2

Homeostasis: Volume and Composition of Body Fluid Compartments

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What is steady-state balance, and, with water balance as an example, what are the elements needed to achieve steady-state balance?
2. What are the volumes of the body fluid compartments, and how do they change under various conditions?
3. How do the body fluid compartments differ with regard to their composition?
4. What determines the resting membrane potential of cells?
5. How do cells regulate their volume in isotonic, hypotonic, and hypertonic solutions?
6. What are the structural features of epithelial cells, how do they carry out vectorial transport, and what are the general mechanisms by which transport is regulated?

Normal cellular function requires that the intracellular composition—with regard to ions, small molecules, water, pH, and a host of other substances—be maintained within a narrow range. This is accomplished by the transport of many substances and water into and out of the cell via membrane transport proteins, as described in Chapter 1. In addition, each day, food and water are ingested, and waste products are excreted from the body. In a healthy individual, these processes occur without significant changes in either the volume of the body fluid compartments or their composition. The maintenance of constant volume and composition of the body fluid compartments (and their temperature in warm-blooded animals and humans) is termed **homeostasis**. The human body has multiple systems designed to achieve homeostasis, the details of which are explained in the various chapters of this book. In this chapter, the basic principles that underlie the maintenance of homeostasis are outlined. In addition, the volume and composition of the various body fluid compartments are defined.

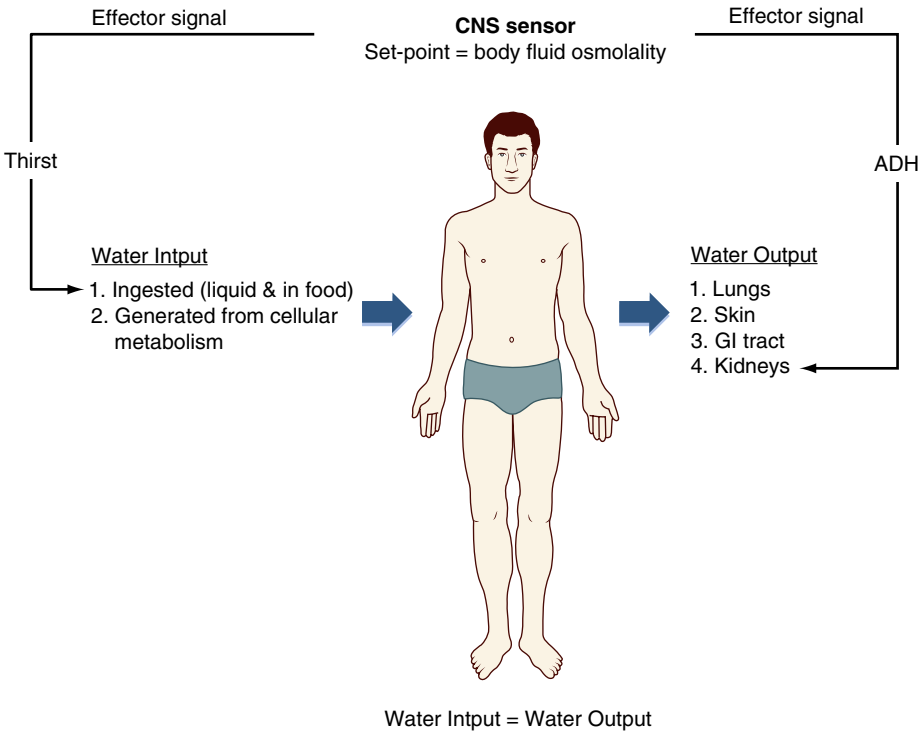
Concept of Steady-State Balance

The human body is an "open system," which means that substances are added to the body each day and, similarly, substances are lost from the body each day. The amounts added to or lost from the body can vary widely, depending on the environment, access to food and water, disease processes, and even cultural norms. In such an open system, homeostasis occurs through the process of **steady-state balance**.

To illustrate the concept of steady-state balance, consider a river on which a dam is built to create a man-made lake. Each day, water enters the lake from the various streams and rivers that feed it. In addition, water is added by underground springs, rain, and snow. At the same time, water is lost through the spillways of the dam and by the process of evaporation. For the level of the lake to remain constant (i.e., steady-state balance), the rate at which water is added, regardless of source, must be exactly matched by the amount of water lost, again regardless of route. Because the addition of water is not easily controlled and the loss by evaporation cannot be controlled, the only way to maintain a constant level of the lake is to regulate the amount that is lost through the spillways.

To understand steady-state balance as it applies to the human body, the following key concepts are important.

1. There must be a "set point" so that deviations from this baseline can be monitored (e.g., the level of the lake in the preceding example, or setting the temperature in a room by adjusting the thermostat).
2. The sensor or sensors that monitor deviations from the set point must generate "effector signals" that can lead to changes in either input or output, or both, to maintain the desired set point (e.g., electrical signals to adjust the spillway in the dam analogy, or electrical signals sent to either the furnace or air conditioner to maintain the proper room temperature).
3. "Effector organs" must respond in an appropriate way to the effector signals generated by the set point monitor (i.e., the spillway gates must operate, and the furnace or air conditioner must turn on).
4. The sensitivity of the system (i.e., how much of a deviation from the set point is tolerated) depends on several factors, including the nature of the sensor (i.e., how much of a deviation from the set point is needed for the sensor to detect the deviation), the time necessary for generation of the effector signals, and how rapidly the effector organs respond to the effector signals.



• **Fig. 2.1** Whole-body steady-state water balance. See text for details. *ADH*, Antidiuretic hormone (also called arginine vasopressin); *CNS*, central nervous system; *GI*, gastrointestinal.

It is important to recognize that deviations from steady-state balance do occur. When input is greater than output, a state of **positive balance** exists. When input is less than output, a state of **negative balance** exists. Although transient periods of imbalance can be tolerated, prolonged states of positive or negative balance are generally incompatible with life.

Fig. 2.1 illustrates several important concepts for the maintenance of steady-state water balance (details related to the maintenance of steady-state water balance are presented in Chapter 35). As depicted in Fig. 2.1, there are multiple inputs and outputs of water, many of which can vary but nevertheless cannot be regulated. For example, the amount of water lost through the lungs depends on the humidity of the air and the rate of respiration (e.g., low humidity and rapid breathing increase water loss from the lungs). Similarly, the amount of water lost as sweat varies according to ambient temperature and physical activity. Finally, water loss via the gastrointestinal tract can increase from a normal level of 100 to 200 mL/day to many liters with acute diarrhea. Of these inputs and outputs, the only two that can be regulated are increased ingestion of water in response to thirst and alterations in urine output by the kidneys (see Chapter 35).

Water balance determines the osmolality of the body fluids. Cells within the hypothalamus of the brain monitor body fluid osmolality for deviations from the set point (normal range: 280–295 mOsm/kg H_2O). When deviations are sensed, two effector signals are generated. One is neural and relates to the individual's sensation of thirst. The other is hormonal (antidiuretic hormone, also called *arginine vasopressin*), which regulates the amount of water excreted by the kidneys. With appropriate responses to these two signals, water input, water output, or both are adjusted to maintain balance and thereby keep body fluid osmolality at the set point.

Volumes and Composition of Body Fluid Compartments

Unicellular organisms maintain their volume and composition through exchanges with the environment they inhabit (e.g., sea water). The billions of cells that constitute the human body must maintain their volume and composition as well, but their task is much more difficult. This challenge, as well as its solution, was first articulated by the French physiologist Claude Bernard (1813–1878). He recognized that although cells within the body cannot maintain their volume and composition through exchanges with the environment, they can do so through exchanges with the fluid environment that surrounds them (i.e., the extracellular fluid). Bernard referred to the extracellular fluid as the *milieu intérieur* ("the environment within"). He also recognized that the organ systems of the body are designed and function to maintain a constant milieu interieur or a "constant internal environment." This in turn allows all cells to maintain their volume and composition through exchanges with the extracellular fluid as a result of membrane transport (see Chapter 1).

Transport by the epithelial cells of the gastrointestinal tract, kidneys, and lungs is the body's interface with the

external environment and control both the intake and excretion of numerous substances, as well as water. The cardiovascular system delivers nutrients to and removes waste products from the cells and tissues and keeps the extracellular fluid well mixed. Finally, the nervous and endocrine systems provide regulation and integration of these important functions.

To provide background for the study of all organ systems, this chapter presents an overview of the normal volume and composition of the body fluid compartments and describes how cells maintain their intracellular composition and volume. Included is a presentation on how cells generate and maintain a membrane potential, which is fundamental for understanding the function of excitable cells (e.g., neurons and muscle cells). Finally, because epithelial cells are so central to the process of regulating the volume and composition of the body fluids, the principles of solute and water transport by epithelial cells are also reviewed.

