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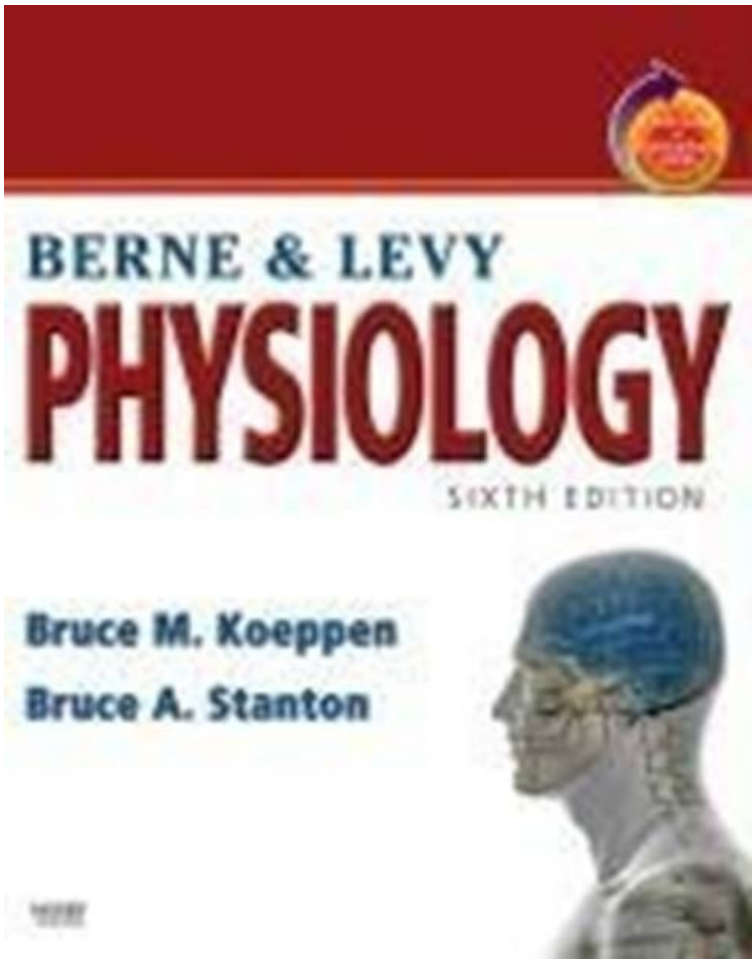
BERNE & LEVY
PHYSIOLOGY
SIXTH EDITION
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SECTION ONE CELLULAR PHYSIOLOGY

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1 Principles of Cell Function

The human body is composed of billions of cells, each with a distinct function. Despite this diversity in cell function, all cells share certain common elements and functions. This chapter provides an overview of these common elements and focuses on the important function of transport of molecules and water into and out of the cell across its plasma membrane.

OVERVIEW OF EUKARYOTIC CELLS

Eukaryotic cells are distinguished by the presence of a membrane-delimited nucleus. With the exception of mature human red blood cells, all cells within the 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. A brief description of the components of a typical eukaryotic cell follows (Fig. 1-1). Readers who desire a more in-depth presentation of this material are encouraged to consult one of the many cellular and molecular biology textbooks currently available.

Nucleus

The nucleus contains the genome of the cell, which in somatic cells is present on 46 chromosomes, 22 pairs of autosomes and one pair of sex chromosomes. Both sperm and eggs contain 23 chromosomes, a copy of each autosome and either a male (X) or a female (Y) sex chromosome. The chromosome is a highly ordered structure containing genes (DNA) and associated proteins (i.e., histones). The nucleus also contains the enzymatic machinery for repair of damaged DNA and for its replication, as well as the enzymes needed to transcribe DNA and yield messenger RNA (mRNA).

Plasma Membrane

The plasma membrane surrounds the cell and separates the contents of the cell from the surrounding extracellular fluid. It serves a number of important functions and is described in greater detail later in the chapter.

