1

Principles of Cell and Membrane Function

LEARNING OBJECTIVES

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

1. What organelles are found in a typical eukaryotic cell, and what is their function?
2. What is the composition of the plasma membrane?
3. What are the major classes of membrane transport proteins, and how do they transport biologically important molecules and ions across the plasma membrane?
4. What is the electrochemical gradient, and how is it used to determine whether the transport of a molecule or an ion across the plasma membrane is active or passive?
5. What are the driving forces for movement of water across cell membrane and the capillary wall?

In addition, the student should be able to define and understand the following properties of physiologically important solutions and fluids:

- Molarity and equivalence
- Osmotic pressure
- Osmolarity and osmolality
- Oncotic pressure
- Tonicity

The human body is composed of billions of cells. Although cells can perform different functions, they share certain common elements. This chapter provides an overview of some of these common elements with a focus on the transport of molecules and water into and out of the cell across its plasma membrane.

Overview of Eukaryotic Cells

Eukaryotic cells are distinguished from prokaryotic cells by the presence of a membrane-delimited nucleus. With a few exceptions (e.g., mature human red blood cells and cells within the lens of the eye), all cells within the human body contain a nucleus. The cell is therefore effectively divided into two compartments: the nucleus and the cytoplasm. The cytoplasm is an aqueous solution containing numerous organic molecules, ions, cytoskeletal elements, and a number of organelles. Many of the organelles are membrane-enclosed compartments that carry out specific cellular function. An idealized eukaryotic cell is depicted in Fig. 1.1, and the primary functions of some components and compartments of the cell are summarized in Table 1.1. Readers who desire a more in-depth presentation of this material are encouraged to consult one of the many textbooks on cell and molecular biology that are currently available.

The Plasma Membrane

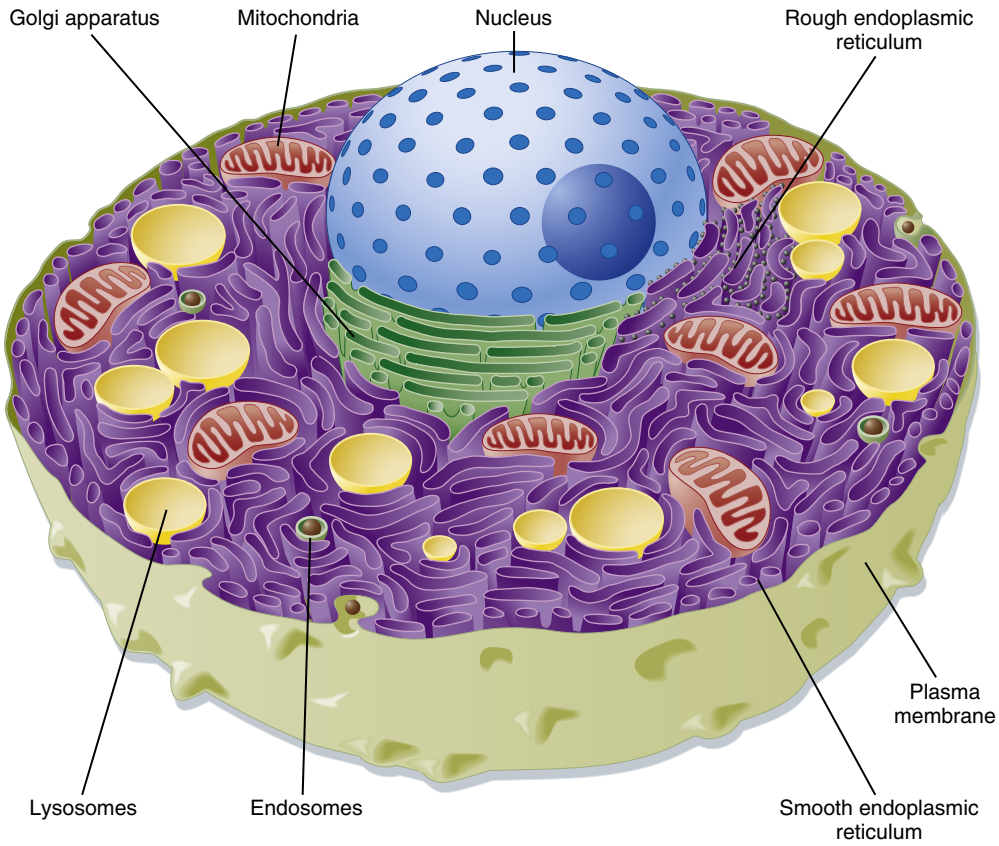
The cells within the body are surrounded by a plasma membrane that separates the intracellular contents from the extracellular environment. Because of the properties of this membrane and, in particular, the presence of specific membrane proteins, the plasma membrane is involved in a number of important cellular functions, including the following:

- Selective transport of molecules into and out of the cell. A function carried out by membrane transport proteins.
- Cell recognition through the use of cell surface antigens.
- Cell communication through neurotransmitter and hormone receptors and through signal transduction pathways.
- Tissue organization, such as temporary and permanent cell junctions, and interaction with the extracellular matrix, with the use of a variety of cell adhesion molecules.
- Membrane-dependent enzymatic activity.
- Determination of cell shape by linkage of the cytoskeleton to the plasma membrane.

In this chapter, the structure and function of the plasma membrane of eukaryotic cells are considered. More specifically, the chapter focuses on the transport of molecules and water across the plasma membrane. Only the principles of membrane transport are presented here. Additional details that relate to specific cells are presented in the various sections and chapters of this book.

Structure and Composition

The plasma membrane of eukaryotic cells consists of a 5-nm-thick lipid bilayer with associated proteins (Fig. 1.2). Some of the membrane-associated proteins are integrated into the lipid bilayer; others are more loosely attached to the inner or outer surfaces of the membrane, often by binding to the integral membrane proteins.



• **Fig. 1.1** Schematic drawing of a eukaryotic cell. The top portion of the cell is omitted to illustrate the nucleus and various intracellular organelles. See text for details.

TABLE 1.1 Primary Functions of Some Eukaryotic Cellular Components and Compartments

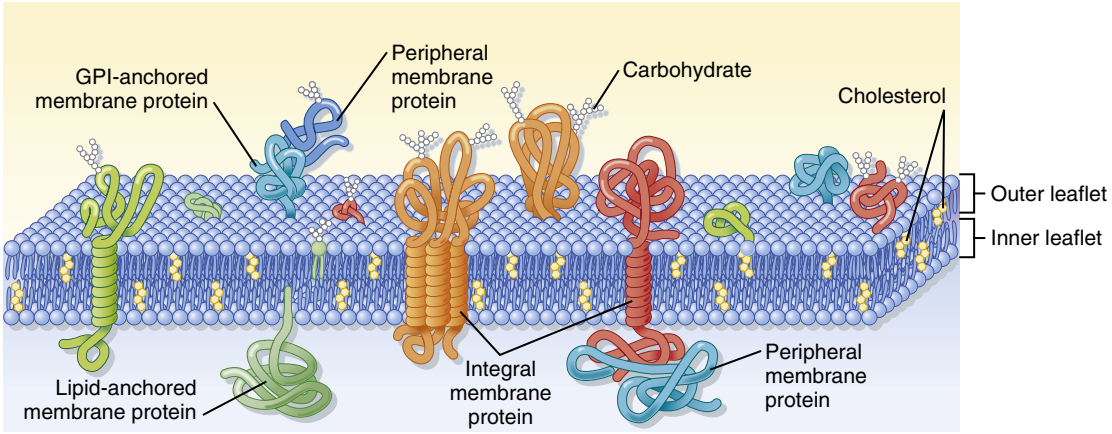
Component	Primary Function
Cytosol	Metabolism, protein synthesis (free ribosomes)
Cytoskeleton	Cell shape and movement, intracellular transport
Nucleus	Genome (22 autosomes and 2 sex chromosomes—in humans), DNA and RNA synthesis
Mitochondria	ATP synthesis by oxidative phosphorylation, Ca^{2+} storage
Smooth endoplasmic reticulum	Synthesis of lipids, Ca^{2+} storage
Free ribosomes	Translation of mRNA into cytosolic proteins
Rough endoplasmic reticulum	Translation of mRNA into membrane-associated proteins or for secretion out of the cell
Lysosome	Intracellular degradation
Endosome	Cellular uptake of cholesterol, removal of receptors from the plasma membrane, uptake of small molecules and water into the cell, internalization of large particles (e.g., bacteria, cell debris)
Golgi apparatus	Modification, sorting, and packaging of proteins and lipids for delivery to other organelles within the cell or for secretion out of the cell
Proteosome	Degradation of intracellular proteins
Peroxisome	Detoxification of substances

ATP, Adenosine triphosphate; *mRNA*, messenger RNA.

