers charge across the membrane has the potential to influence the V_m. Such transporters are said to be **electrogenic**. As might be expected, the contribution of various electrogenic transporters to the V_m is highly variable from cell to cell. For example, the Na^+,K^+-ATPase transports three Na^+ and two K^+ ions and thus transfers one net positive charge across the membrane. However, the direct contribution of the Na^+,K^+-ATPase to the V_m of most cells is only a few millivolts at the most. Similarly, the contribution of other electrogenic transporters, such as the $3Na^+$-Ca^{++} antiporter and the Na^+-glucose symporter, is minimal. The major determinants of the V_m are ion channels. The type (e.g., selectivity), number, and activity (e.g., gating) of these channels determine the magnitude of the V_m. As described in Chapter 5, rapid changes in ion channel activity underly the action potential in neurons and other excitable cells, such as those of skeletal and cardiac muscle (see Chapters 12 and 13).

As ions move across the membrane through a channel, they generate a current. As described in Chapter 1, this current can be measured, even at the level of a single channel. By convention, the current generated by the movement of cations into the cell, or the movement of anions out of the cell, is defined as negative current. Conversely, the movement of cations out of the cell, or the movement of anions into the cell, is defined as positive current. Also by convention, the magnitude of the V_m is expressed in relation to the outside of the cell; thus for a cell with a V_m of –80 mV, the interior of the cell is electrically negative in relation to the outside of the cell.

The current carried by ions moving through a channel depends on the driving force for that ion and on the conductance of the channel. As described in Chapter 1, the driving force is determined by the energy in the concentration gradient for the ion across the membrane (E_i), as calculated by the Nernst equation (Eq. 1.5a) and the V_m:

(Equation 2.3)

$$\text{Driving force} = V_m - E_i$$

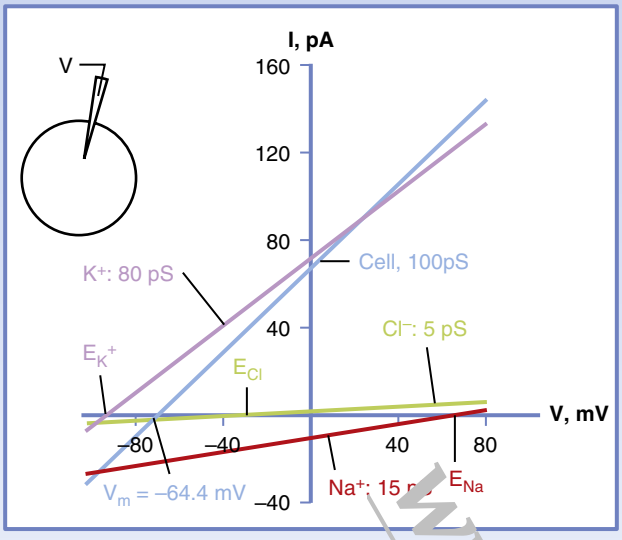
Thus as defined by **Ohm's law**, the ion current through the channel (I_i) is determined as follows:

(Equation 2.4)

$$I_i = (V_m - E_i) \times g_i$$

where g_i is the conductance of the channel. For a cell, the conductance of the membrane to a particular ion (G_i) is determined by the number of ion channels in the membrane and by the amount of time each channel is in the open state.

[f] In muscle cells, in which contraction is regulated by the intracellular $[Ca^{++}]$, the maintenance of a low intracellular $[Ca^{++}]$ during the relaxed state involves not only the activity of the plasma membrane $3Na^+$-Ca^{++} antiporter and the Ca^{++}-ATPase but also a Ca^{++}-ATPase molecule located in the smooth endoplasmic reticulum (see Chapters 12 to 14).