Definition and Volumes of Body Fluid Compartments

Water makes up approximately 60% of the body's weight; variability among individuals is a function of the amount of adipose tissue. Because the water content of adipose tissue is lower than that of other tissue, increased amounts of adipose tissue reduce the fraction of water in the total body as a percentage of weight. The percentage of body weight attributed to water also varies with age. In newborns, it is approximately 75%. This decreases to the adult value of 60% by the age of 1 year.

As illustrated in Fig. 2.2, **total body water** is distributed between two major compartments, which are divided by the cell membrane.[a] The **intracellular fluid (ICF)** compartment is the larger compartment and contains approximately two-thirds of the total body water. The remaining third is contained in the **extracellular fluid (ECF)** compartment. The volumes of total body water, ICF, and ECF in liters are calculated as follows:

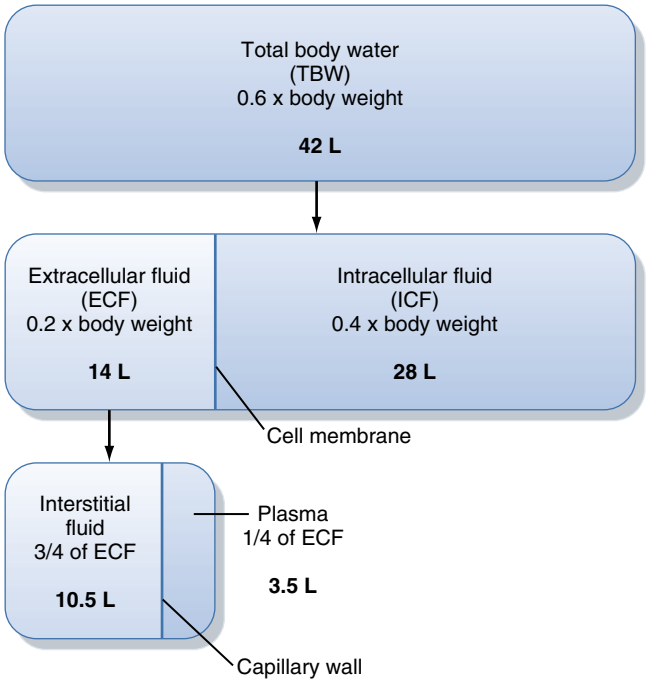
$$\text{Total body water} = 0.6 \times (\text{body weight})$$
$$\text{ICF} = 0.4 \times (\text{body weight})$$
$$\text{ECF} = 0.2 \times (\text{body weight})$$

The ECF compartment is further subdivided into interstitial fluid and plasma. The ECF also includes fluid contained within bone and dense connective tissue, as well as the cerebrospinal fluid. The interstitial fluid surrounds the cells in the various tissues of the body and makes up three-fourths of the ECF volume. Plasma is contained within the vascular compartment and represents the remaining fourth of the ECF. In some pathological conditions, additional fluid may accumulate in what is referred to as a *third space*. Third-space collections of fluid are part of the ECF; an example is the accumulation of fluid in the peritoneal cavity **(ascites)** of individuals with liver disease.

Movement of Water Between Body Fluid Compartments

As depicted in Fig. 2.2, water moves between the ICF and ECF compartments across the plasma membranes of cells, and it moves between the vascular (plasma) and interstitial compartments across capillary walls. The pathways and driving forces for this water movement are different across cell membranes, in comparison to the capillary walls.

Movement of water between the ICF and ECF compartments, across cell membranes, occurs through aquaporins expressed in the plasma membrane (see Chapter 1). The driving force for this water movement is an osmotic pressure difference. The osmotic pressure of both the ICF and ECF is determined by the molecules/ions present in these fluids. For simplicity, these can be divided into (1) molecules of low molecular weight (e.g., glucose) and ions (e.g., Na^+) and (2) macromolecules (e.g., proteins). The osmotic pressures of both the ICF and ECF are in the range of 280 to 295 mOsm/kg H_2O. For the ECF, the low-molecular-weight molecules and ions account for nearly all of this pressure because the osmotic pressure contributed by proteins is only 1 to 2 mOsm/kg H_2O. The molecules/ions contributing to the osmotic pressure within the cell are less well understood, but they also include low-molecular-weight molecules (e.g., glucose), ions



• **Fig. 2.2** Relationship between the volumes of the various body fluid compartments. The actual values shown are for an individual weighing 70 kg. (Modified from Levy MN, Koeppen BM, Stanton BA. *Berne & Levy's Principles of Physiology*. 4th ed. St. Louis: Mosby; 2006.)

[a]In these and all subsequent calculations, it is assumed that 1 L of fluid (e.g., ICF and ECF) has a mass of 1 kg. Although 1 L of the ICF and ECF has a mass of slightly more than 1 kg, this simplification allows conversion from measurements of body weight to volume of body fluids.

(e.g., Na^+), and macromolecules (e.g., proteins). The fact that cell volume remains constant when ECF osmolality is constant means that the osmotic pressure inside the cells is equal to that of the ECF. If an osmotic pressure difference did exist, the cells would either swell or shrink, as described in the section "Nonisotonic Cell Volume Regulation."

Movement of water between the vascular (plasma) compartment and the interstitial fluid compartment occurs across the capillary wall. The amount of water that moves across the capillary wall and the mechanism of the water movement vary depending on the capillary. For example, in the capillary sinusoids of the liver, endothelial cells are often separated by large gaps (discontinuous capillary). As a result, water and all components of the plasma (and some cellular elements) can pass easily across the wall. Other capillaries are lined by endothelial cells that contain fenestrations that are up to 80 to 100 nm in diameter (e.g., in the kidneys). These fenestrations allow all components of the plasma (only cellular elements of blood cannot pass through the fenestrations) to move across the capillary wall. Some capillaries (e.g., in the brain) form a relatively tight barrier to water and small molecules and ions, and water movement occurs through small pores on the endothelial cell surface or through clefts between adjacent endothelial cells. These pores and clefts allow water and molecules smaller than 4 nm to pass. In addition, a small amount of water traverses the capillary wall via pinocytosis by endothelial cells.

The driving forces for fluid (water) movement across the capillary wall are hydrostatic pressure and oncotic pressure (i.e., osmotic pressure generated by proteins). Collectively, these are called the *Starling forces*. Capillary fluid movement is discussed in detail in Chapter 17; in brief, hydrostatic pressure within the capillary (as a result of the pumping of the heart and the effect of gravity on the column of blood in the vessels feeding a capillary) is a force that causes fluid to move out of the capillary. Hydrostatic pressure in the surrounding interstitial tissue opposes the effect of the capillary hydrostatic pressure. The oncotic pressure of the plasma in the capillary tends to draw fluid from the interstitium into the capillary. The oncotic pressure of the interstitial fluid opposes this. Depending on the capillary bed, proteins can cross the capillary wall to varying degrees. For example, very little protein crosses the wall of skeletal muscle capillaries and the capillaries in the glomerulus of the kidneys. In contrast, proteins readily cross the wall of the liver capillaries (i.e., sinusoids). The degree to which proteins cross the capillary wall is quantitated by a reflection coefficient (σ). If no protein crosses the capillary wall, $\sigma = 1$, and if proteins freely cross the capillary wall, $\sigma = 0$. Thus the amount of fluid moving across the wall of the capillary is determined as follows:

(Equation 2.1)

$$\text{Fluid flow } (Q_f) = K_f\left[\left(P_c - P_i\right) - \sigma\left(\pi_c - \pi_i\right)\right]$$

where

Q_f = fluid movement
K_f = filtration constant (measure of surface area + intrinsic permeability)
P_c = capillary hydrostatic pressure
P_i = interstitial fluid hydrostatic pressure
π_c = capillary (plasma) oncotic pressure
π_i = interstitial fluid oncotic pressure
σ = reflection coefficient for protein across the capillary wall.

Depending on the magnitude of these forces, fluid may move out of the capillary or into the capillary.

The compositions of the various body fluid compartments differ; however, as described later, the osmolalities of the fluid within these compartments are essentially identical.[b] Thus the compartments are in "osmotic equilibrium." In addition, any change in the osmolality of one compartment quickly causes water to redistribute across all compartments, which brings them back into osmotic equilibrium. Because of this rapid redistribution of water, measuring the osmolality of plasma or serum,[c] which is easy to do, reveals the osmolality of the other body fluid compartments (i.e., interstitial fluid and intracellular fluid).