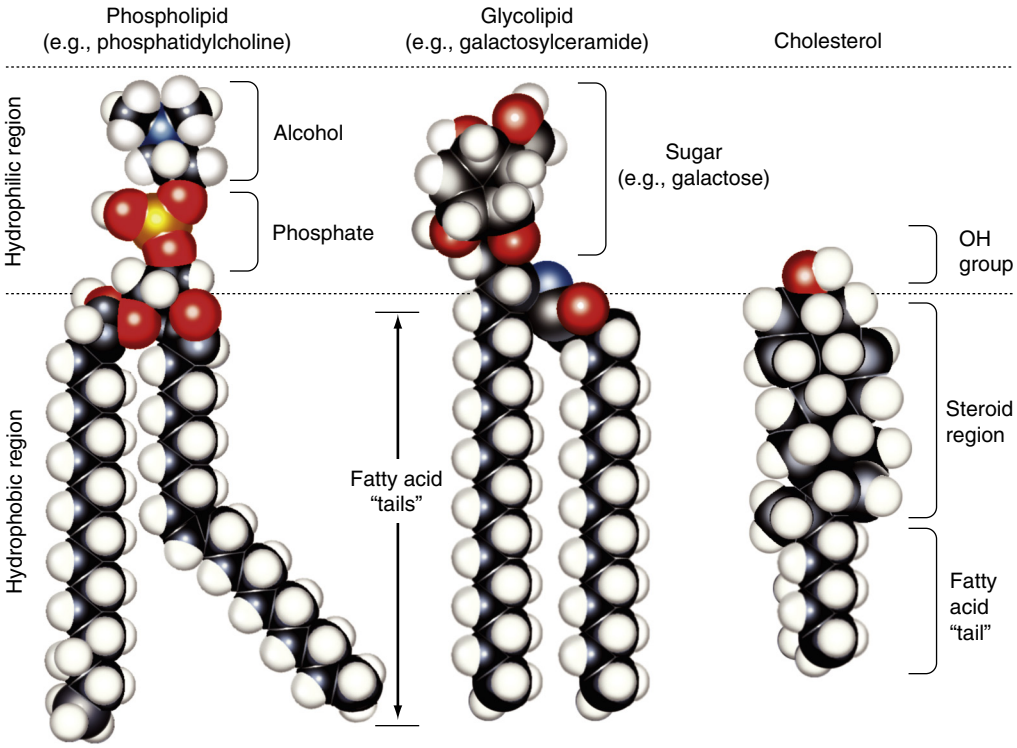
Membrane Lipids

The major lipids of the plasma membrane are **phospholipids** and **phosphoglycerides.** Phospholipids are amphipathic molecules that contain a charged (or polar) hydrophilic head and two (nonpolar) hydrophobic fatty acyl chains (Fig. 1.3). The amphipathic nature of the phospholipid molecule is critical for the formation of the bilayer: The hydrophobic fatty acyl chains form the core of the bilayer, and the polar head groups are exposed on the surface.

The majority of membrane phospholipids have a glycerol "backbone" to which are attached the fatty acyl chains, and an alcohol is linked to glycerol via a phosphate group. The common alcohols are choline, ethanolamine, serine, inositol, and glycerol. Another important phospholipid,



• **Fig. 1.2** Schematic diagram of the cell plasma membrane. Not shown are lipid rafts. See text for details. *GPI*, Glycosylphosphatidylinositol. (Modified from Cooper GM. *The Cell—A Molecular Approach.* 2nd ed. Washington, DC: Sinauer; 2000, Fig. 12.3.)



• **Fig. 1.3** Models of the major classes of plasma membrane lipids, depicting the hydrophilic and hydrophobic regions of the molecules. The molecules are arranged as they exist in one leaflet of the bilayer. The opposing leaflet is not shown. One of the fatty acyl chains in the phospholipid molecule is unsaturated. The presence of this double bond produces a "kink" in the fatty acyl chain, which prevents tight packing of membrane lipids and increases membrane fluidity. (Modified from Hansen JT, Koeppen BM. *Netter's Atlas of Human Physiology.* Teterboro, NJ: Icon Learning Systems; 2002.)

TABLE 1.2 Plasma Membrane Lipids

Phospholipid	Primary Location in Membrane
Phosphatidylcholine	Outer leaflet
Sphingomyelin	Outer leaflet
Phosphatidylethanolamine	Inner leaflet
Phosphatidylserine	Inner leaflet
Phosphatidylinositol*	Inner leaflet

*Involved in signal transduction.

sphingomyelin, has the amino alcohol sphingosine as its "backbone" instead of glycerol. Table 1.2 lists these common phospholipids. The fatty acyl chains are usually 14 to 20 carbons in length and may be saturated or unsaturated (i.e., contain one or more double bonds).

The phospholipid composition of the membrane varies among different cell types and even between the bilayer leaflets. For example, in the erythrocyte plasma membrane, phosphatidylcholine and sphingomyelin are found predominantly in the outer leaflet of the membrane, whereas phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol are found in the inner leaflet. As described in detail in Chapter 3, phosphatidylinositol plays an important role in signal transduction, and its location in the inner leaflet of the membrane facilitates this signaling role.

The sterol molecule **cholesterol** is also a critical component of the bilayer (see Fig. 1.3). It is found in both leaflets and serves to stabilize the membrane at normal body temperature (37°C). As much as 50% of the lipids found in the membrane can be cholesterol. A minor lipid component of the plasma membrane is **glycolipids.** These lipids, as their name indicates, consist of two fatty acyl chains linked to polar head groups that consist of carbohydrates (see Fig. 1.3). As discussed in the section on Membrane Proteins, one glycolipid, glycosylphosphatidylinositol (GPI), plays an important role in anchoring proteins to the outer leaflet of the membrane. Both cholesterol and glycolipids, like the phospholipids, are amphipathic, and they are oriented with their polar groups on the outer surface of the leaflet in which they are located. Their hydrophobic portion is thus located within the interior of the bilayer.

The lipid bilayer is not a static structure. The lipids and associated proteins can diffuse within the plane of the membrane. The fluidity of the membrane is determined by temperature and by its lipid composition. As temperature increases, the fluidity of the membrane increases. The presence of unsaturated fatty acyl chains in the phospholipids and glycolipids also increases membrane fluidity. If a fatty acyl chain is unsaturated, the presence of a double bond introduces a "kink" in the molecule (see Fig. 1.3). This kink prevents the molecule from associating closely with surrounding lipids, and, as a result, membrane fluidity is increased. Although the lipid bilayer is "fluid," movement of proteins in the membrane can be constrained or limited. For example, membrane proteins can be anchored to components of the intracellular cytoskeleton, which limits their movement. Membrane domains can also be isolated from one another. An important example of this can be found in epithelial tissues. Junctional complexes (e.g., tight junctions) separate the plasma membrane of epithelial cells into two domains: apical and basolateral (see Chapter 2). The targeted localization of membrane proteins into one or other of these domains allows epithelial cells to carry out vectorial transport of substances from one side of the epithelium to the opposite side. The ability to carry out vectorial transport is crucial for the functioning of several organ systems (e.g., the gastrointestinal tract and kidneys). In addition, some regions of the membrane contain lipids (e.g., sphingomyelin and cholesterol) that aggregate into what are called **lipid rafts.** These lipid rafts often have an association with specific proteins, which diffuse in the plane of the membrane as a discrete unit. Lipid rafts appear to serve a number of functions. One important function of these rafts is to segregate signaling molecules.

Membrane Proteins

As much as 50% of the plasma membrane is composed of proteins. These membrane proteins are classified as integral, lipid-anchored, or peripheral.

Integral membrane proteins are imbedded in the lipid bilayer, where hydrophobic amino acid residues are associated with the hydrophobic fatty acyl chains of the membrane lipids. Many integral membrane proteins span the bilayer; such proteins are termed **transmembrane proteins.** Transmembrane proteins have both hydrophobic and hydrophilic regions. The hydrophobic region, often in the form of an α helix, spans the membrane. Hydrophilic amino acid residues are then exposed to the aqueous environment on either side of the membrane. Transmembrane proteins may pass through the membrane multiple times.

AT THE CELLULAR LEVEL

There is a superfamily of membrane proteins that serve as receptors for many hormones, neurotransmitters, and numerous drugs. These receptors are coupled to heterotrimeric G proteins and are termed *G protein–coupled receptors* (see Chapter 3). These proteins span the membrane with seven α-helical domains. The binding site of each ligand is either on the extracellular portion of the protein (large ligands) or in the membrane-spanning portion (small ligands), whereas the cytoplasmic portion binds to the G protein. This superfamily of membrane proteins makes up the third largest family of genes in humans. Nearly half of all nonantibiotic prescription drugs are targeted toward G protein–coupled receptors.

A protein can also be attached to the membrane via **lipid anchors.** The protein is covalently attached to a lipid molecule, which is then embedded in one leaflet of the bilayer.

GPI anchors proteins to the outer leaflet of the membrane. Proteins can be attached to the inner leaflet via their amino-terminus by fatty acids (e.g., myristate or palmitate) or via their carboxyl-terminus by prenyl anchors (e.g., farnesyl or geranylgeranyl).