	Intracellular [ ] mEq/L	Extracellular [ ] mEq/L	Nernst potential, mV
Na^+	12	145	[illegible]
K^+	120	4	[illegible]
Cl^-	30	105	–33.5

• **Fig. 2.4** Current-voltage relationship of a hypothetical cell containing Na^+-, K^+-, and Cl^--selective channels. Membrane currents are plotted over a range of membrane voltages (i.e., current-voltage relationships). Each ion current is calculated with the use of Ohm's law, the Nernst equilibrium potential for the ion (E_{Cl}, E_K, and E_{Na}), and the membrane conductance for the ion. The current-voltage relationship for the whole cell is also shown. Total cell current (I_{cell}) was calculated with the chord conductance equation (see Eq. 2.7). Because 80% of cell conductance is due to K^+, the resting membrane voltage (V_m) of –64.4 mV is near to that of the Nernst equilibrium potential for K^+.

As illustrated in Fig. 2.4, the V_m is the voltage at which there is no net ion flow into or out of the cell. Thus for a cell that has ion channels selective for Na^+, K^+, and Cl^-,

(Equation 2.5)

$$I_{Na^+} + I_{k+} + I_{Cl^-} = 0$$

or

(Equation 2.6)

$$\left[\left(V_m - E_{Na^+}\right)\times G_{Na^+}\right] + \left[\left(V_m - E_{K^+}\right)\times G_{K^+}\right] + \left[\left(V_m - E_{Cl^-}\right)\times G_{Cl^-}\right] = 0$$

Solving for V_m yields

(Equation 2.7)

$$V_m = E_{Na^+} + \frac{G_{Na^+}}{\sum G} + E_{K^+} + \frac{G_{K^+}}{\sum G} + E_{Cl^-}\frac{G_{Cl^-}}{\sum G}$$

where $\sum G = G_{Na^+} + G_{K^+} + G_{Cl^-}$.

Inspection of Eq. 2.7, which is often called the **chord conductance equation**, reveals that the V_m will be near to the Nernst equilibrium potential of the ion to which the membrane has the highest conductance. In Fig. 2.4, 80% of the membrane conductance is attributable to K^+; as a result, V_m is near to the Nernst equilibrium potential for K^+ (E_{K^+}). For most cells at rest, the membrane has a high conductance to K^+, and thus the V_m approximates E_{K^+}. Moreover, the V_m is greatly influenced by the magnitude of E_{K^+}, which in turn is greatly influenced by changes in the $[K^+]$ of the ECF. For example, if the intracellular $[K^+]$ is 120 mEq/L and the extracellular $[K^+]$ is 4 mEq/L, E_{K^+} has a value of –90.8 mV. If the extracellular $[K^+]$ is increased to 7 mEq/L, E_{K^+} would be –79.9 mV. This change in E_{K^+} **depolarizes** the V_m (i.e., V_m is less negative). Conversely, if the extracellular $[K^+]$ is decreased to 2 mEq/L, E_{K^+} becomes –109.4 mV, and the V_m **hyperpolarizes** (i.e., V_m is more negative).

IN THE CLINIC

Changes in the extracellular $[K^+]$ can have important effects on excitable cells, especially those of the heart. A decrease in extracellular $[K^+]$ **(hypokalemia)** hyperpolarizes the V_m of cardiac myocytes and, in so doing, makes initiating an action potential more difficult, because a larger depolarizing current is needed to reach the threshold potential (see Chapter 16). If severe, hypokalemia can lead to cardiac arrhythmias, and eventually the heart can stop contracting **(asystole)**. An increase in the extracellular $[K^+]$ **(hyperkalemia)** can be equally deleterious to cardiac function. With hyperkalemia, the V_m is depolarized, and it is easier to initiate an action potential. However, once the action potential fires the channels become inactivated, and are unable to initiate another action potential, until they are reactivated by normal repolarization of the V_m. Because the V_m is depolarized in hyperkalemia, the channels stay in an inactivated state. Thus depolarization of the V_m with hyperkalemia can lead to cardiac arrhythmias and loss of cardiac muscle contraction.