Mitochondria

It is currently thought that mitochondria evolved from an aerobic prokaryote that lived within primitive eukaryotic cells. Mitochondria synthesize ATP and thus provide the energy needed to power many vital cell functions. They contain their own DNA, which codes for a number of the enzymes needed for oxidative phosphorylation (other mitochondrial enzymes are synthesized in the cytoplasm and imported into the mitochondria), as well as the RNA needed for the transcription and translation of mitochondrial DNA. Mitochondria are composed of two membranes separated by an intermembrane space. The outer mitochondrial membrane lets molecules up to 5 kDa in size cross. Thus, the composition of the intermembrane space is similar to that of cytoplasm with respect to small molecules and ions. The inner membrane is folded into numerous cristae and is the site where ATP is generated through the process of oxidative phosphorylation. The interior of mitochondria (i.e., matrix) contains the enzymes involved in the citric acid cycle and those involved in oxidation of fatty acids. In addition to producing ATP, mitochondria can serve as a site for sequestration of Ca^{++}.

Rough Endoplasmic Reticulum

The rough endoplasmic reticulum (rER) is an extensive membrane network throughout the cytoplasm and is especially well developed in cells that produce and secrete proteins (e.g., pancreatic acinar cell, plasma cell). Attached to the membrane are ribosomes, which when viewed with an electron microscope, impart the "rough" appearance characteristic of this organelle. The rER is the site of translation of mRNA and posttranslational modification of proteins that are destined to be secreted from the cell or are targeted to the plasma membrane or other membranous organelles (e.g., Golgi

apparatus, lysosomes).

Golgi Apparatus

Proteins synthesized in the rER are transferred to the Golgi apparatus via coated vesicles. On electron micrographs the Golgi apparatus appears as a stack of flattened membrane sacs. Vesicles from the rER fuse with sacs that are in close proximity to the rER (i.e., the cis-Golgi network). The proteins then traverse through the Golgi membrane sacs, also via coated vesicles, and in this process they may undergo additional posttranslational modification (e.g., glycosylation). The Golgi apparatus also sorts the proteins and packages them for delivery to other parts of the cell (e.g., plasma membrane, lysosome, secretory granule). The sorting and packaging of proteins occur in the trans-Golgi network.