Peripheral proteins may be associated with the polar head groups of the membrane lipids, but they more commonly bind to integral or lipid-anchored proteins.

In many cells, some of the outer leaflet lipids, as well as many of the proteins exposed on the outer surface of the membrane, are glycosylated (i.e., have short chains of sugars, called *oligosaccharides,* attached to them). These glycolipids and glycoproteins are components of the "cell coat" called the glycocalyx. The glycocalyx establishes an extracellular microenvironment at the surface of the cell membrane. Depending on the cell, the glycocalyx may be involved in metabolism (e.g., in the gastrointestinal tract), cell recognition (e.g., cell surface antigens), and formation of cell-cell interactions (e.g., attachment of neutrophils to vascular endothelial cells).

Membrane Transport

Although plasma membrane proteins perform many important cellular functions, as noted previously, the remainder of this chapter focuses on one group of plasma membrane proteins: the membrane transport proteins, or transporters. It has been estimated that approximately 10% of human genes (≈2000) code for transporters. They are also targets for numerous drugs.

The normal function of cells requires the continuous movement of water and solutes into and out of the cell. The intracellular and extracellular fluids are composed primarily of H_2O, in which solutes (e.g., ions, glucose, amino acids) are dissolved. The plasma membrane, with its hydrophobic core, is an effective barrier to the movement of virtually all of these biologically important solutes. It also restricts the movement of water across the membrane. The presence of specific membrane transporters in the membrane is responsible for the movement of these solutes and water across the membrane.

Membrane Transport Proteins

Membrane transporters have been classified in several different ways. In this chapter, the transporters are divided into four general groups: water channels, ion channels, solute carriers, and adenosine triphosphate (ATP)–dependent transporters. Table 1.3 lists these groups of membrane transporters, their modes of transport, and estimates of the rates at which they transport molecules or ions across the membrane.

Water Channels

Water channels, or **aquaporins (AQPs)**, are the main routes for water movement into and out of the cell. Although water can cross the plasma membrane through other membrane transporters (e.g., glucose transporter, urea transporter), these routes for water movement across the plasma membrane are secondary to the AQPs. The AQPs are widely distributed throughout the body (e.g., the brain, lungs, kidneys, salivary glands, gastrointestinal tract, and liver). Cells express different AQP isoforms, and some cells even express multiple isoforms. For example, cells in the collecting ducts of the kidneys express AQP3 and AQP4 in their basolateral membrane and AQP2 in their apical membrane. Moreover, the abundance of AQP2 in the apical membrane is regulated by antidiuretic hormone (also called arginine vasopressin), which is crucial for the ability of the kidneys to concentrate the urine (see Chapter 35).

Although all AQP isoforms allow the passive movement of H_2O across the membrane, some isoforms also provide a pathway for other molecules (e.g., glycerol, urea, mannitol, purines, pyrimidines, CO_2, and NH_3) to cross the membrane. Because glycerol was one of the first molecules identified as crossing the membrane via some AQPs, this group of AQPs is collectively called *aquaglyceroporins* (see also Chapter 34). Regulation of the amount of H_2O that can enter or leave the cell via AQPs occurs primarily by altering the number of AQPs in the membrane.

TABLE 1.3 Major Classes of Plasma Membrane Transporters

Class	Transport Mode	Transport Rate
Pore[a]	Open (not gated)	Up to 10^9 molecules/sec
Channel	Gated	10^6–10^8 molecules/sec
Solute carrier	Cycle	10^2–10^4 molecules/sec
ATP-dependent	Cycle	10^2–10^4 molecules/sec

[a]Examples include porins that are found in the outer membrane of mitochondria, and water channels (i.e., aquaporins) that function as a pore.

ATP, Adenosine triphosphate.

AT THE CELLULAR LEVEL

Each AQP molecule consists of six membrane-spanning domains and a central water-transporting pore. Four AQP monomers assemble to form a homotetramer in the plasma membrane, with each monomer functioning as a water channel.

Ion Channels

Ion channels are found in all cells and are especially important for the function of excitable cells (e.g., neurons and muscle cells). Ion channels are classified by their selectivity, conductance, and mechanism of channel gating (i.e., opening and closing). *Selectivity* is defined as the nature of the ions that pass through the channel. At one extreme, ion channels can be highly selective, in that they allow only a specific ion through. At the other extreme, they may be nonselective, allowing all or a group of cations or anions

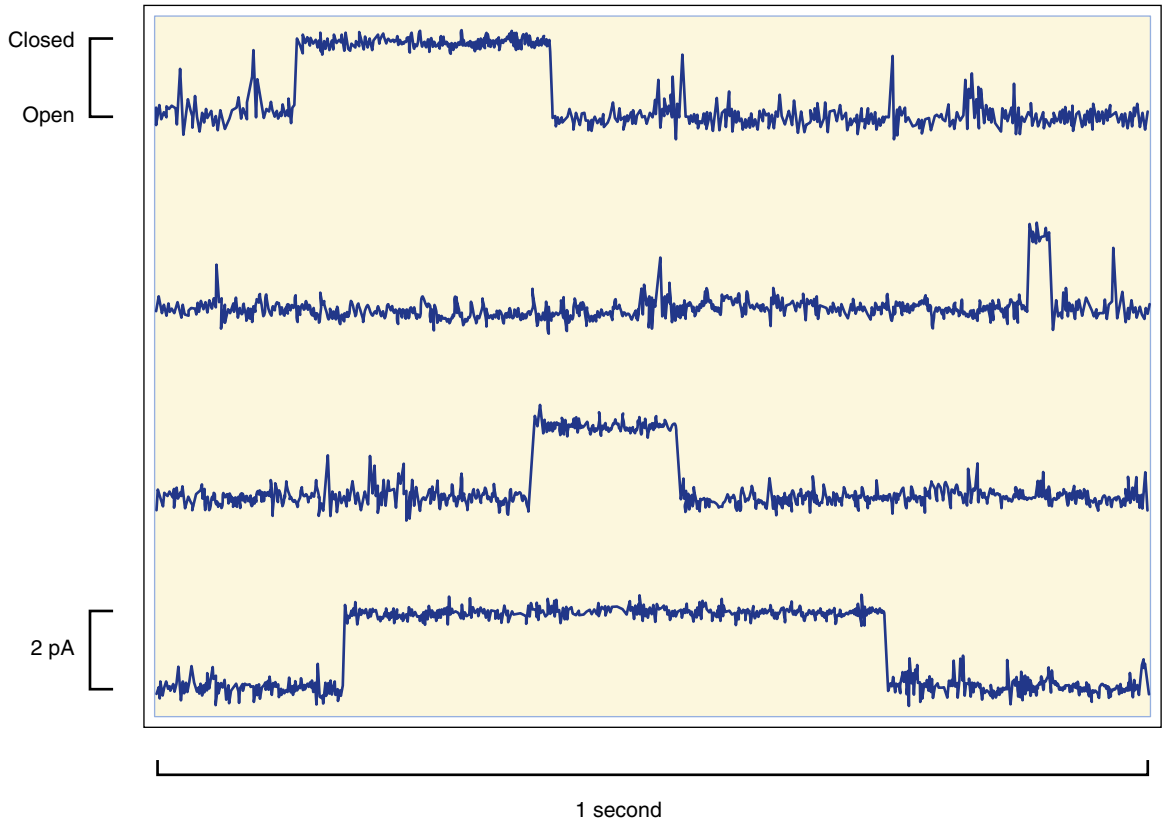
through. *Channel conductance* refers to the number of ions that pass through the channel and is typically expressed in picosiemens (pS). The range of conductance is considerable: Some channels have a conductance of only 1 to 2 pS, whereas others have a conductance of more than 100 pS. For some channels, the conductance varies, depending on the direction in which the ion is moving. For example, if the channel has a larger conductance when ions are moving into the cell than when they are moving out of the cell, the channel is said to be an *inward rectifier.* Moreover, ion channels fluctuate between an open state and a closed state, a process called *gating* (Fig. 1.4). Factors that can control gating include membrane voltage, extracellular agonists or antagonists (e.g., acetylcholine is an extracellular agonist that controls the gating of a cation-selective channel in the motor end plate of skeletal muscle cells; see Chapter 6), intracellular messengers (e.g., Ca^{++}, ATP, cyclic guanosine monophosphate), and mechanical stretch of the plasma membrane. Ion channels can be regulated by a change in the number of channels in the membrane or by gating of the channels.