As described later, Na^+ is a major constituent of the ECF. Because of its high concentration in comparison with other molecules and ions, Na^+ (and its attendant anions, primarily Cl^- and HCO_3^-) is the major determinant of the osmolality of this compartment. Accordingly, it is possible to obtain an approximate estimate of the ECF osmolality by simply doubling the sodium concentration $[Na^+]$. For example, if a blood sample is obtained from an individual, and the $[Na^+]$ of the serum is 145 mEq/L, its osmolality can be estimated as follows:

(Equation 2.2)

$$\text{Plasma Osmolality} = 2(\text{serum}[Na^+]) = 290\,\text{m Osm/kg}H_2O$$

In contrast to water, the movement of ions across cell membranes is more variable from cell to cell and depends on the presence of specific membrane transport proteins (see the section "Composition of Body Fluid Compartments"). Consequently, in trying to understand the physiology of fluid shifts between body fluid compartments, it can be assumed that while water moves freely between the compartments, there is little net movement of solutes. For most situations, this is a reasonable assumption.

[b]Some exceptions do exist. The cerebrospinal fluid is part of the ECF, but its osmolality is slightly higher than that of the ECF elsewhere in the body. Also, regions within the kidney can have osmolalities that are either less than or greater than that of the ECF. However, these volumes are small (≈150 mL) in comparison with the total volume of the ECF (≥12 L).

[c]Serum is derived from clotted blood. Thus serum differs from plasma by the absence of clotting factors. With regard to osmolality and the concentrations of other molecules and ions, the osmolality and concentrations in plasma and serum are virtually identical.

IN THE CLINIC

In some clinical situations, it is possible to obtain a more accurate estimate of the serum osmolality, and thus the osmolalities of the ECF and ICF, by also considering the osmoles contributed by glucose and urea, as these are the next most abundant solutes in the ECF (the other components of the ECF contribute only a few additional milliosmoles). Accordingly, serum osmolality can be estimated as follows:

$$\text{Serum osmolality} = 2(\text{serum } [Na^+]) + \frac{[\text{glucose}]}{18} + \frac{[\text{urea}]}{2.8}$$

The glucose and urea concentrations are expressed in units of milligrams per deciliter (dividing by 18 for glucose and 2.8 for urea* allows conversion from the units of milligrams per deciliter to millimoles per liter and thus to milliosmoles per kilogram of H_2O). This estimation of serum osmolality is especially useful in treating patients who have an elevated serum glucose concentration secondary to diabetes mellitus, and in patients with chronic renal failure, whose serum urea concentration is elevated because of reduced renal excretion.

As discussed in Chapter 1, the ability of a substance to cause water to move across the plasma membrane of a cell depends on whether the substance itself crosses the membrane. Recall Eq. 1.9:

$$\Pi_e = \sigma(nCRT)$$

where Π_e = the effective osmotic pressure and σ = the reflection coefficient for the substance. For many cells, glucose and urea cross the cell membrane. Although they contribute to serum osmolality, as measured by a laboratory osmometer where all molecules are "effective osmoles," they are ineffective osmoles for water movement across many, but not all, cell membranes. In contrast, Na^+ is an "effective osmole" for water movement across the plasma membrane of virtually all cells. Eq. 2.2 gives the best estimate of the effective osmolality of the serum.

*The urea concentration in plasma is measured as the nitrogen in the urea molecule, or blood urea nitrogen (BUN).

To illustrate the physiologic characteristics of fluid shifts, consider what happens when solutions containing various amounts of NaCl are added to the ECF.[d]

Example 1: Addition of Isotonic Sodium Chloride to the Extracellular Fluid

Addition of an isotonic NaCl solution (e.g., intravenous infusion of 0.9% NaCl: osmolality ≈ 290 mOsm/kg H_2O)[e] to the ECF increases the volume of this compartment by the volume of fluid administered. Because this fluid has the same osmolality as does the ECF, and therefore the ICF, there is no driving force for fluid movement between these compartments, and the volume of the ICF remains unchanged. Although Na^+ can cross cell membranes, it is effectively restricted to the ECF by the activity of the Na^+,K^+-ATPase, which is present in the plasma membrane of all cells (see the section "Ionic Composition of Cells"). Therefore, there is no net movement of the infused isotonic NaCl solution into cells.

[d]Fluids are usually administered intravenously. When electrolyte solutions are infused by this route, equilibration between plasma and interstitial fluid is rapid (i.e., minutes) because of the high permeability of many capillary walls for water and electrolytes. Thus these fluids are essentially added to the entire ECF.

[e]A 0.9% NaCl solution (0.9 g NaCl/100 mL) contains 154 mmol/L of NaCl. Because NaCl does not dissociate completely in solution (i.e., 1.88 Osm/mol), the osmolality of this solution is 290 mOsm/kg H_2O, which is very similar to that of normal ECF.

IN THE CLINIC

Neurosurgical procedures and cerebrovascular accidents (strokes) often result in the accumulation of interstitial fluid in the brain (i.e., edema) and swelling of the neurons. Because the brain is enclosed within the skull, edema can raise intracranial pressure and thereby disrupt neuronal function, which leads to coma and death. The blood-brain barrier, which separates the cerebrospinal fluid and brain interstitial fluid from blood, can be permeated freely by water but not by most other substances. As a result, excess fluid in brain tissue can be removed by imposing an osmotic gradient across the blood-brain barrier. Mannitol can be used for this purpose. Mannitol is a sugar (molecular weight, 182 g/mol) that does not readily cross the blood-brain barrier and membranes of cells (neurons and other cells in the body). Therefore, mannitol is an effective osmole, and intravenous infusion results in the movement of interstitial fluid out of the brain by osmosis.

Example 2: Addition of Hypotonic Sodium Chloride to the Extracellular Fluid

Addition of a hypotonic NaCl solution to the ECF (e.g., intravenous infusion of 0.45% NaCl; osmolality ≅ 145 mOsm/kg H_2O) decreases the osmolality of this fluid compartment, which results in the movement of water into the ICF. After osmotic equilibration, the osmolalities of the ICF and ECF are again equal but lower than before the infusion, and the volume of each compartment is increased. The increase in ECF volume is greater than the increase in ICF volume.

Example 3: Addition of Hypertonic Sodium Chloride to the Extracellular Fluid

Addition of a hypertonic NaCl solution to the ECF (e.g., intravenous infusion of 3% NaCl: osmolality ≅ 1000 mOsm/kg H_2O) increases the osmolality of this compartment, which results in the movement of water out of cells. After osmotic equilibration, the osmolalities of the ECF and ICF are again equal but higher than before the infusion. The volume of the ECF is increased, whereas that of the ICF is decreased.

Composition of Body Fluid Compartments

The compositions of the ECF and ICF differ considerably. The ICF has significantly more proteins and macromolecules than the ECF. There are also differences in the concentrations of many ions. The composition of the ICF is maintained by the action of a number of specific cell membrane transport proteins. Principal among these transporters is the Na^+,K^+-adenosine triphosphatase (Na^+,K^+-ATPase),

IN THE CLINIC

Fluid and electrolyte disorders are observed commonly in clinical practice (e.g., in patients with vomiting or diarrhea, or both). In most instances, these disorders are self-limited, and correction of the disorder occurs without need for intervention. However, more severe or prolonged disorders may necessitate fluid replacement therapy. Such therapy may be administered orally, with special electrolyte solutions, or intravenously.

Intravenous solutions are available in many formulations. The type of fluid administered to a particular patient is dictated by the patient's need. For example, if an increase in the patient's vascular volume is necessary, a solution containing substances that do not readily cross the capillary wall is infused (e.g., 5% protein or dextran solutions). The oncotic pressure generated by the albumin molecules causes fluid to be retained in the vascular compartment, which expands its volume. Expansion of the ECF is accomplished most often with isotonic saline solutions (e.g., 0.9% NaCl or lactated Ringer solution). As already noted, administration of an isotonic NaCl solution does not result in the development of an osmotic pressure gradient across the plasma membrane of cells. Therefore, the entire volume of the infused solution remains in the ECF.

Patients whose body fluids are hyperosmotic need hypotonic solutions. These solutions may be hypotonic NaCl (e.g., 0.45% NaCl) or 5% dextrose in water (D_5W). Administration of the D_5W solution is equivalent to the infusion of distilled water because the dextrose is metabolized to CO_2 and water. Administration of these fluids increases the volumes of both the ICF and ECF. In addition, patients whose body fluids are hypotonic need hypertonic solutions. These are typically NaCl-containing solutions (e.g., 3% or 5% NaCl). These solutions expand the volume of the ECF but decrease the volume of the ICF. Other constituents, such as electrolytes (e.g., K^+) or drugs, can be added to intravenous solutions to tailor the therapy to the patient's fluid, electrolyte, and metabolic needs.

which converts the energy in ATP into ion and electrical gradients, which can in turn be used to drive the transport of other ions and molecules by means of ion channels and solute carriers (e.g., symporters and antiporters).