Eq. 2.7 also defines the limits for the membrane potential. In the example depicted in Fig. 2.4, it is apparent that the V_m cannot be more negative than E_{K^+} (–90.8 mV), as would be the case if the membrane were only conductive to K^+. Conversely, the V_m could not be more positive than E_{Na^+} (66.6 mV); such a condition would be met if the membrane were conductive only to Na^+. The dependence of the V_m on the conductance of the membrane to specific ions is the basis by which action potentials in excitable cells are generated (Fig. 2.5). As noted previously, in all excitable cells, the membrane at rest is conductive predominantly to K^+, and thus V_m is near E_{K^+}. When an action potential is initiated, Na^+-channels open and the membrane is now conductive predominantly to Na^+. As a result, V_m now approaches E_{Na^+}. The generation of action potentials is discussed in more detail in Chapter 5.

the development of the V_m (in which the cell's interior is electrically negative), that in turn drives Cl^- and other anions out of the cell. Thus through the activity of the Na^+,K^+-ATPase, the number of intracellular osmotically active particles is reduced from what would be caused by the Gibbs-Donnan effect, and cell volume is maintained in isotonic solutions.

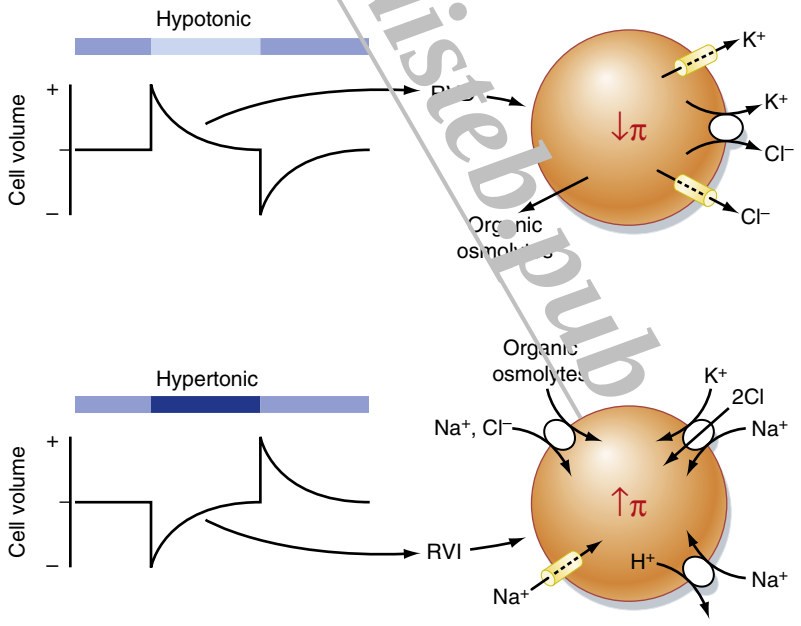
Nonisotonic Cell Volume Regulation

Most cells throughout the body are bathed with isotonic ECF, the composition of which is tightly regulated (see Chapter 35). However, certain regions within the body are not isotonic (e.g., the medulla of the kidney), and with disorders of water balance, the ECF can become either hypotonic or hypertonic. When this occurs, cells either swell or shrink. Cell swelling or shrinkage can result in cell damage or death, but many cells have mechanisms that limit the degree to which the cell volume changes. These mechanisms are particularly important for neurons, in which swelling within the confined space of the skull can lead to serious neurological damage.