Solute Carriers

Solute carriers (denoted *SLCs* by the HUGO Gene Nomenclature Committee) represent a large group of membrane transporters categorized into more than 50 families; almost 400 specific transporters have been identified to date. These carriers can be divided into three groups according to their mode of transport. One group, **uniporters** (or **facilitated transporters**), transports a single molecule across the membrane. The transporter that brings glucose into the cell (glucose transporter 1 [GLUT-1], or SLC2A1) is an important member of this group. The second group, **symporters** (or **cotransporters**), couples the movement of two or more molecules/ions across the membrane. As the name implies, the molecules/ions are transported in the same direction. The Na^+,K^+,$2Cl^-$ symporter found in the kidney (NKCC2, or SLC12A1), which is crucial for diluting and concentrating the urine (see Chapter 34), is a member of this group. The third group, **antiporters** (or **exchange transporters**), also couples the movement of two or more molecules/ions across the membrane; in this case, however, the molecules/ions are transported in opposite directions. The Na^+-H^+ antiporter is a member of this group of solute carriers. One isoform of this antiporter (NHE-1, or SLC9A1) is found in all cells and plays an important role in regulating intracellular pH.

Adenosine Triphosphate–Dependent Transporters

The ATP-dependent transporters, as their name implies, use the energy in ATP to drive the movement of molecules/ions across the membrane. There are two groups of ATP-dependent transporters: the **ATPase ion transporters** and the **ATP-binding cassette (ABC) transporters.** The ATPase ion



• **Fig. 1.4** Recording of current flow through a single ion channel. The channel spontaneously fluctuates between an open state and a closed state. The amplitude of the current is approximately 2 pA (2×10^{-12} amps); that is, 12.5 million ions/second cross the membrane.

transporters are subdivided into P-type ATPases and V-type ATPases.[a] The P-type ATPases are phosphorylated during the transport cycle. Na^+,K^+-ATPase is an important example of a P-type ATPase. With the hydrolysis of each ATP molecule, it transports three Na^+ ions out of the cell and two K^+ ions into the cell. Na^+,K^+-ATPase is present in all cells and plays a critical role in establishing cellular ion and electrical gradients, as well as maintaining cell volume (see Chapter 2).

AT THE CELLULAR LEVEL

Na^+,K^+-ATPase (also called the *Na^+,K^+-pump* or just the *Na^+-pump*) is found in all cells and is responsible for establishing the gradients of Na^+ and K^+ across the plasma membrane. These gradients in turn provide energy for several essential cell functions (see Chapter 2). Na^+,K^+-ATPase is composed of three subunits (α, β, and γ), and the protein exists in the membrane with a stoichiometric composition of 1α, 1β, 1γ. The α subunit contains binding sites for Na^+,K^+ and ATP. It is also the subunit that binds cardiac glycosides (e.g., ouabain), which specifically inhibit the enzyme. It has a transmembrane domain and three intracellular domains: phosphorylation (P-domain), nucleotide binding (N-domain), and actuator (A-domain). Although the α subunit is the functional subunit of the enzyme (i.e., it hydrolyzes ATP, binds Na^+ and K^+, and translocates them across the membrane), it cannot function without the β subunit. The β subunit is responsible for targeting the α subunit to the membrane and also appears to modulate the kinetic properties of the Na^+,K^+-ATPase. The α and β subunits can carry out Na^+ and K^+ transport in the absence of the γ subunit. However, like the β subunit, the γ subunit appears to play a regulatory role by modulating Na^+ affinity and the kinetics of the enzyme.

V-type H^+-ATPases are found in the membranes of several intracellular organelles (e.g., endosomes, lysosomes); as a result, they are also referred to as *vacuolar H^+-ATPases.* The H^+-ATPase in the plasma membrane plays an important role in urinary acidification (see Chapter 37).

ABC transporters represent a large group of membrane transporters. They are found in both prokaryotic and eukaryotic cells, and they have amino acid domains that bind ATP (i.e., ABC domains). Seven subgroups of ABC transporters are found in humans and more than 40 specific transporters have been identified to date. They transport a diverse group of molecules/ions, including Cl^-, cholesterol, bile acids, drugs, iron, and organic anions.

Because biologically important molecules enter and leave cells through membrane transporters, membrane transport is specific and regulated. Although some membrane transporters are ubiquitously expressed in all cells (e.g., Na^+,K^+-ATPase), the expression of many other transporters is limited to specific cell types. This specificity of expression tailors the function of the cell to the organ system in which it is located (e.g., the sodium-glucose–linked transporters SGLT-1 and SGLT-2 in the epithelial cells of the intestines and renal proximal tubules). In addition, the amount of a molecule being transported across the membrane can be regulated. Such regulation can take place through altering the number of transporters in the membrane or altering the rate or kinetics of individual transporters (e.g., the time an ion channel stays in the open versus closed state), or both.

[a]Another type of ATPases, F-type ATPases, is found in the mitochondria, and they are responsible for ATP synthesis. They are not considered in this chapter.

IN THE CLINIC

Cystic fibrosis is an autosomal recessive disease characterized by chronic lung infections, pancreatic insufficiency, and infertility in boys and men. Death usually occurs because of respiratory failure. It is most prevalent in white people and is the most common lethal genetic disease in this population, occurring in 1 per 3000 live births. It is a result of mutations in a gene on chromosome 7 that codes for an ABC transporter. To date, more than 2000 mutations in the gene have been identified. The most common mutation is a deletion of a phenylalanine at position 508 (Phe508del). Because of this deletion, degradation of the protein by the endoplasmic reticulum in enhanced, and, as a result, the transporter does not reach the plasma membrane. This transporter, called **cystic fibrosis transmembrane conductance regulator (CFTR),** normally functions as a Cl^- and HCO_3^- channel and also regulates other membrane transporters (e.g., the epithelial Na^+ channel [ENaC]). Thus in individuals with cystic fibrosis, epithelial transport is defective, which is responsible for the pathophysiologic process. For example, in patients not affected by cystic fibrosis, the epithelial cells that line the airway of the lung are covered with a layer of mucus that entraps inhaled particulates and bacteria. Cilia on the epithelial cells then transport the entrapped material out of the lung, a process termed *mucociliary transport* (see Chapter 26 for more details). In patients with cystic fibrosis, the inability to secrete Cl^-, Na^+, HCO_3^-, and H_2O results in an increase in the viscosity of the airway surface mucus; thus the cilia cannot transport the entrapped bacteria and other pathogens out of the lung. This in turn leads to recurrent and chronic lung infections. The inflammatory process that accompanies these infections ultimately destroys the lung tissue, causing respiratory failure and death. In 2019, the U.S. Food and Drug Administration approved elexacaftor/ivacaftor/tezacaftor (Trikafta), a drug that increases the amount of Phe508del CFTR in the plasma membrane. Trikafta, approved for patients with at least one Phe508del mutation (~90% of the cystic fibrosis population), reduces clinical exacerbations and substantially improves lung function.

Vesicular Transport

Solute and water can be brought into the cell through a process of **endocytosis** and released from the cell through the process of **exocytosis.** Endocytosis is the process whereby a piece of the plasma membrane pinches off and is internalized into the cell interior, and exocytosis is the process whereby vesicles inside the cell fuse with the plasma membrane. In both of these processes, the integrity of the plasma membrane is maintained, and the vesicles allow for the transfer of the contents among cellular compartments. In some cells (e.g., the epithelial cells lining the gastrointestinal tract), endocytosis across one membrane of the cell is

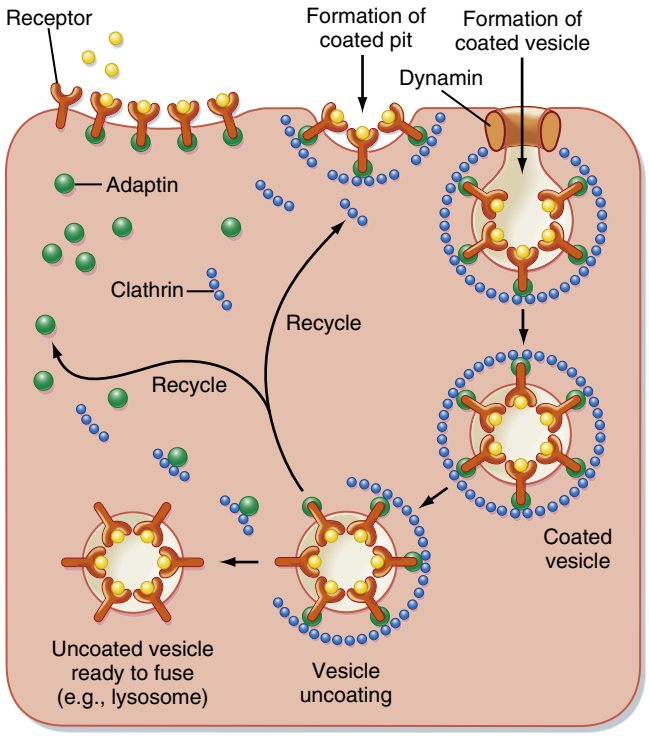
AT THE CELLULAR LEVEL

Proteins within the plasma membrane of cells are constantly being removed and replaced with newly synthesized proteins. One mechanism by which membrane proteins are "tagged" for replacement is by the attachment of ubiquitin to the cytoplasmic portion of the protein. Ubiquitin is a 76–amino acid protein that is covalently attached to the membrane protein (usually to lysine) by a class of enzymes called *ubiquitin protein ligases.* One important group of these ligases is the developmentally downregulated protein 4 (Nedd4)/Nedd4-like family. Once a membrane protein is ubiquitinated, it undergoes endocytosis (see below) and is degraded either by lysosomes or by the proteosome. Cells also contain deubiquitinating enzymes (DUBs). Thus the amount of time a protein stays in the plasma membrane depends on the rate that ubiquitin groups are added by the ligases versus the rate that they are removed by the DUBs. For example, Na^+ reabsorption by the collecting ducts of the kidneys is stimulated by the adrenal hormone aldosterone (see Chapters 34 and 35). One of the actions of aldosterone is to inhibit Nedd4-2. This prevents ubiquitination of ENaC in the apical membrane of epithelial cells. Thus the channels are retained for a longer period of time in the membrane, and as a result, more Na^+ enters the cell and is thereby reabsorbed.