The compositions of the plasma and interstitial fluid compartments of the ECF are similar because those compartments are separated only by the capillary endothelium, a barrier that ions and small molecules can permeate. The major difference between the interstitial fluid and plasma is that the latter contains significantly more protein. Although this differential concentration of protein can affect the distribution of cations and anions between these two compartments by the Gibbs-Donnan effect (see the section "Isotonic Cell Volume Regulation" for details), this effect is small, and the ionic compositions of the interstitial fluid and plasma can be considered to be identical.

Maintenance of Cellular Homeostasis

Normal cellular function requires that the ionic composition of the ICF be tightly controlled. For example, the activity of some enzymes is pH dependent; therefore, intracellular pH must be regulated. In addition, the intracellular composition of other electrolytes is similarly held within a narrow range. This is necessary for the establishment of the membrane potential, a cell property especially important for the normal function of excitable cells (e.g., neurons and muscle cells) and for intracellular signaling (e.g., intracellular $[Ca^{++}]$; see Chapter 3 for details). Finally, the volume of cells must be maintained because shrinking or swelling of cells can lead to cell damage or death. The regulation of intracellular composition and cell volume is accomplished through the activity of specific transporters in the plasma membrane of the cells. This section is a review of the mechanisms by which cells maintain their intracellular ionic environment and their membrane potential and by which they control their volume.

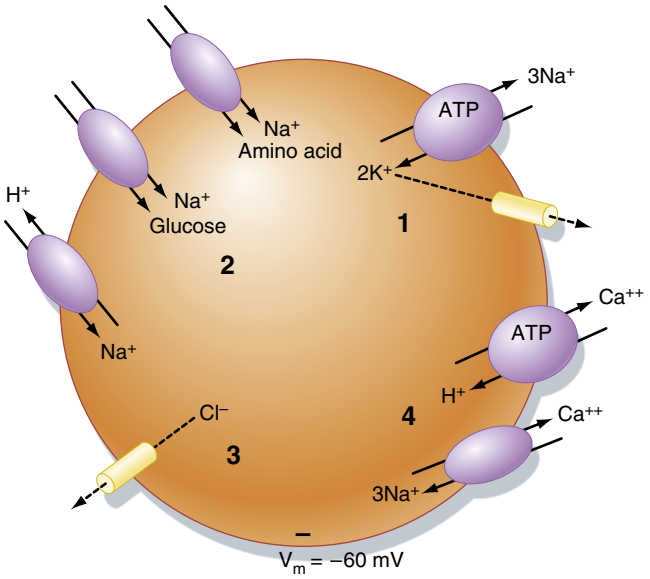
Ionic Composition of Cells

The intracellular ionic composition of cells varies from tissue to tissue. For example, the intracellular composition of neurons is different from that of muscle cells, both of which differ from that of blood cells. Nevertheless, there are similar patterns, and these are presented in Table 2.1. In comparison with the ECF, the ICF is characterized by a low $[Na^+]$ and a high $[K^+]$. This is the result of the activity of the Na^+,K^+-ATPase, which transports three Na^+ ions out of the cell and two K^+ ions into the cell for each ATP molecule hydrolyzed. As discussed later in this chapter, the activity of the Na^+,K^+-ATPase not only is important for establishing the cellular Na^+ and K^+ gradients but also is involved in determining, indirectly, the cellular gradients for many other ions and molecules. Of importance is that the cellular K^+ gradient generated by the activity of the Na^+,K^+-ATPase is a major determinant of the membrane voltage because of the leak of K^+ out of the cell through K^+-selective channels (see the section "Membrane Potential"). Thus the Na^+,K^+-ATPase converts the energy in ATP into ion gradients (i.e., Na^+ and K^+) and a voltage gradient (i.e., membrane voltage).

TABLE 2.1 Ionic Composition of a Typical Cell

Ion	Extracellular Fluid	Intracellular Fluid
Na^+	135–147 mEq/L	10–15 mEq/L
K^+	3.5–5.0 mEq/L	120–150 mEq/L
Cl^-	95–105 mEq/L	20–30 mEq/L
HCO_3^-	22–28 mEq/L	12–16 mEq/L
*Ca^{++}	2.1–2.8 (total) mmol/L	
	1.1–1.4 (ionized) mmol/L	≈10^{-7} M (ionized) mmol/L
*Pi	1.0–1.4 (total) mmol/L	
	0.5–0.7 (ionized) mmol/L	0.5–0.7 (ionized) mmol/L

*Ca^{++} and Pi ($H_2PO_4^-/HPO_4^{-2}$) are bound to proteins and other organic molecules. In addition, large amounts of Ca^{++} can be sequestered within cells. Large amounts of Pi are present in cells as part of organic molecules, such as adenosine triphosphate (ATP).



• **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)

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

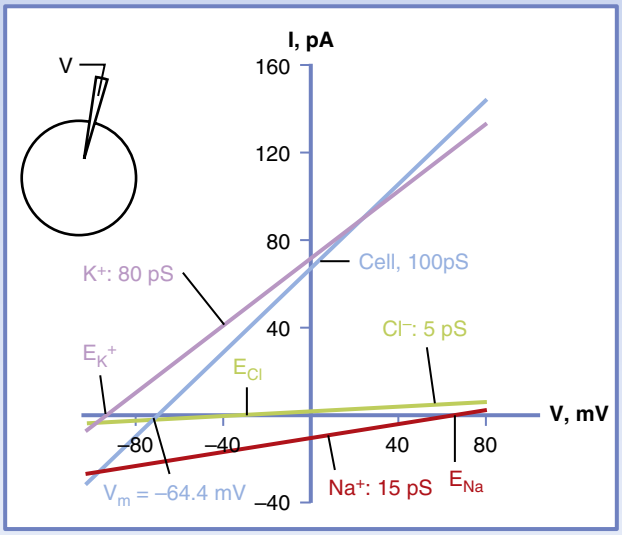
Thus as defined by **Ohm's law**, the ion current through the channel (I_i) is determined as follows:

(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 E_i, mV
Na^+	12	145	66.6
K^+	120	4	–90.8
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)

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

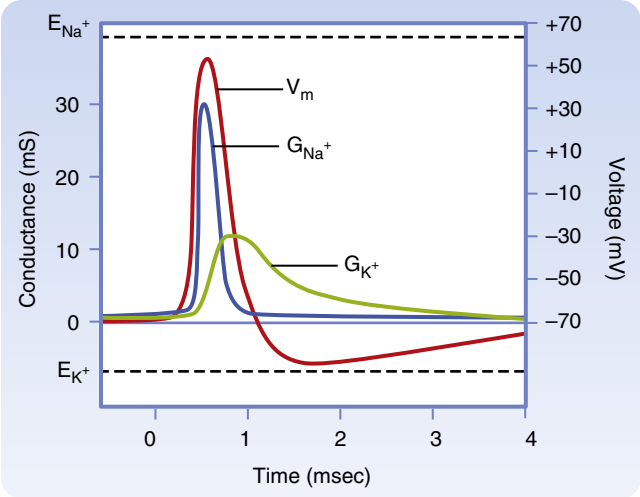
where $\sum G = G_{Na^+} + G_{K^+} + G_{Cl^-}$.

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).

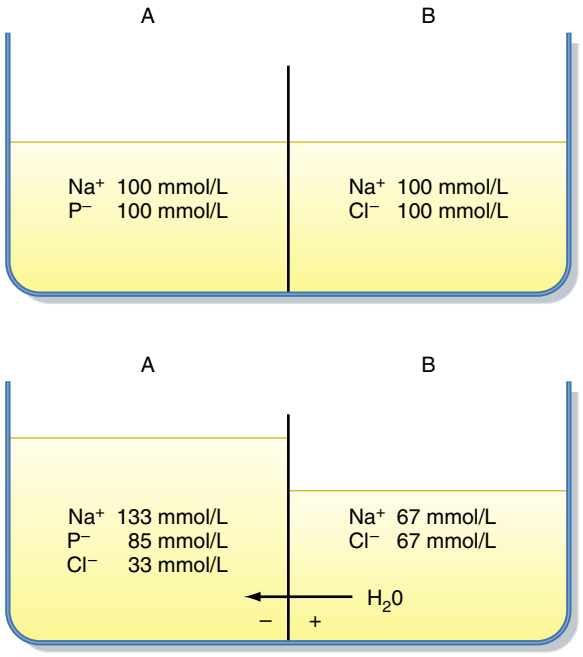
IN THE CLINIC

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.



• **Fig. 2.5** Nerve action potential showing the changes in Na^+ and K^+ conductances (G_{Na^+} and G_{K^+}, Respectively) and the membrane potential (V_m). At rest, the membrane has a high K^+ conductance, and V_m is near the Nernst equilibrium potential for K^+ (E_{K^+}). With the initiation of the action potential, there is a large increase in the Na^+ conductance of the membrane, and the V_m approaches the Nernst equilibrium potential for Na^+ (E_{Na^+}). The increase in Na^+ conductance is transient, and the K^+ conductance then increases above its value before the action potential. This hyperpolarizes the cell as V_m approaches E_{K^+}. As the K^+ conductance returns to its baseline value, V_m returns to its resting value of −70 mV. (Modified from Levy MN, Koeppen BM, Stanton BA. *Berne & Levy's Principles of Physiology.* 4th ed. St. Louis: Mosby; 2006.)