Smooth Endoplasmic Reticulum

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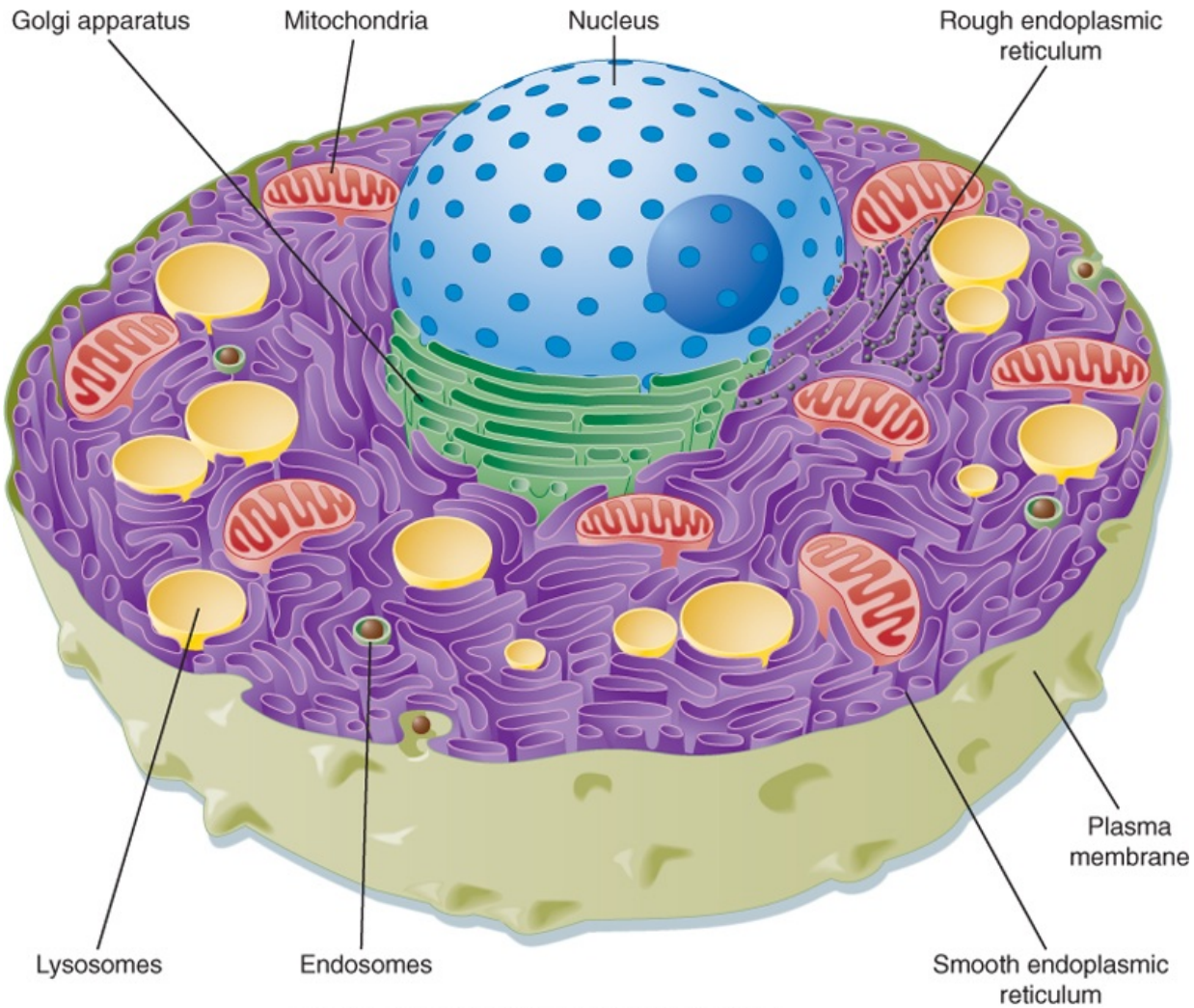

Figure 1-1 Schematic drawing of a eukaryotic cell. The top portion of the cell has been removed to illustrate the nucleus and various intracellular organelles. See text for details.

The smooth endoplasmic reticulum (sER) is devoid of ribosomes and therefore appears "smooth" on electron micrographs. It is a site where many substances are modified and detoxified (e.g., pesticides). Hydrophobic molecules can be converted to water-soluble molecules in the sER, thus facilitating their excretion from the body by the liver and kidneys. The sER is also the site for the synthesis of fats and lipids. For example, the cells of the adrenal gland that secrete the steroid hormone cortisol have an extensive sER. Similarly, the cells within the ovaries and testes that secrete estrogens and testosterone have a well-developed sER. In skeletal and cardiac muscle, the sER, which is called the sarcoplasmic reticulum in these cells, serves to sequester Ca^{++}. Thus, it plays an important role in controlling contraction.

Lysosomes

Lysosomes are part of the endocytic system of the cell (see later) and serve a degradative function. They are membrane-bound organelles with an acidic interior (pH ≈4.5), and they contain a number of digestive enzymes (e.g., proteases, nucleases, lipases, glycosidases). Lysosomes degrade material that is brought into the cell via the processes of endocytosis and phagocytosis. They also degrade intracellular organelles, a process called autophagy, and some intracellular proteins. Much of what is degraded is then recycled by the cell. The process of degradation is not random and in a number of instances is targeted. For example, chaperone proteins (e.g., heat shock protein 73) can direct intracellular proteins to the lysosome. In addition, plasma membrane proteins can be targeted for endocytosis and eventual degradation by lysosomes through attachment of specific groups (e.g., ubiquitin) to the protein. These groups act as signals for degradation of the protein.

Proteasomes

Like lysosomes, proteasomes serve a degradative function. However, proteasomes are not membrane bound. They serve to degrade primarily intracellular proteins that have been targeted (e.g., ubiquitinated) for degradation. They may also degrade some membrane-associated proteins.