followed by exocytosis across the opposite membrane. This allows the transport of substances inside the vesicles across the epithelium, a process termed **transcytosis.**

Endocytosis occurs by three mechanisms. The first is **pinocytosis,** which consists of the nonspecific uptake of small molecules and water into the cell. Pinocytosis is a prominent feature of the endothelial cells that line capillaries and is responsible for a portion of the fluid exchange that occurs across these vessels. The second form of endocytosis, **phagocytosis,** allows for the cellular internalization of large particles (e.g., bacteria, cell debris). This process is an important characteristic of cells in the immune system (e.g., neutrophils and macrophages). Often, but not always, phagocytosis is a receptor-mediated process. For example, macrophages have receptors on their surface that bind the Fc portion of immunoglobulins. When bacteria invade the body, they are often coated with antibody, a process called opsonization. These bacteria then attach to the membrane of macrophages via the fragment crystallizable (Fc) portion of the immunoglobulin, undergo phagocytosis, and are destroyed inside the cell. The third mechanism of endocytosis is **receptor-mediated endocytosis,** which allows the uptake of specific molecules into the cell. In this form of endocytosis, molecules bind to receptors on the surface of the cell. Endocytosis involves a number of accessory proteins including adaptin, clathrin, and the GTPase dynamin (Fig. 1.5).

Exocytosis can be either constitutive or regulated. Constitutive exocytosis occurs, for example, in plasma cells that are secreting immunoglobulin or in fibroblasts secreting collagen. Regulated secretion occurs in endocrine cells, neurons, and exocrine glandular cells (e.g., pancreatic acinar cells). In these cells, the secretory product (e.g., hormone, neurotransmitter, or digestive enzyme), after synthesis and processing in the rough endoplasmic reticulum and Golgi



• **Fig. 1.5** Receptor-mediated endocytosis. Receptors on the surface of the cell bind the ligand. A clathrin-coated pit is formed with adaptin linking the receptor molecules to clathrin. Dynamin, a guanosine triphosphatase (GTPase), assists in separation of the endocytic vesicle from the membrane. Once inside the cell, the clathrin and adaptin molecules dissociate and are recycled. The uncoated vesicle is then ready to fuse with other organelles in the cell (e.g., lysosomes). (Adapted from Ross MH, Pawlina W. *Histology.* 5th ed. Baltimore: Lippincott Williams & Wilkins; 2006.)

apparatus, is stored in the cytoplasm in secretory granules until an appropriate signal for secretion is received. These signals may be hormonal or neural. Once the cell receives

IN THE CLINIC

Cholesterol is an important component of cells (e.g., it is a key component of membranes). However, most cells are unable to synthesize cholesterol and therefore must obtain it from the blood. Normally, cholesterol is ingested in the diet, and it is transported through the blood in association with lipoproteins. Low-density lipoproteins (LDLs) in the blood carry cholesterol to cells, where they bind to LDL receptors in the plasma membrane. After the receptors bind LDL, they collect into "coated pits" and undergo endocytosis as clathrin-coated vesicles. Once inside the cell, the endosomes release LDL and then recycle the LDL receptors back to the cell surface. Inside the cell, LDL is then degraded in lysosomes, and the cholesterol is made available to the cell. Defects in the LDL receptor prevent cellular uptake of LDL. Individuals with this defect have elevated levels of blood LDL, often called "bad cholesterol," because it is associated with the development of cholesterol-containing plaques in the smooth muscle layer of arteries. This process, atherosclerosis, is associated with an increased risk for heart attacks as a result of occlusion of the coronary arteries.

the appropriate stimulus, the secretory vesicle fuses with the plasma membrane and releases its contents into the extracellular fluid. Fusion of the vesicle with the membrane is mediated by a number of accessory proteins. One important group is the SNARE (**s**oluble *N*-ethylmaleimide sensitive fusion protein [**N**SF] **a**ttachment protein **re**ceptors) proteins. These membrane proteins help target the secretory vesicle to the plasma membrane. The process of secretion is usually triggered by an increase in the concentration of intracellular Ca^{++} ($[Ca^{++}]$). However, two notable exceptions to this general rule exist: (1) Renin secretion by the juxtaglomerular cells of the kidney occurs with a decrease in intracellular Ca^{++} (see Chapters 34 and 35), as does (2) the secretion of parathyroid hormone by the parathyroid gland (see Chapter 40).

Basic Principles of Solute and Water Transport

As already noted, the plasma membrane, with its hydrophobic core, is an effective barrier to the movement of virtually all biologically important molecules into or out of the cell. Thus membrane transport proteins provide the pathway that allows transport to occur into and out of cells. However, the presence of a pathway is not sufficient for transport to occur; an appropriate driving force is also required. In this section, the basic principles of diffusion, active and passive transport, and osmosis are presented. These topics are discussed in greater depth, as appropriate, in the other sections of the book.

Diffusion

Diffusion is the process by which molecules move spontaneously from an area of high concentration to one of low concentration. Thus wherever a concentration gradient exists, diffusion of molecules from the region of high concentration to the region of low concentration dissipates the gradient (as discussed later, the establishment of concentration gradients for molecules requires the expenditure of energy). Diffusion is a random process driven by the thermal motion of the molecules. **Fick's first law of diffusion** quantifies the rate at which a molecule diffuses from point A to point B:

(Equation 1.1)

$$J = -DA\frac{\Delta C}{\Delta X}$$

where

J = the flux or rate of diffusion per unit time
D = the diffusion coefficient
A = the area across which the diffusion is occurring
ΔC = the concentration difference between points A and B
ΔX = the distance along which diffusion is occurring

The diffusion coefficient takes into account the thermal energy of the molecule, its size, and the viscosity of the medium through which diffusion is taking place. For spherical molecules, D is approximated by the **Stokes-Einstein equation:**

(Equation 1.2)

$$D = \frac{kT}{6\pi r\eta}$$

where

k = Boltzmann's constant
T = temperature in degrees Kelvin
r = radius of the molecule
η = viscosity of the medium

According to Eqs. 1.1 and 1.2, the rate of diffusion will be faster for small molecules than for large molecules. In addition, diffusion rates are high at elevated temperatures, in the presence of large concentration gradients, and when diffusion occurs in a low-viscosity medium. With all other variables held constant, the rate of diffusion is linearly related to the concentration gradient.

Fick's equation can also be applied to the diffusion of molecules across a barrier, such as a lipid bilayer. When applied to the diffusion of a molecule across a bilayer, the diffusion coefficient (D) incorporates the properties of the bilayer and especially the ability of the molecule to diffuse through the bilayer. To quantify the interaction of the molecule with the bilayer, the term *partition coefficient* (β) is used. For a molecule that "dissolves" equally in the fluid bathing the lipid bilayer (e.g., water) and in the lipid bilayer, $\beta = 1$. If the molecule dissolves more easily in the lipid bilayer, $\beta > 1$; and if it dissolves less easily in the lipid bilayer, $\beta < 1$. For a simple lipid bilayer, the more lipid soluble the molecule is, the larger the partition coefficient is, and thus the diffusion coefficient—therefore the rate of diffusion of the molecule across the bilayer—is greater. In this situation, ΔC represents the concentration difference across the membrane, A is the membrane area, and ΔX is the thickness of the membrane.

Another useful equation for quantitating the diffusion of molecules across the plasma membrane (or any membrane) is as follows:

(Equation 1.3)

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

where

J = the flux or rate of diffusion across the membrane
P = the permeability coefficient
C_i = the concentration of the molecule inside the cell
C_o = the concentration of the molecule outside the cell

This equation is derived from Fick's equation (Eq. 1.1). P incorporates D, ΔX, A, and the partition coefficient (β). P is expressed in units of velocity (e.g., centimeters per second), and C the units of moles/cm^3. Thus the units of flux are moles per square centimeter per second (mol/cm^2/sec). Values for P can be obtained experimentally for any molecule and bilayer.

As noted, the phospholipid portion of the plasma membrane represents an effective barrier to many biologically important molecules. Consequently, diffusion through the lipid phase of the plasma membrane is not an efficient process for movement of these molecules across the membrane. It has been estimated that for a cell 20 μm in diameter, with a

plasma membrane composed only of phospholipids, dissipation of a urea gradient imposed across the membrane would take approximately 8 minutes. Similar gradients for glucose and amino acids would take approximately 14 hours to dissipate, whereas ion gradients would take years to dissipate.