In general, when a cell is exposed to nonisotonic ECF, volume-regulatory responses are activated within seconds to minutes to restore cell volume (Fig. 2.7). With cell swelling, a regulatory volume decrease response transports osmotically active particles (osmolytes) out of the cell, reducing the intracellular osmotic pressure and thereby restoring cell volume to normal. Conversely with cell shrinking a regulatory volume increase response transports osmolytes into the cell, raising the intracellular osmotic pressure and thereby restoring cell volume to normal. These osmolytes include ions and organic molecules such as polyols (sorbitol and myo-inositol), methylamines (glycerophosphorylcholine and betaine), and some amino acids (taurine, glutamate, and β-alanine). If the cell is exposed

IN THE CLINIC

The ECF of individuals with disorders in water balance may be either hypotonic (positive water balance) or hypertonic (negative water balance). With a decrease in ECF osmolality, neurons and glial cells swell as water enters the cell. To minimize this swelling, the neurons and glial cells reduce intracellular osmolytes. If the ECF osmolality is corrected (i.e., increased) too quickly, the neurons and glial cells then shrink because of the reduced number of intracellular osmolytes. This response to a rapid correction of ECF osmolality can lead to cell damage. Damage to the glial cells that synthesize myelin within the brain can result in demyelinization. This demyelinization response, termed *osmotic demyelinization syndrome,* can affect any of the white matter of the brain, but especially regions of the pons. These effects are often irreversible. Therefore, correction of disorders of water balance is usually accomplished slowly to avoid this serious neurological complication.



• **Fig. 2.7** Volume regulation of cells in hypotonic and hypertonic media. **Top**, When cells are exposed to a hypotonic medium, they swell and then undergo a volume-regulatory decrease (RVD). The RVD involves loss of KCl and organic osmolytes from the cell. The decrease in cellular KCl and organic osmolytes causes intracellular osmotic pressure to decrease, water leaves the cell, and the cell returns to nearly its original volume. **Bottom**, When cells are exposed to a hypertonic medium, they shrink and then undergo a volume-regulatory increase (RVI). During the RVI, NaCl and organic osmolytes enter the cell. The increase in the activity of Na^+,K^+-ATPase (not depicted) enhances the exchange of Na^+ for K^+ so that the K^+ (and Cl^-) content of the cell is increased. The increase in cellular KCl, along with a rise in intracellular organic osmolytes, increases intracellular osmotic pressure, which brings water back into the cell, and the cell volume returns to nearly its original volume. π, The oncotic pressure inside the cell.

to the nonisotonic ECF for an extended period of time, the cell alters the intracellular levels of the organic osmolytes through metabolic processes.

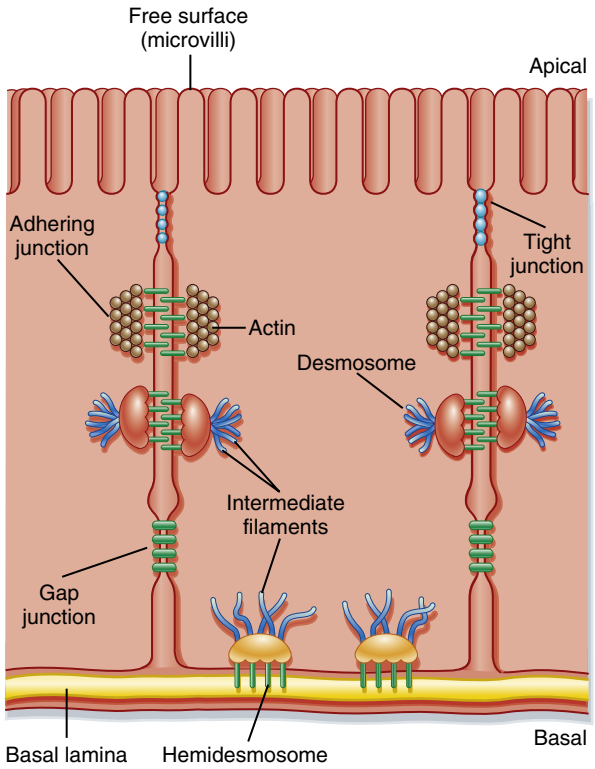
The regulatory volume increase response results in the rapid uptake of NaCl and a number of organic osmolytes. To increase cell volume there is an activation of the Na^+-H^+ antiporter (NHE-1), the $1Na^+,1K^+,2Cl^-$ symporter (NKCC-1), and a number of cation-selective channels, which together bring NaCl into the cell. The Na^+,K^+-ATPase then extrudes the Na^+ in exchange for K^+, so that ultimately the KCl content of the cell is increased. Several organic osmolyte transporters are also activated to increase cell volume. These include a $3Na^+,1Cl^-$-taurine symporter, a $3Na^+,2Cl^-$-betaine symporter, a $2Na^+$–myo-inositol symporter, and a Na^+–amino acid symporter. These transporters use the energy in the Na^+ and Cl^- gradients to drive the secondary active uptake of these organic osmolytes into cells.