• **Fig. 2.6** The Gibbs-Donnan effect. **Top**, Two solutions are separated by a membrane that is permeable by Na^+, Cl^-, and H_2O but not permeable by protein (P^-). The osmolality of solution A is identical to that of solution B. **Bottom**, Cl^- diffuses from compartment B to compartment A down its concentration gradient. This causes compartment A to become electrically negative with regard to compartment B. The membrane voltage then drives the diffusion of Na^+ from compartment B to compartment A. The accumulation of additional Na^+ and Cl^- in compartment A increases its osmolality and causes water to flow from compartment B to compartment A (Note: the increase volume of compartment A results in a lower [P^-]). If the container containing the two solutions were sealed at the top so that water could not move from compartment B to compartment A, the pressure in compartment A would increase as the number of osmotically active particles increases in that compartment.

Regulation of Cell Volume

As already noted, changes in cell volume can lead to cell damage and death. Cells have developed mechanisms to regulate their volume. Most cells are highly permeable to water because of the presence of aquaporins in their plasma membranes. As discussed in Chapter 1, osmotic pressure gradients across the cell membrane that are generated by effective osmoles cause water to move either into or out of the cell, which result in changes in cell volume. Thus cells swell when placed in hypotonic solutions and shrink when placed in hypertonic solutions (see the section "Nonisotonic Cell Volume Regulation"). However, even when a cell is placed in an isotonic solution, the maintenance of cell volume is an active process requiring the expenditure of ATP and specifically the activity of the Na^+,K^+-ATPase.

Isotonic Cell Volume Regulation

The importance of the Na^+,K^+-ATPase in isotonic cell volume regulation can be appreciated by the observation that red blood cells swell when chilled (i.e., reduced ATP synthesis) or when the Na^+,K^+-ATPase is inhibited by cardiac glycosides (e.g., ouabain, digoxin [Lanoxin]). The necessity for energy expenditure to maintain cell volume in an isotonic solution is the result of the effect of intracellular proteins on the distribution of ions across the plasma membrane: the so-called **Gibbs-Donnan effect** (Fig. 2.6).

The Gibbs-Donnan effect occurs when a membrane separating two solutions can be permeated by some but not all of the molecules in solution. As noted previously, this effect accounts for the small differences in the ionic compositions of the plasma and the interstitial fluid. In this case, the capillary endothelium represents the membrane, and the plasma proteins are the molecules whose ability to permeate across the capillary is restricted. For cells, the membrane is the plasma membrane, and the impermeant molecules are the intracellular proteins and organic molecules.

As depicted in Fig. 2.6, the presence of impermeant molecules (e.g., protein) in one compartment results over time in the accumulation of permeant molecules/ions in the same compartment. This increases the number of osmotically active particles in the compartment containing the impermeant anions, which in turn increases the osmotic pressure, and water thereby enters that compartment. For cells, the Gibbs-Donnan effect would increase the number of osmotically active particles in the cell and result in cell swelling. However, the activity of the Na^+,K^+-ATPase counteracts the Gibbs-Donnan effect by actively extruding cations (three Na^+ ions are extruded, whereas two K^+ ions are brought into the cell). In addition, the K^+ gradient established by the Na^+,K^+-ATPase allows for

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.

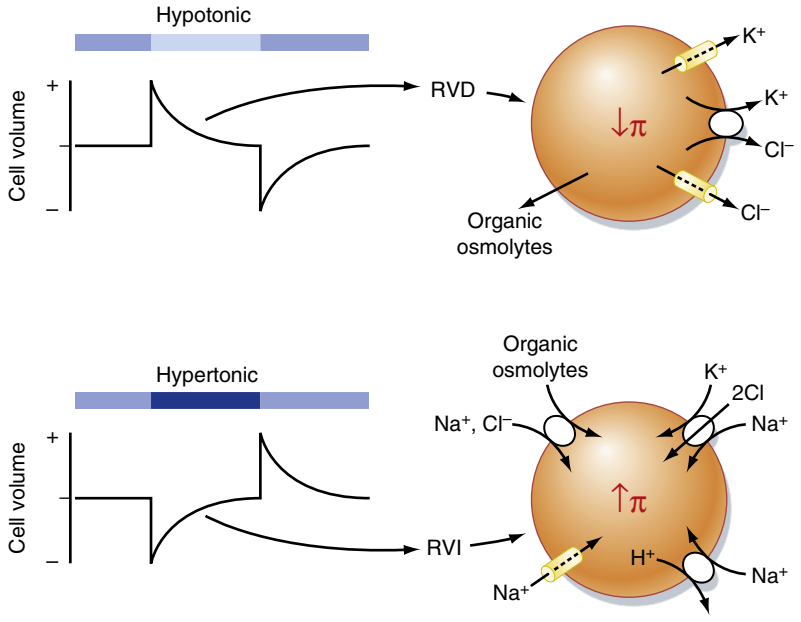
Nonisotonic Cell Volume Regulation

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 demyelination. This demyelination 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.

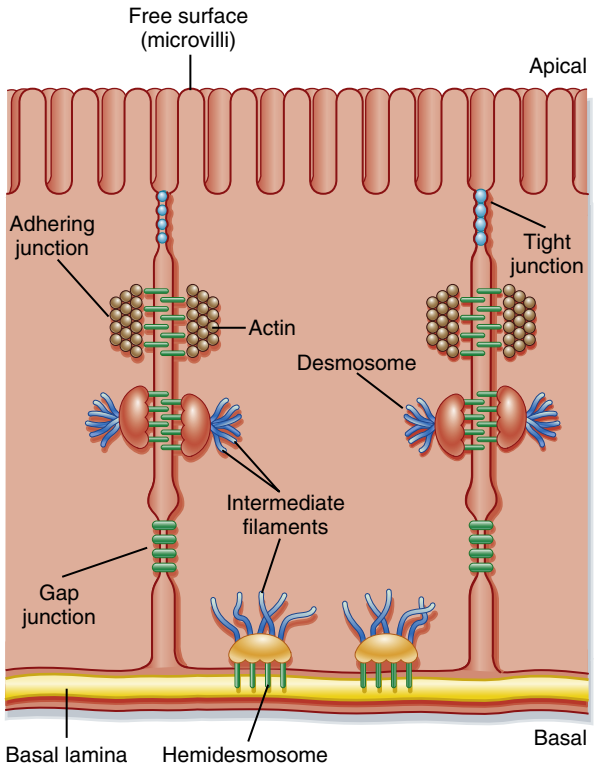
The regulatory volume increase response results in the rapid uptake of NaCl and a number of organic osmolytes. To increase cell volume there is an activation of the Na^+-H^+ antiporter (NHE-1), the $1Na^+,1K^+,2Cl^-$ symporter (NKCC-1), and a number of cation-selective channels, which together bring 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).

channel. The channel may be gated, and when it is open, it allows the movement of ions and small molecules between cells. Because of their low electrical resistance, they effectively couple electrically one cell to the adjacent cell.

The tight junction serves two main functions. It divides the cell into two membrane domains (apical and basolateral) and, in so doing, restricts the movement of membrane lipids and proteins between these two domains. This so-called fence function allows epithelial cells to carry out vectorial transport from one surface of the cell to the opposite surface by segregating membrane transporters to one or other of the membrane domains. They also serve as a pathway for the movement of water, ions, and small molecules across the epithelium. This pathway between the cells is referred to as the **paracellular pathway**, as opposed to the **transcellular pathway** through the cells.

AT THE CELLULAR LEVEL

Epithelial cell tight junctions (also called **zonula occludens**) are composed of several integral membrane proteins, including **occludins, claudins**, and several members of the immunoglobulin superfamily (e.g., the **junctional adhesion molecule [JAM]**). Occludins and claudins are transmembrane proteins that span the membrane of one cell and link to the extracellular portion of the same molecule in the adjacent cell. Cytoplasmic linker proteins (e.g., tight junction protein [ZO-1, ZO-2, and ZO-3]) then link the membrane spanning proteins to the cytoskeleton of the cell.