As noted previously, the vast majority of biologically important molecules cross cell membranes via specific membrane transporters, rather than by diffusing through the lipid portion of the membrane. Nevertheless, Eq. 1.3 can be and has been used to quantitate the diffusion of molecules across many biological membranes. When this is done, the value of the permeability coefficient (P) reflects the properties of the pathway (e.g., membrane transporter or, in some cases, multiple transporters) that the molecule uses to cross the membrane.

Despite the limitations of using diffusion to describe and understand the transport of molecules across cell membranes, it is also important for understanding gas exchange in the lungs (see Chapter 24), the movement of molecules through the cytoplasm of the cell, and the movement of molecules between cells in the extracellular fluid. For example, one of the physiological responses of skeletal muscle to exercise is the recruitment or opening of capillaries that are not perfused at rest. This opening of previously closed capillaries increases capillary density and thereby reduces the diffusion distance between the capillary and the muscle fiber so that oxygen and cellular fuels (e.g., fatty acids and glucose) can be delivered more quickly to the contracting muscle fiber. In resting muscle, the average distance of a muscle fiber from a capillary is estimated to be 40 μm. However, with exercise, this distance decreases to 20 μm or less.

Electrochemical Gradient

The **electrochemical gradient** (also called the **electrochemical potential difference**) is used to quantitate the driving force acting on a molecule to cause it to move across a membrane. The electrochemical gradient for any molecule ($\Delta\mu_x$) is calculated as follows:

(Equation 1.4)

$$\Delta\mu_x = RT\,ln\frac{[X]_i}{[X]_o} + z_xFV_m$$

where

R = the gas constant
T = temperature in degrees Kelvin
ln = natural logarithm
$[X]_i$ = the concentration of X inside the cell
$[X]_o$ = the concentration of X outside the cell
z_x = the valence of charged molecules
F = the Faraday constant
V_m = the membrane potential ($V_m = V_i - V_o$)[b]

[b]By convention, membrane voltages are determined and reported with regard to the exterior of the cell. In a typical cell, the resting membrane potential (V_m) is negative. Positive V_m values can be observed in some excitable cells at the peak of an action potential.

The electrochemical gradient is a measure of the free energy available to carry out the useful work of transporting the molecule across the membrane. It has two components: The first component represents the energy in the concentration gradient for X across the membrane **(chemical potential difference)**. The second component **(electrical potential difference)** represents the energy associated with moving charged molecules (e.g., ions) across the membrane when a membrane potential exits (i.e., $V_m \neq 0$ mV). Thus for the movement of glucose across a membrane, only the concentrations of glucose inside and outside of the cell need to be considered (Fig. 1.6*A*). However, the movement of K^+ across the membrane, for example, would be determined both from the K^+ concentrations inside and outside of the cell and from the membrane voltage (see Fig. 1.6*B*).

Eq. 1.4 can be used to derive the **Nernst equation** for the situation in which a molecule is at equilibrium across the membrane (i.e., $\Delta\mu = 0$):

(Equation 1.5a)

$$0 = RT\,ln\frac{[X]_i}{[X]_o} + z_xFV_m$$

$$-RT\,ln\frac{[X]_i}{[X]_o} = z_xFV_m$$

$$V_m = -\frac{RT}{z_xF}\,ln\frac{[X]_i}{[X]_o}$$

Alternatively,

(Equation 1.5b)

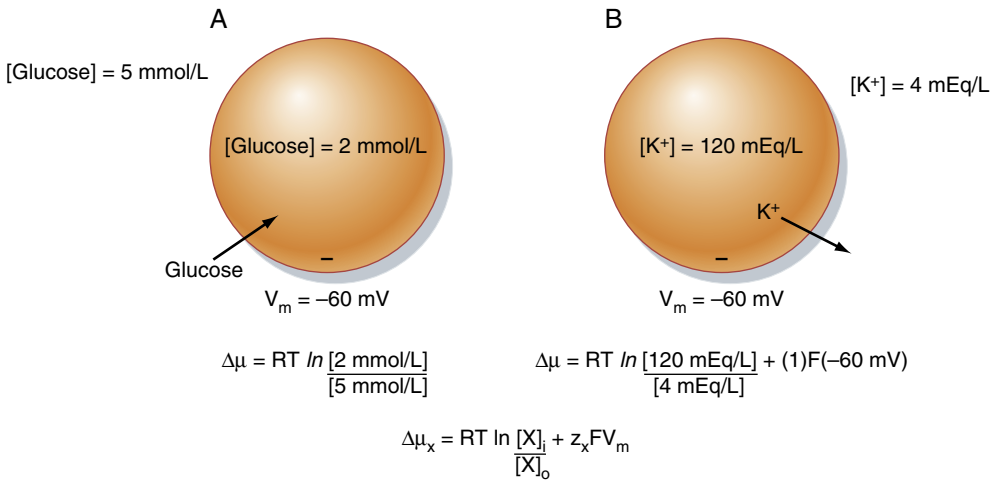
$$V_m = \frac{RT}{z_xF}\,ln\frac{[X]_o}{[X]_i}$$

The value of V_m calculated with the Nernst equation represents the equilibrium condition and is referred to as the **Nernst equilibrium potential** ($\mathbf{E_x}$, the V_m at which there is no net transport of the molecule across the membrane). It should be apparent that the Nernst equilibrium potential quantitates the energy in a concentration gradient and expresses that energy in millivolts. For example, for the cell depicted in Fig. 1.6*B*, the energy in the K^+ gradient (derived from the Nernst equilibrium potential for K^+ [E_{K^+}]) is proportional to 90.8 mV (causing K^+ to move out of the cell). This is opposite to, and of greater magnitude than, the energy in the membrane voltage (V_m = –60 mV), which causes K^+ to enter the cell. As a result, the electrochemical gradient is such that the net movement of K^+ across the membrane will be out of the cell. Another way to state this is that the net driving force for K^+ ($V_m - E_{K^+}$) is 30.8 mV (driving K^+ out of the cell). This is described in more detail in Chapter 2.

The Nernst equation, at 37°C, can be written as follows by replacing the natural logarithm function with the base 10 logarithm function:

(Equation 1.6a)

$$E_x = -\frac{61.5\text{ mV}}{z_x}\,log\frac{[X]_i}{[X]_o}$$



• **Fig. 1.6** Electrochemical gradients and cellular transport of molecules. **A,** Because glucose is uncharged, the electrochemical gradient is determined solely by the concentration gradient for glucose across the cell membrane. As shown, the glucose concentration gradient would be expected to drive glucose into the cell. **B,** Because K^+ is charged, the electrochemical gradient is determined by both the concentration gradient and the membrane voltage (V_m). The Nernst equilibrium potential for K^+ (E_{K^+}), calculated with Eq. 1.5a, is –90.8 mV (E_{K^+} V_m at equilibrium). The energy in the concentration gradient, which drives K^+ out of the cell, is thus proportional to +90.8 mV. The membrane voltage of –60 mV drives K^+ into the cell. Thus the electrochemical gradient, or net driving force, is 2.97 kJ/mol (equivalent to 30.8 mV), which drives K^+ out of the cell.

or

(Equation 1.6b)

$$E_x = \frac{61.5\ mV}{z_x} log \frac{[X]_o}{[X]_i}$$

These are the most common forms of the Nernst equation in use. In these equations, it is apparent that for a univalent ion (e.g., Na^+, K^+, Cl^-), a 10-fold concentration gradient across the membrane is equivalent in energy to an electrical potential difference of 61.5 mV (at 37° C), and a 100-fold gradient is equivalent to an electrical potential difference of 123 mV. Similarly, for a divalent ion (e.g., Ca^{++}), a 10-fold concentration gradient is equivalent to a 30.7-mV electrical potential difference, because z in Eqs. 1.6a and 1.6b is equal to 2.

Active and Passive Transport

When the net movement of a molecule across a membrane occurs in the direction predicted by the electrochemical gradient, that movement is termed **passive transport**. Thus for the examples given in Fig. 1.6, the movement of glucose into the cell and the movement of K^+ out of the cell would be considered passive transport. Transport that is passive is sometimes referred to as either "downhill transport" or "transport with the electrochemical gradient." In contrast, if the net movement of a molecule across the membrane is opposite to that predicted by the electrochemical gradient, that movement is termed **active transport**, a process that requires the input of energy (e.g., ATP). Active transport is sometimes referred to as either "uphill transport" or "transport against the electrochemical gradient."