The regulatory volume decrease response results in the loss of KCl and organic osmolytes from the cell. The loss of KCl occurs through the activation of a wide range of K^+-selective, Cl^--selective, and anion-selective channels (the specific channels involved vary depending on the cell), as well as through activation of K^+-Cl^- symporters. Some of the organic osmolytes appear to leave the cell via anion channels (e.g., volume-sensitive organic osmolyte-anion channels).

Several mechanisms are involved in activation of these various transporters during the volume-regulatory responses. Changes in cell volume appear to monitored by the cytoskeleton, by changes in macromolecular crowding and ionic strength of the cytoplasm, and by channels whose gating is influenced, either directly or indirectly, by stretch of the plasma membrane (e.g., stretch-activated cation channels). A number of second messenger systems may also be involved in these responses (e.g., intracellular $[Ca^{++}]$, calmodulin, protein kinase A, and protein kinase C), but the precise mechanisms have not been defined completely.

Principles of Epithelial Transport

Epithelial cells are arranged in sheets and provide the interface between the external world and the internal environment (i.e., ECF) of the body. Depending on their location, epithelial cells serve many important functions, such as establishing a barrier to microorganisms (lungs, gastrointestinal tract, and skin), prevention of the loss of water from the body (skin), and maintenance of a constant internal environment (lungs, gastrointestinal tract, and kidneys). The latter function is a result of the ability of epithelial cells to carry out regulated vectorial transport (i.e., transport from one side of the epithelial cell sheet to the opposite side). In this section, the principles of epithelial transport are reviewed. The transport functions of specific epithelial cells are discussed in the appropriate chapters throughout this book.



• **Fig. 2.8** Schematic of an epithelial cell, illustrating the various adhering junctions. The tight junction separates the apical membrane from basolateral membrane (see text for details).