Of these junctional proteins, claudins appear to be important in determining the permeability characteristics of the tight junction, especially with regard to cations and anions. Certain claudins serve as barrier proteins that restrict the movement of ions through the tight junction, whereas others form a "pore" that facilitates the movement of ions through the junction. Thus the permeability characteristics of the tight junction of an epithelium are determined by the complement of claudins expressed by the cell. For example, the proximal tubule of the kidney is termed a "leaky" epithelium, in which water and solutes (e.g., Na^+) move through the junction. Claudin 4 and claudin 10 are expressed in the tight junction of proximal tubule cells. In contrast, the collecting duct of the kidney is considered a "tight" epithelium, with restricted movement of ions through the tight junction. Collecting duct cells express claudins 3, 4, 7, 8, 10, and 18.

The function of claudins can be regulated at several levels, including gene expression, post-translational modification, interactions with cytoplasmic scaffolding proteins, and interactions with other claudins in the same membrane (*cis*-interaction), as well as with claudins of adjacent cells (*trans*-interaction). The mineralocorticoid hormone aldosterone stimulates Na^+ reabsorption by distal segments of the renal nephron (see Chapters 34 and 35). In addition to the hormone's effect on Na^+ transporters in the cell, aldosterone also upregulates expression of claudin 8 in the tight junction. The increased expression of claudin 8 reduces the ability of Na^+ to permeate the tight junction, which then reduces the backward leak of Na^+ from the interstitium into the tubule lumen, thereby allowing more efficient Na^+ reabsorption by the epithelium.

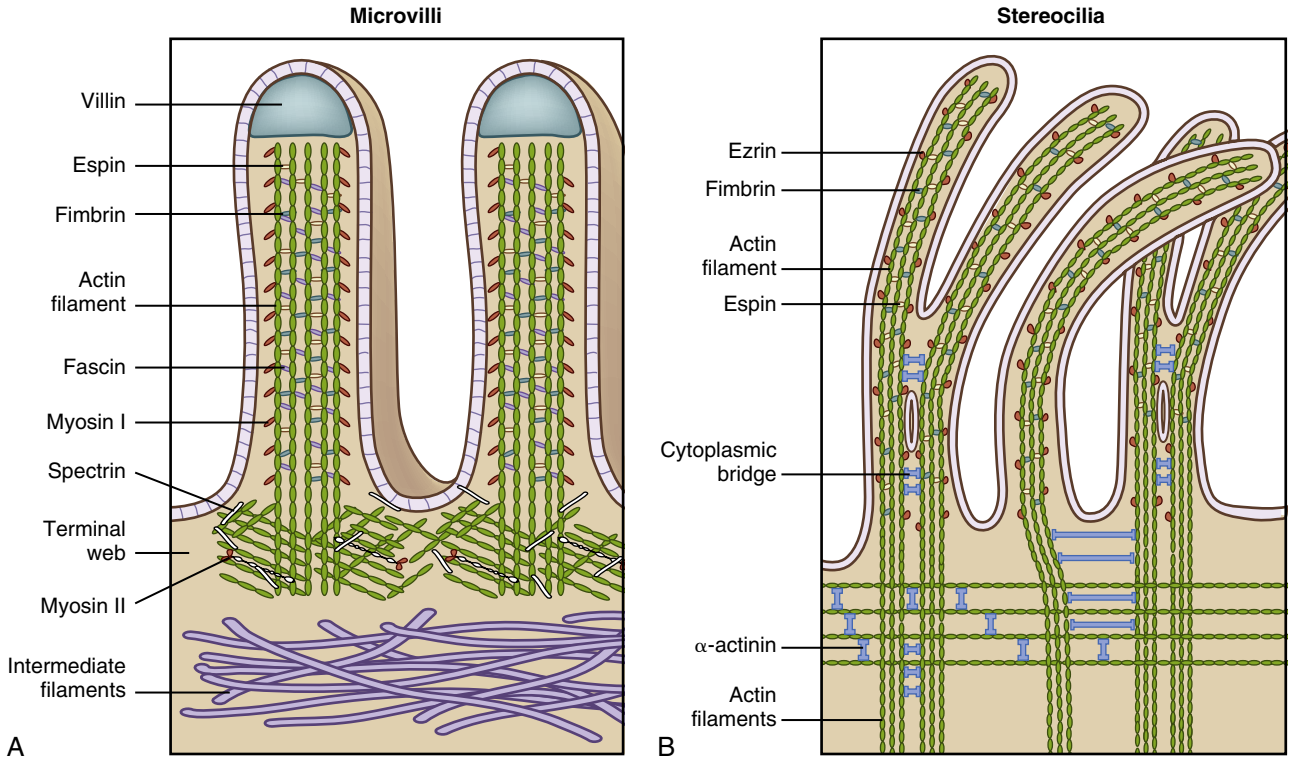
IN THE CLINIC

Mutations in the gene that codes for claudin 16 result in the autosomal recessive condition known as *familial hypomagnesemia, hypercalciuria, and nephrocalcinosis* (FHHNC). Claudin 16 is found in the tight junction of the thick ascending portion of Henle's loop in the kidneys and serves as a route for the paracellular reabsorption of Ca^{++} and Mg^{++} from the tubular fluid. Individuals with FHHNC lack functional copies of claudin 16, and reabsorption of these divalent ions is thus reduced, which leads to hypomagnesemia, hypercalciuria, and nephrocalcinosis.

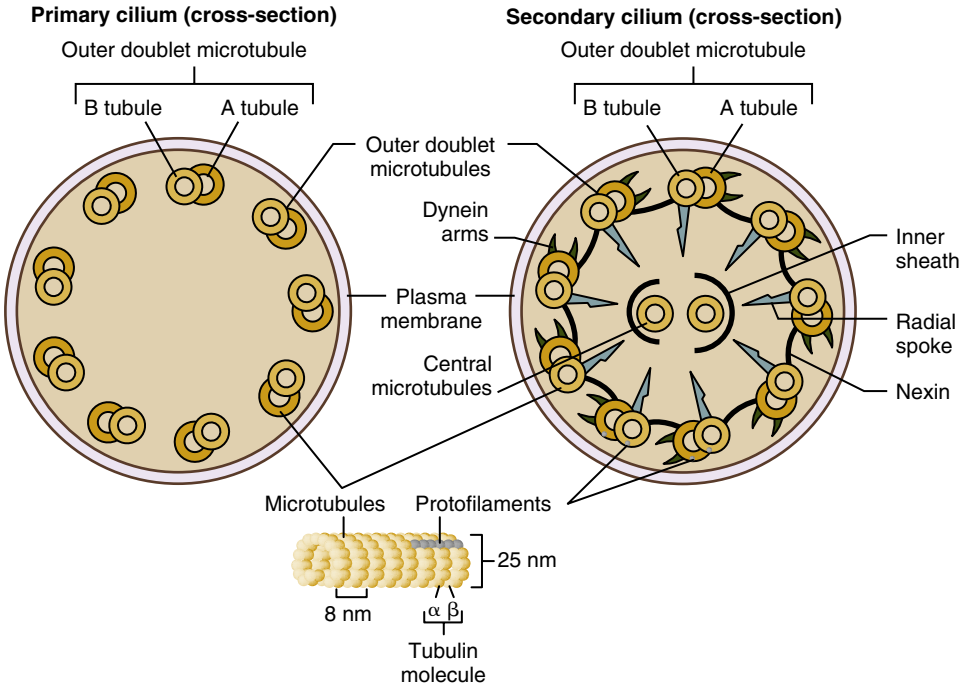
The apical surface of epithelial cells may have specific structural features. One such feature is **microvilli** (Fig. 2.9*A*). Microvilli are small (typically 1–3 μm in length), nonmotile projections of the apical plasma membrane that serve to increase surface area. They are commonly located on cells that must transport large quantities of ions, water, and molecules (e.g., epithelial cells lining the small intestine and cells of the renal proximal tubule). The core of the microvilli is composed of actin filaments and a number of accessory proteins. This actin core is connected to the cytoskeleton of the cell via the terminal web (a network of actin fibers at the base of the microvilli) and provides structural support for the microvilli. Another surface feature is stereocilia (see Fig. 2.9*B*). Stereocilia are long (up to 120 μm), nonmotile membrane projections that, like microvilli, increase the surface area of the apical membrane. They are found in the epididymis of the testis and in the "hair cells" of the inner ear. Their core also contains actin filaments and accessory proteins.

A third apical membrane feature is **cilia** (Fig. 2.10). Cilia may be either motile (called *secondary cilia*) or nonmotile (called *primary cilia*). The motile cilia contain a microtubule core arranged in a characteristic "9+2" pattern (nine pairs of microtubules around the circumference of the cilium, and one pair of microtubules in the center). Dynein is the molecular motor that drives the movement of the cilium. Motile cilia are characteristic features of the epithelial cells that line the respiratory tract. They pulsate in a synchronized manner and serve to transport mucus and inhaled particulates out of the lung, a process termed **mucociliary transport** (see Chapter 26). Nonmotile cilia serve as mechanoreceptors and are involved in determining left-right asymmetry of organs during embryological development, as well as sensing the flow rate of fluid in the nephron of the kidneys (see Chapter 33). Only a single nonmotile cilium is found in the apical membrane of cells. Nonmotile cilia have a microtubule core ("9+0" arrangement) and lack a motor protein.