In the various classes of plasma membrane transport proteins, the movement of H_2O through water channels is a passive process (see later discussion), as is the movement of ions through ion channels and the transport of molecules via uniporters (e.g., transport of glucose via GLUT-1). The ATPase-dependent transporters can use the energy in ATP to drive active transport of molecules (e.g., Na^+,K^+-ATPase, H^+-ATPase, or ABC transporters). Because the transport is directly coupled to the hydrolysis of ATP, it is referred to as **primary active transport**. Solute carriers that couple movement of two or more molecules (e.g., $3Na^+$,Ca^{++} antiporter) often transport one or more molecules (one Ca^{++} molecule in this example) against their respective electrochemical gradient through the use of the energy in the electrochemical gradient of the other molecule or molecules (three Na^+ in this example). When this occurs, the molecule or molecules transported against their electrochemical gradient are said to be transported by **secondary active transport** mechanisms (Fig. 1.7).

Osmosis and Osmotic Pressure

The movement of water across cell membranes occurs by the process of **osmosis.** The movement of water is passive, with the driving force for this movement being the osmotic pressure difference across the cell membrane. Fig. 1.8 illustrates the concept of osmosis and the measurement of the osmotic pressure of a solution.

Osmotic pressure is determined by the number of solute molecules dissolved in the solution. It is not dependent on factors such as the size of the molecules, their mass, or their chemical nature (e.g., valence). Osmotic pressure (π),

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Glucose is transported by the epithelial cells that line the gastrointestinal tract (small intestine), and by cells that form the proximal tubules of the kidneys. In the gastrointestinal tract, the glucose is absorbed from ingested food. In the kidney, the proximal tubule reabsorbs the glucose that was filtered across the glomerular capillaries and thereby prevents it from being lost in the urine. The uptake of glucose into the epithelial cell from the lumen of the small intestine and from the lumen of the proximal tubule is a secondary active process involving the sodium-glucose–linked transporters SGLT-1 and SGLT-2. SGLT-2 transports one glucose molecule with one Na^+ ion, and the energy in the electrochemical gradient for Na^+ (into the cell) drives the secondary active uptake of glucose. According to the following equation, for calculating the electrochemical gradient, and if the membrane potential (V_m) is –60 mV and there is a 10-fold $[Na^+]$ gradient across the membrane, an approximate 100-fold glucose gradient could be generated by SGLT-2:

$$\frac{[\text{Glucose}]_i}{[\text{Glucose}]_o} = \frac{[Na^+]_o}{[Na^+]_i} \times 10^{-V_m/61.5\,\text{mV}}$$

Thus, if the intracellular glucose concentration was 2 mmol/L, the cell could lower the extracellular glucose concentration to approximately 0.02 mmol/L. However, by increasing the number of Na^+ ions transported with glucose from one to two, SGLT-1 can generate a nearly 10,000-fold glucose gradient:

$$\frac{[\text{Glucose}]_i}{[\text{Glucose}]_o} = \left(\frac{[Na^+]_o}{[Na^+]_i}\right)^2 \times 10^{-2V_m/61.5\,\text{mV}}$$

Again, if the intracellular glucose concentration is 2 mmol/L, SGLT-1 could remove virtually all glucose from either the lumen of the small intestine or the lumen of the proximal tubule (i.e., the luminal glucose concentration ≅ 0.0002 mmol/L).

measured in atmospheres (atm), is calculated by **van't Hoff's law** as follows:

(Equation 1.7)

$$\pi = nCRT$$

where

n = number of dissociable particles per molecule
C = total solute concentration
R = gas constant
T = temperature in degrees Kelvin

For a molecule that does not dissociate in water, such as glucose or urea, a solution containing 1 mmol/L of these molecules at 37°C can exert an osmotic pressure of 2.54×10^{-2} atm, as calculated with Eq. 1.7 and the following values:

n = 1
C = 0.001 mol/L
R = 0.082 atm L/mol K
T = 310 °K

Because 1 atm equals 760 mm Hg at sea level, π for this solution can also be expressed as 19.3 mm Hg. Alternatively, osmotic pressure is expressed in terms of osmolarity (see the following section). Regardless of the molecule, a solution containing 1 mmol/L of the molecule therefore exerts an osmotic pressure proportional to 1 mOsm/L.

For molecules that dissociate in a solution, n of Eq. 1.7 will have a value other than 1. For example, a 150-mmol/L solution of NaCl has an osmolarity of approximately 300 mOsm/L because each molecule of NaCl dissociates into a Na^+ and a Cl^- ion (i.e., n = 2).[c] If dissociation of a molecule into its component ions is not complete, n will not be an integer. Accordingly, osmolarity for any solution can be calculated as follows:

(Equation 1.8)

$$\text{Osmolarity} = \text{concentration} \times \text{number of dissociable particles}$$
$$\text{mOsm / L} = \text{mmol / L} \times \text{number of particles / mole}$$

Osmolarity Versus Osmolality

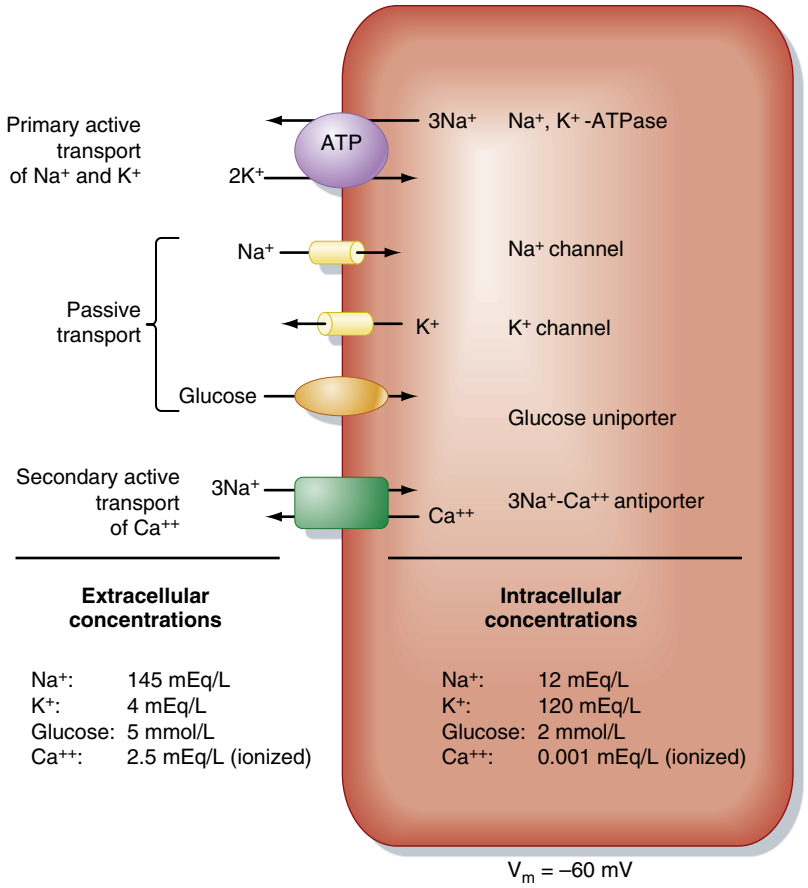
The terms *osmolarity* and *osmolality* are frequently confused and incorrectly interchanged. *Osmolarity* refers to the osmotic pressure generated by the dissolved solute molecules in 1 L of solvent, whereas osmolality is the number of molecules dissolved in 1 kg of solvent. For dilute solutions, as encountered in most physiologic settings, the difference between osmolarity and osmolality is insignificant, as is the contribution of the solute particles to volume and mass of the solvent. Importantly measurements of osmolarity are temperature dependent because the volume of the solvent varies with temperature (i.e., the volume is larger at higher temperatures). In contrast, osmolality, which is based on the mass of the solvent, is temperature independent. For this reason, *osmolality* is the preferred term for biologic systems and is used throughout this book. Because the solvent in biological solutions and bodily fluids is water, and because of the dilute nature of biological solutions and bodily solutions, osmolalities are expressed as milliosmoles per kilogram of water (mOsm/kg H_2O).

Tonicity

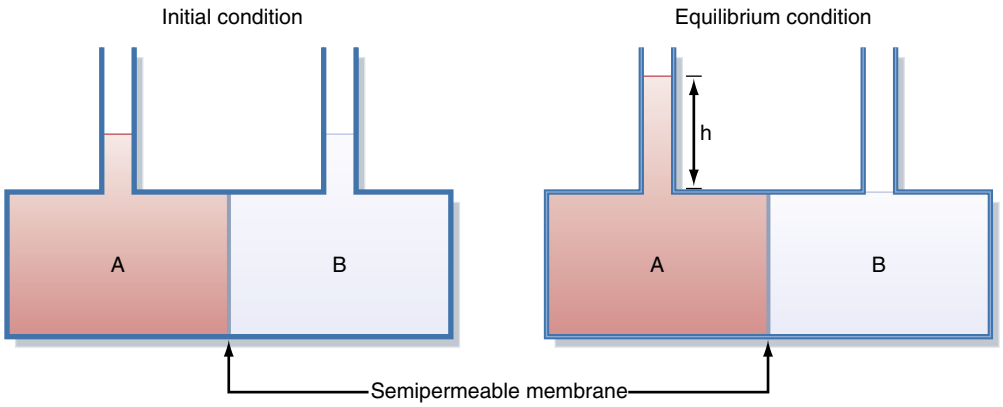
The tonicity of a solution is related to the effect of the solution on the volume of a cell. Solutions that do not change the volume of a cell are said to be **isotonic.** A **hypotonic** solution causes a cell to swell, whereas a **hypertonic** solution causes a cell to shrink. Although related to osmolality, tonicity also accounts for the ability of the molecules in solution to cross the cell membrane.