Epithelial Structure

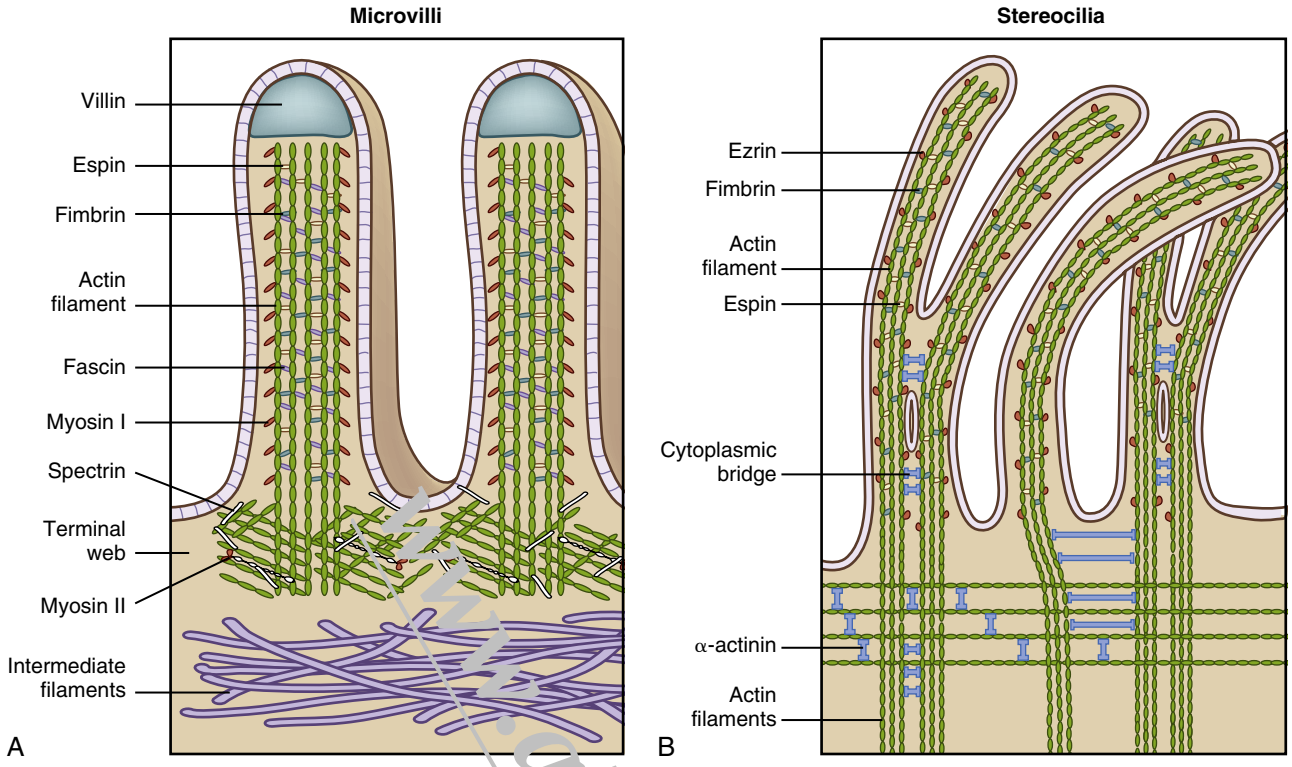
Fig. 2.8 shows a schematic representation of an epithelial cell. The free surface of the epithelial layer is referred to as the *apical membrane*. It is in contact with the external environment (e.g., air within the alveoli and larger airways of the lungs and the contents of the gastrointestinal tract) or with extracellular fluids (e.g., glomerular filtrate in the nephrons of the kidneys and the secretions of the ducts of the pancreas or sweat glands). The basal side of the epithelium rests on a basal lamina, which is secreted by the epithelial cells, and this in turn is attached to the underlying connective tissue.

Epithelial cells are connected to one another and to the underlying connective tissue by a number of specialized junctions (see Fig. 2.8). The **adhering junction, desmosomes**, and **hemidesmosomes** provide mechanical adhesion by linking together the cytoskeleton of adjacent cells (adhering junction and desmosome) or to the underlying connective tissue (hemidesmosome). The **gap junction** and **tight junction** play important physiological roles.