As noted previously, the tight junction effectively divides the plasma membrane of an epithelial cell into two domains: an apical surface and a basolateral surface. The basolateral membrane of many epithelial cells is folded or invaginated. This is especially so for epithelial cells that have high transport rates. These invaginations serve to increase



• **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.)



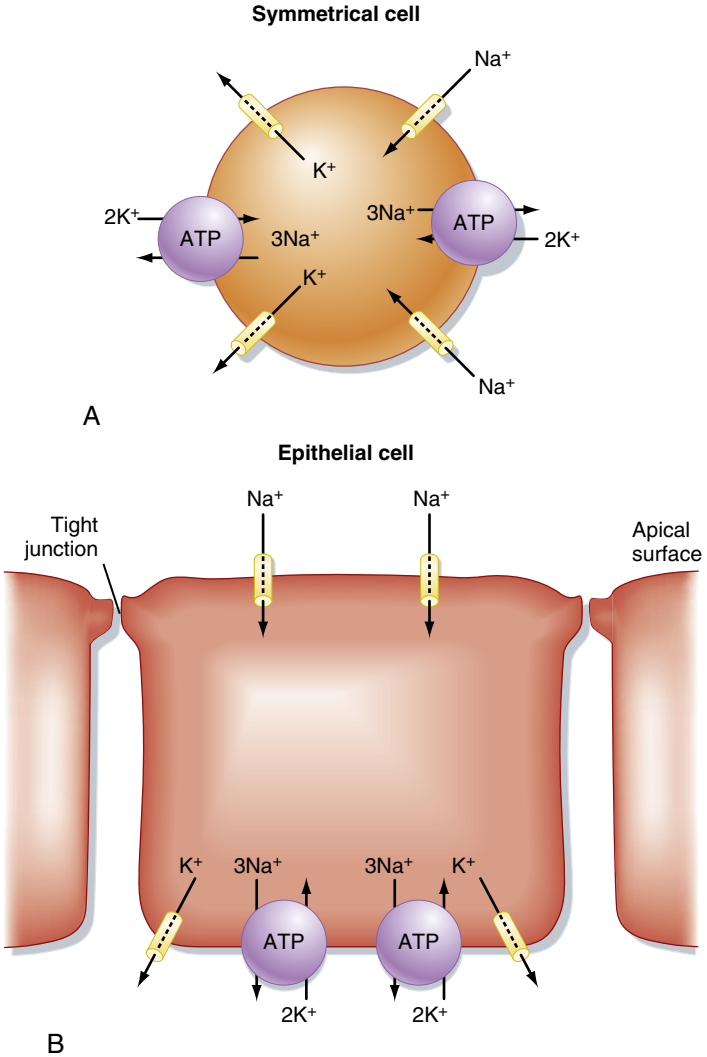
• **Fig. 2.10** Cilia are apical membrane specializations of some epithelial cells. Cilia are 5 to 10 μm in length and contain arrays of microtubules, as depicted in these cross-sectional diagrams. **Left**, The primary cilium has nine peripheral microtubule arrays. It is nonmotile and serves as a mechanoreceptor (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



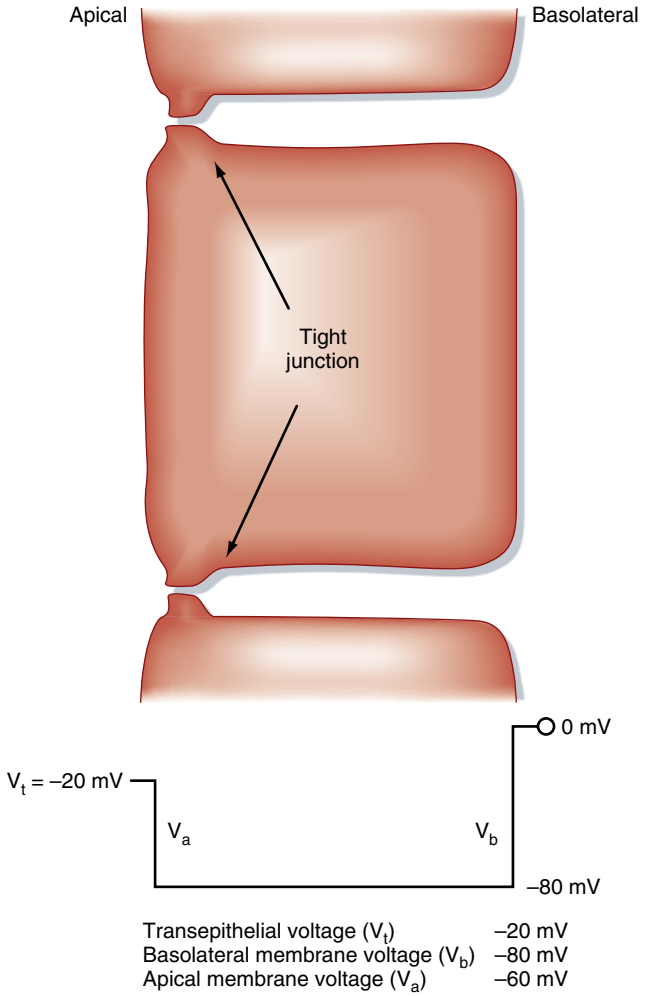
• **Fig. 2.11** In symmetrical cells (**A**; e.g., red blood cells), membrane transport proteins are distributed over the entire surface of the cell. Epithelial cells **(B)**, in contrast, are asymmetrical and target various membrane transport proteins to either the apical or the basolateral membrane. 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.

epithelial cells except the choroid plexus and retinal pigment epithelium,[h] the Na^+,K^+-ATPase channel is located in the basolateral membrane of the cell. Numerous K^+-selective channels are in epithelial cells and may be located in either membrane domain. Through the establishment of these chemical and voltage gradients, the transport of other ions and solutes can be driven (e.g., Na^+-glucose symporter, Na^+-H^+ antiporter, $1Na^+$,$1K^+$,$2Cl^-$ symporter, $1Na^+$-$3HCO_3^-$ symporter). The direction of transepithelial transport (reabsorption or secretion) depends simply on which membrane domain the transporters are located. Because of the dependence on the Na^+,K^+-ATPase, epithelial transport requires the expenditure of energy. Other ATP-dependent transporters, such as the H^+-ATPase, H^+,K^+-ATPase, and a host of ABC transporters—such as P-glycoprotein (PGP) and multidrug resistance-associated protein 2 (MRP2), which transport xenobiotics (drugs), and cystic fibrosis transmembrane conductance regulator (CFTR), which transports Cl^-—are involved in epithelial transport.

Solutes and water can be transported across an epithelium by traversing both the apical and basolateral membranes **(transcellular transport)** or by moving between the cells across the tight junction **(paracellular transport)**. Solute transport via the transcellular route is a two-step process, in which the solute molecule is transported across both the apical and basolateral membrane. Uptake into the cell, or transport out of the cell, may be either a passive or an active process. Typically, one of the steps is passive, and the other is active. For the example shown in Fig. 2.11*B*, the uptake of Na^+ into the cell across the apical membrane through the Na^+-selective channel is passive and driven by the electrochemical gradient for Na^+. The exit of Na^+ from the cell across the basolateral membrane is primary active transport via the Na^+,K^+-ATPase. Because a transepithelial gradient for Na^+ can be generated by this process (i.e., the [Na^+] in the apical compartment can be reduced below that of the basolateral compartment), the overall process of transepithelial Na^+ transport is said to be active. Any solute that is actively transported across an epithelium must be transported via the transcellular pathway.