Consider two solutions: a 300-mmol/L solution of sucrose and a 300-mmol/L solution of urea. Both solutions have an osmolality of 300 mOsm/kg H_2O and therefore are said to be **isosmotic** (i.e., they have the same osmolality). When red blood cells—which for the purpose of this illustration also have an intracellular fluid osmolality of 300 mOsm/kg H_2O—are placed in the two solutions, those in the sucrose

[c] NaCl does not completely dissociate in water. The value for n is 1.88 rather than 2. However, for simplicity, the value of 2 is most often used.



• **Fig. 1.7** Examples of several membrane transporters, illustrating primary active, passive, and secondary active transport. See text for details. *ATP*, Adenosine triphosphate.



• **Fig. 1.8** Schematic representation of osmotic water movement and the generation of an osmotic pressure. Compartment A and compartment B are separated by a semipermeable membrane (i.e., the membrane is highly permeable by water but impermeable by solute). Compartment A contains a solute, whereas compartment B contains only distilled water. Over time, water moves by osmosis from compartment B to compartment A. (Note: This water movement is driven by the concentration gradient for water. Because of the presence of solute particles in compartment A, the concentration of water in compartment A is less than that in compartment B. Consequently, water moves across the semipermeable membrane from compartment B to compartment A down its concentration gradient.) This causes the level of fluid to be raised in compartment A and lowered in compartment B. At equilibrium, the hydrostatic pressure exerted by the column of water (h) stops the net movement of water from compartment B to A. Thus at equilibrium, the hydrostatic pressure is equal and opposite to the osmotic pressure exerted by the solute particles in compartment A. (Redrawn from Koeppen BM, Stanton BA. *Renal Physiology.* 4th ed. St. Louis: Mosby; 2006.)

solution maintain their normal volume, whereas those placed in urea swell and eventually burst. Thus the sucrose solution is isotonic and the urea solution is hypotonic. The differential effect of these solutions on red blood cell volume is related to the permeability of the red blood cell plasma membrane to sucrose and urea. The red blood cell membrane contains uniporters for urea. Thus urea easily crosses the cell membrane (i.e., the cell is permeable by urea), driven by the concentration gradient (i.e., extracellular urea concentration > intracellular urea concentration). In contrast, the red blood cell membrane does not contain sucrose transporters, and sucrose cannot enter the cell (i.e., the cell is impermeable by sucrose).

To exert an osmotic pressure across a membrane, a molecule must not cross the membrane. Because the red blood cell membrane is impermeable by sucrose, it exerts an osmotic pressure equal and opposite to the osmotic pressure generated by the contents within the red blood cell (in this case, 300 mOsm/kg H_2O). In contrast, urea is readily able to cross the red blood cell membrane, and it cannot exert an osmotic pressure to balance that generated by the intracellular solutes of the red blood cell. Consequently, sucrose is termed an **effective osmole,** whereas urea is an **ineffective osmole.**

To take into account the effect of a molecule's ability to permeate the membrane on osmotic pressure, it is necessary to rewrite Eq. 1.7 as follows:

(Equation 1.9)

$$\pi_e = \sigma(nCRT)$$

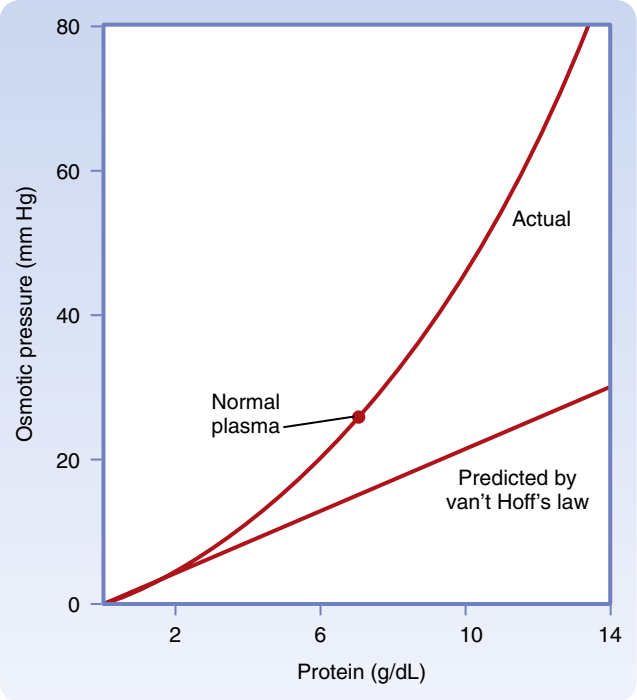
where σ is the **reflection coefficient** (or **osmotic coefficient**) and is a measure of the relative ability of the molecule to cross the cell membrane, and π_e is the "effective osmotic pressure."

For a molecule that can freely cross the cell membrane, such as urea in the preceding example, σ = 0, and no effective osmotic pressure is exerted (e.g., urea is an ineffective osmole for red blood cells). In contrast, σ = 1 for a solute that cannot cross the cell membrane (in the preceding example, sucrose). Such a substance is said to be an effective osmole. Many molecules are neither completely able nor completely unable to cross cell membranes (i.e., 0 < σ < 1) and generate an osmotic pressure that is only a fraction of what is expected from the molecules' concentration in solution.

Oncotic Pressure

Oncotic pressure is the osmotic pressure generated by large molecules (especially proteins) in solution. As illustrated in Fig. 1.9, the magnitude of the osmotic pressure generated by a solution of protein does not conform to van't Hoff's law. The cause of this anomalous relationship between protein concentration and osmotic pressure is not completely understood, but it appears to be related to the size and shape of the protein molecule. For example, the correlation with van't Hoff's law is more precise with small, globular proteins than with larger protein molecules.

The oncotic pressure exerted by proteins in human plasma has a normal value of approximately 26 to 28 mm Hg.



• **Fig. 1.9** Relationship between the concentration of plasma proteins in solution and the osmotic pressure (oncotic pressure) they generate. Protein concentration is expressed in grams per deciliter. Normal plasma protein concentration is indicated. Note how the actual pressure generated exceeds that predicted by van't Hoff's law.

Although this pressure appears to be small in relation to osmotic pressure (28 mm Hg ≅ 1.4 mOsm/kg H_2O), it is an important force involved in fluid movement across capillaries (see Chapter 17).

Specific Gravity

The total concentration of all molecules in a solution can also be measured as specific gravity. Specific gravity is defined as the weight of a volume of solution divided by the weight of an equal volume of distilled water. Thus the specific gravity of distilled water is 1. Because biological fluids contain a number of different molecules, their specific gravities are greater than 1. For example, normal human plasma has a specific gravity in the range of 1.008 to 1.010.

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The specific gravity of urine is sometimes measured in clinical settings and used to assess the urine-concentrating ability of the kidneys. The specific gravity of urine varies in proportion to its osmolality. However, because specific gravity depends both on the number of molecules and on their weight, the relationship between specific gravity and osmolality is not always predictable. For example, in patients who have received an injection of radiocontrast dye (molecular weight > 500 g/mole) for x-ray studies, values of urine specific gravity can be high (1.040 to 1.050), even though the urine osmolality is similar to that of plasma (e.g., 300 mOsm/kg H_2O).

Key Points

- The plasma membrane is a lipid bilayer composed of phospholipids and cholesterol, into which are embedded a wide range of proteins. One class of these membrane proteins (membrane transport proteins or transporters) is involved in the selective and regulated transport of molecules into and out of the cell. These transporters include water channels (aquaporins), ion channels, solute carriers, and ATP-dependent transporters.
- The movement of molecules across the plasma membrane through ion channels and solute carriers is driven by chemical concentration gradients and electrical potential differences (charged molecules only). The electrochemical gradient is used to quantitate this driving force. ATP-dependent transporters use the energy in ATP to transport molecules across the membrane and often establish the chemical and electrical gradients that then drive the transport of other molecules through channels and by the solute carriers. Water movement through aquaporins is driven by an osmotic pressure difference across the membrane.
- Transport across the membrane is classified as passive or active. Passive transport is the movement of molecules as expected from the electrochemical gradient for that molecule. Active transport represents transport against the electrochemical gradient. Active transport is further divided into primary active and secondary active transport. Primary active transport is directly coupled to the hydrolysis of ATP (e.g., ATP-dependent transporters). Secondary active transport occurs with coupled solute carriers, for which passive movement of one or more molecules drives the active transport of other molecules (e.g., Na^+-glucose symporter, Na^+-H^+ antiporter).