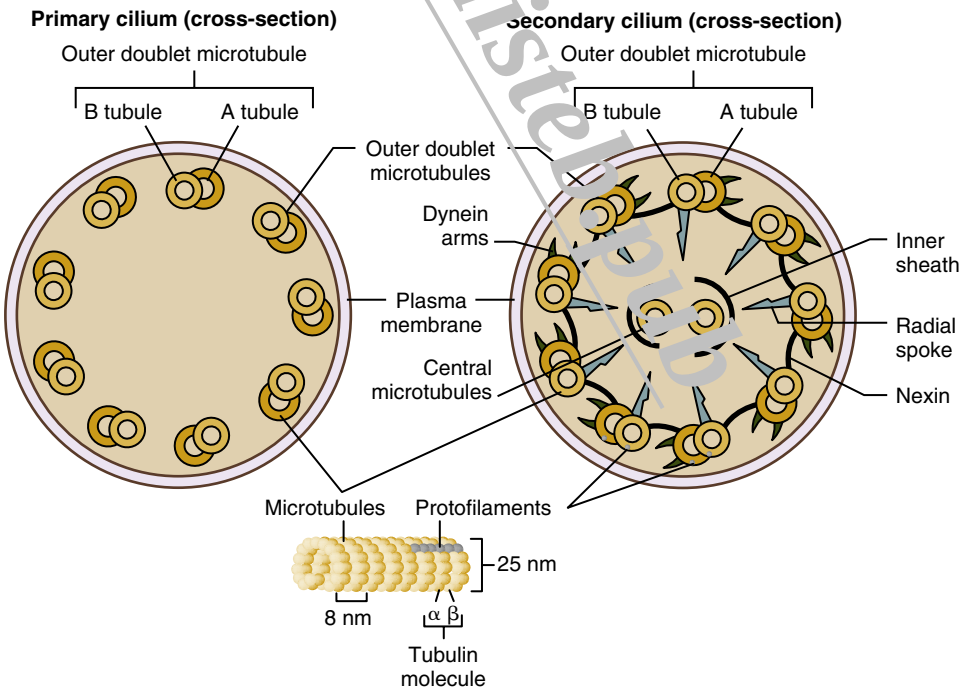
Gap junctions provide low-resistance connections between cells.[g]

The functional unit of the gap junction is the **connexon**. The connexon is composed of six integral membrane protein subunits called **connexins**. A connexon in one cell is aligned with the connexon in the adjacent cell, forming a

[g]Gap junctions are not limited to epithelial cells. A number of other cells also have gap junctions (e.g., cardiac myocytes and smooth muscle cells).



• **Fig. 2.9** Illustration of apical membrane specializations of epithelial cells (Not drawn to scale). **A**, Microvilli 1 to 3 µm in length serve to increase the surface area of the apical membrane (e.g., those of the epithelial cells of the small intestine). **B**, Stereocilia can be up to 120 µm in length (e.g., those of the epididymis of the male reproductive tract). Both microvilli and stereocilia have a core structure composed primarily of actin, with a number of associated proteins. Both are nonmotile. (Redrawn from Pawlina W. *Histology: A Text and Atlas, with Correlated Cell and Molecular Biology.* 7th ed. Philadelphia: Wolters Kluwer Health; 2016.)