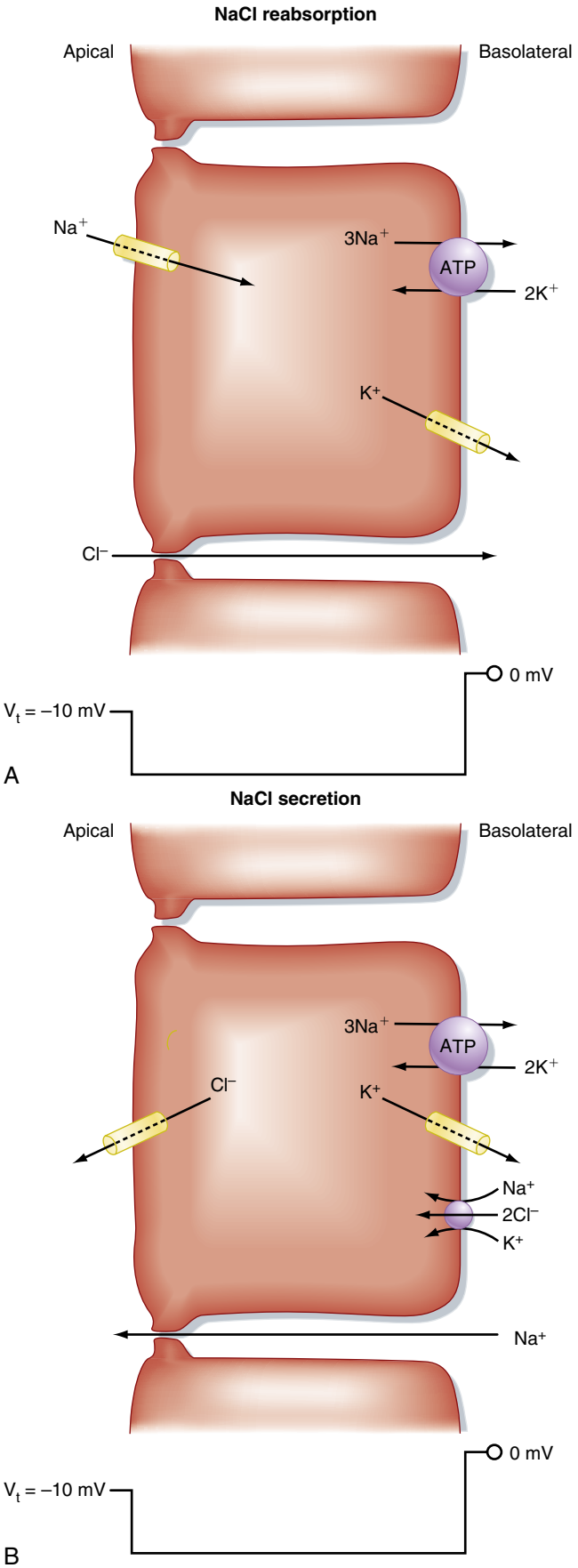
Depending on the epithelium, the paracellular pathway is an important route for transepithelial transport of solute and water. As noted, the permeability characteristics of the paracellular pathway are determined, in large part, by the specific claudins that are expressed by the cell. Thus the tight junction can have low permeability for solutes, water, or both, or it can have a high permeability. For epithelia in which there are high rates of transepithelial transport, the tight junctions typically have a high permeability (i.e., are leaky). Examples of such epithelia include the proximal tubule of the renal nephron and the early segments of the small intestine (e.g., duodenum and jejunum). If the epithelium must establish large transepithelial gradients for solutes, water, or both, the tight junctions typically have low permeability (i.e., are tight). Examples of this type of epithelium include the collecting duct of the renal nephron, the urinary bladder, and the terminal portion of the colon. In addition, the tight junction may be selective for certain solutes (e.g., cation versus anion selective).

All solute transport that occurs through the paracellular pathway is passive in nature. The two driving forces for this transport are the transepithelial concentration gradient for the solute and, if the solute is charged, the transepithelial voltage (Fig. 2.12). The transepithelial voltage may be oriented with the apical surface electrically negative in relation to the basolateral surface as shown in Fig. 2.12, or it may be oriented with the apical surface electrically positive in relation to the basolateral surface. The polarity and magnitude of the transepithelial voltage are determined by the specific membrane transporters in the apical and basolateral membranes, as well as by the permeability characteristics of the tight junction.



• **Fig. 2.12** The electrical profile across an epithelial cell. The magnitude of the membrane voltages, and the transepithelial voltage are determined by the various membrane transport proteins in the apical and basolateral membranes. The transepithelial voltage is equal to the sum of the apical and basolateral membrane voltages (see text for details).

[h]The choroid plexus is located in the ventricles of the brain and secretes the cerebrospinal fluid. The Na^+,K^+-ATPase is located in the apical membrane of these cells.



• **Fig. 2.13** The role of the paracellular pathway in epithelial transport. **A,** Na^+ transport through the cell generates a transepithelial voltage that then drives the passive movement of Cl^- through the tight junction. NaCl reabsorption results. **B**, Cl^- transport through the cell generates a transepithelial voltage that then drives the passive transport of Na^+ through the tight junction. NaCl secretion results.

It is important to recognize that transcellular transport processes set up the transepithelial chemical and voltage gradients, which in turn can drive paracellular transport. This is illustrated in Fig. 2.13 for an epithelium that reabsorbs NaCl and for an epithelium that secretes NaCl. In both epithelia, the transepithelial voltage is oriented with the apical surface electrically negative in relation to the basolateral surface. For the NaCl-reabsorbing epithelium, the transepithelial voltage is generated by the active, transcellular reabsorption of Na^+. This voltage in turn drives Cl^- reabsorption through the paracellular pathway. In contrast, for the NaCl-secreting epithelium, the transepithelial voltage is generated by the active transcellular secretion of Cl^-. Na^+ is then secreted passively via the paracellular pathway, driven by the negative transepithelial voltage.

Transepithelial Water Movement

Water movement across epithelia is passive and driven by transepithelial osmotic pressure gradients. Water movement can occur by a transcellular route involving aquaporins in both the apical and basolateral membranes.[i] In addition, water may also move through the paracellular pathway. In the NaCl-reabsorbing epithelium depicted in Fig. 2.13*A*, the reabsorption of NaCl from the apical compartment lowers the osmotic pressure in that compartment, whereas the addition of NaCl to the basolateral compartment raises the osmotic pressure in that compartment. As a result, a transepithelial osmotic pressure gradient is established that drives the movement of water from the apical to the basolateral compartment (i.e., reabsorption). The opposite occurs with NaCl-secreting epithelia (see Fig. 2.13*B*), in which the transepithelial secretion of NaCl establishes a transepithelial osmotic pressure gradient that drives water secretion.

In some epithelia (e.g., proximal tubule of the renal nephron), the movement of water across the epithelium via the paracellular pathway can drive the movement of additional solute. This process is termed **solvent drag** and reflects the fact that solutes dissolved in the water will traverse the tight junction with the water.

As is the case with the establishment of transepithelial concentration and voltage gradients, the establishment of transepithelial osmotic pressure gradients requires transcellular transport of solutes by the epithelial cells.

[i]Different aquaporin isoforms are often expressed in the apical and basolateral membrane. In addition, multiple isoforms may be expressed in one or more of the membrane domains.

Regulation of Epithelial Transport

Epithelial transport must be regulated to meet the homeostatic needs of the individual. Depending on the epithelium, this regulation involves neural or hormonal mechanisms, or both. For example, the enteric nervous system of the gastrointestinal tract regulates solute and water transport by the epithelial cells that line the intestine and colon. Similarly, the sympathetic nervous system regulates transport by the epithelial cells of the renal nephron. Aldosterone, a steroid hormone produced by the adrenal cortex (see Chapter 43), is an example of a hormone that stimulates NaCl transport by the epithelial cells of the colon, renal nephron, and sweat ducts. Epithelial cell transport can also be regulated by locally produced and locally acting substances, a process termed **paracrine regulation**. The stimulation of HCl secretion in the stomach by histamine is an example of this process. Cells that are located near the epithelial cells of the stomach release histamine, which acts on the HCl-secreting cells of the stomach (parietal cells) and stimulates them to secrete HCl.

When acted upon by a regulatory signal, the epithelial cell may respond in several different ways, including:

- Retrieval of transporters from the membrane, by endocytosis, or insertion of transporters into the membrane from an intracellular vesicular pool, by a process called *exocytosis*
- Change in activity of membrane transporters (e.g., ion channel gating)
- Synthesis of specific transporters, and their insertion into the membrane

The first two mechanisms can occur quite rapidly (seconds to minutes), but the synthesis of transporters takes additional time (minutes to days).

Key Concepts

- The body maintains steady-state balance for water and a number of important solutes. This occurs when input into the body equals output from the body. For each solute and water, there is a normal set point. Deviations from this set point are monitored (i.e., when input ≠ output), and effector mechanisms are activated that restore balance. This balance is achieved by adjustment of either intake or excretion of water and solutes. Thereafter, input and output are again equal to maintain balance.
- The Na^+,K^+-ATPase and K^+-selective channels are critically important in establishing and maintaining the intracellular composition, the membrane potential (V_m), and cell volume. Na^+,K^+-ATPase converts the energy in ATP into potential energy of ion gradients and the membrane potential. The ion and electrical gradients created by this process are then used to drive the transport of other ions and other molecules, especially by solute carriers (i.e., symporters and antiporters).
- Epithelial cells constitute the interface between the external world and the internal environment of the body. Vectorial transport of solutes and water across epithelia helps maintain steady-state balance for water and a number of important solutes. Because the external environment constantly changes, and because dietary intake of food and water is highly variable, transport by epithelia is regulated to meet the homeostatic needs of the individual.