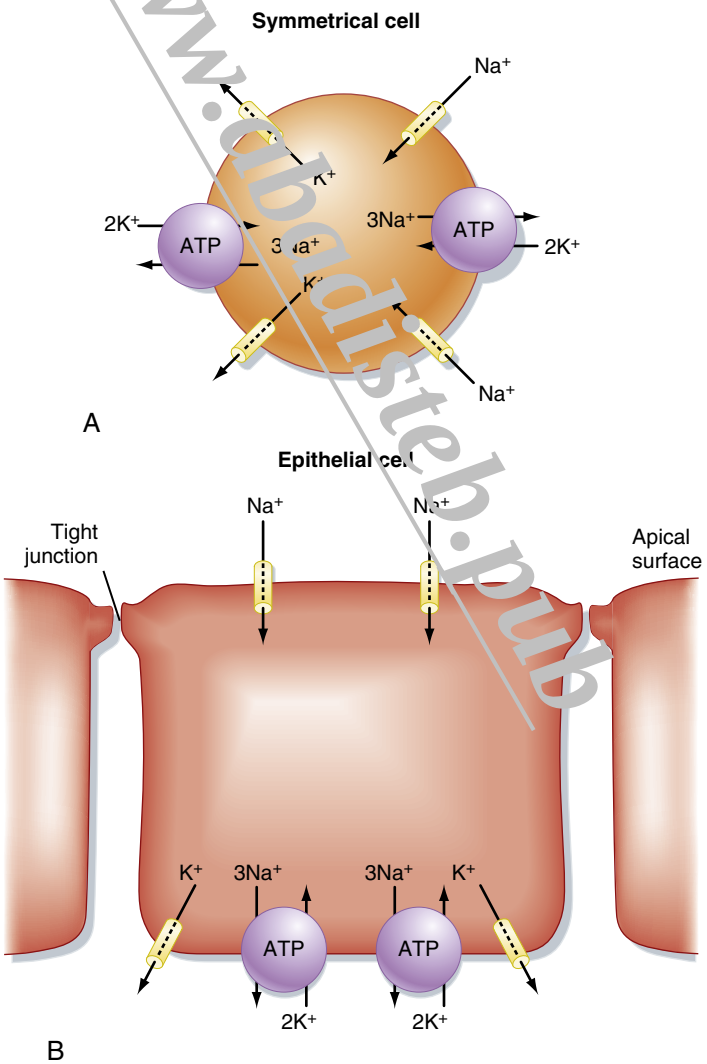
• **Fig. 2.10** Cilia are apical membrane specializations of some epithelial cells. Cilia are 5 to 10 µm in length and contain arrays of microtubules, as depicted in these cross-sectional diagrams. **Left**, The primary cilium has nine peripheral microtubule arrays. It is nonmotile and serves as a mechanoreceptor (e.g., cells of the renal collecting duct). Cells that have a primary cilium have only a single cilium. **Right**, The secondary cilium has a central pair of microtubules in addition to the nine peripheral microtubule arrays. Also in the secondary cilium, the motor protein dynein is associated with the microtubule arrays and therefore is motile. A single cell can have thousands of secondary cilia on its apical surface (e.g., epithelial cells of the respiratory tract). (Redrawn from Rodat-Despoix L, Delmas P. Ciliary functions in the nephron. *Pflugers Archiv*. 2009;458:179.)

the membrane surface area to accommodate the large number of membrane transporters (e.g., Na^+,K^+-ATPase) needed in the membrane.

Vectorial Transport

Because the tight junction divides the plasma membrane into two domains (i.e., apical and basolateral), epithelial cells are capable of vectorial transport, whereby an ion or molecule can be transported from one side of the epithelial sheet to the opposite side (Fig. 2.11). The accomplishment of vectorial transport requires that specific membrane transport proteins be targeted to and remain in one or the other of the membrane domains. In the example shown in Fig. 2.11, the Na^+ channel is present only in the apical membrane, whereas the Na^+,K^+-ATPase and the K^+ channels are confined to the basolateral membrane. The operation of the Na^+,K^+-ATPase and the leakage of K^+ out of the cell across the basolateral membrane set up a large electrochemical gradient for Na^+ to enter the cell across the apical membrane through the Na^+ channel (intracellular [Na^+] < extracellular [Na^+], and V_m which is oriented with the cell's interior electrically negative with respect to the cell's exterior). The Na^+ is then pumped out of the cell by the Na^+,K^+-ATPase, and vectorial transport from the apical side of the epithelium to the basolateral side of the epithelium occurs. Transport from the apical side to the basolateral side of an epithelium is termed either **absorption** or **reabsorption**: For example, the uptake of nutrients from the lumen of the gastrointestinal tract is termed *absorption*, whereas the transport of NaCl and water from the lumen of the renal nephrons is termed *reabsorption.* Transport from the basolateral side of the epithelium to the apical side is termed **secretion**.

As noted previously, the Na^+,K^+-ATPase and K^+-selective channels play an important role in establishing cellular ion gradients for Na^+ and K^+ and in generating the V_m. In all



• **Fig. 2.11** In symmetrical cells (**A**; e.g., red blood cells), membrane transport proteins are distributed over the entire surface of the cell. Epithelial cells **(B)**, in contrast, are asymmetrical and target various membrane transport proteins to either the apical or the basolateral membrane. When the transporters are confined to a membrane domain, vectorial transport can occur. In the cell depicted, Na^+ is transported from the apical surface to the basolateral surface. *ATP*, Adenosine triphosphate.