Free Ribosomes

Ribosomes are located throughout the cytoplasm and are not associated with the endoplasmic reticulum. They translate mRNA for cytosolic proteins, as well as proteins that will neither be secreted from the cell nor incorporated into membrane structures (e.g., mitochondrial enzymes).

Peroxisomes

Peroxisomes (also called microbodies) are membrane-bound organelles that contain various oxidative enzymes (e.g., catalase). These oxidative enzymes can detoxify a number of compounds and oxidize fatty acids. In the liver, peroxisomes metabolize ethanol to acetaldehyde.

Cytoskeleton

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The cytoskeleton of the cell consists of actin filaments (also called microfilaments), intermediate filaments, and microtubules. Actin filaments in muscle cells are critical components of the contractile apparatus. In other cells they are involved in locomotion (e.g., macrophages). Actin also makes up the core of microvilli and links the interior of the cell to adjacent cells through some cell junctions (e.g., zonula adherens and zonula occludens). There are several different classes of intermediate filaments, and they can vary by cell type. For example, keratin filaments are found in epithelial cells, whereas neurofilaments are found in neurons. Intermediate filaments are primarily structural in function and can link the interior of the cell to adjacent cells and the surrounding extracellular matrix through desmosomes and hemidesmosomes, respectively. Microtubules serve multiple functions within the cell, including intracellular transport of vesicles, chromosome movement during mitosis and meiosis, and movement of cilia and flagella (e.g., tail of spermatozoa). They are formed from α- and β-tubulin dimers and change length by either adding or removing tubulin dimers. In general, a microtubule-organizing center exists near the cell's nucleus, and microtubules grow out from this center toward the periphery of the cell. As noted, microtubules can move intracellular vesicles within the cell (e.g., transport of neurotransmitter-containing vesicles from the cell body of the neuron down the axon); such movement is driven by motor proteins. One motor protein, **kinesin,** drives transport from the center of the cell toward the periphery, whereas another motor protein, **dynein,** drives movement in the opposite direction. Dynein is the motor protein that drives the movement of both cilia and flagella.

THE PLASMA MEMBRANE

IN THE CLINIC

Microtubules are the target of a number of antitumor drugs (e.g., vincristine and taxol) because disruption of these structures impairs cell division in the highly mitotic tumor cells. Vincristine prevents polymerization of the tubulin dimers and thus prevents the formation of microtubules. As a result, the mitotic spindle cannot form, and the cell cannot divide. Taxol stabilizes the microtubules and thus arrests cells in mitosis.

Kartagener's syndrome is an autosomal recessive disorder in which dynein is

missing in cilia and, in males, the flagella of sperm. Accordingly, males with this syndrome are infertile. Because the cilia of the epithelial cells that line the respiratory track work to remove inhaled pathogens, a process termed **mucociliary transport** (see Chapter 20), both men and women with this syndrome are susceptible to repeated lung infections.

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, in particular, the presence of specific membrane proteins, the plasma membrane is involved in a number of important cellular functions, including

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

Membranes also surround the various organelles within the cell. The organelle membranes not only subdivide the cell into compartments but are also the site of many important intracellular processes (e.g., electron transport by the inner mitochondrial membrane).

In this chapter the structure and function of the plasma membrane of eukaryotic cells is considered. More specifically, the chapter focuses on transport of molecules and water across the plasma membrane. Only the principles of membrane transport are presented here. Additional details as related to specific cells are presented in the various sections and chapters of the 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, whereas others are more loosely attached to the inner and outer surfaces of the membrane, often by binding to the integral membrane proteins. Because the lipids and proteins can diffuse within the plane of the membrane and the appearance of the membrane varies regionally as a result of the presence of different membrane proteins, this depiction of the structure of the plasma membrane is often termed the **fluid mosaic model.**

Membrane Lipids

The major lipids of the plasma membrane are **phospholipids** or **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 formation of the bilayer, with the hydrophobic fatty acyl chains forming the core of the bilayer and the polar head groups exposed on the surface.

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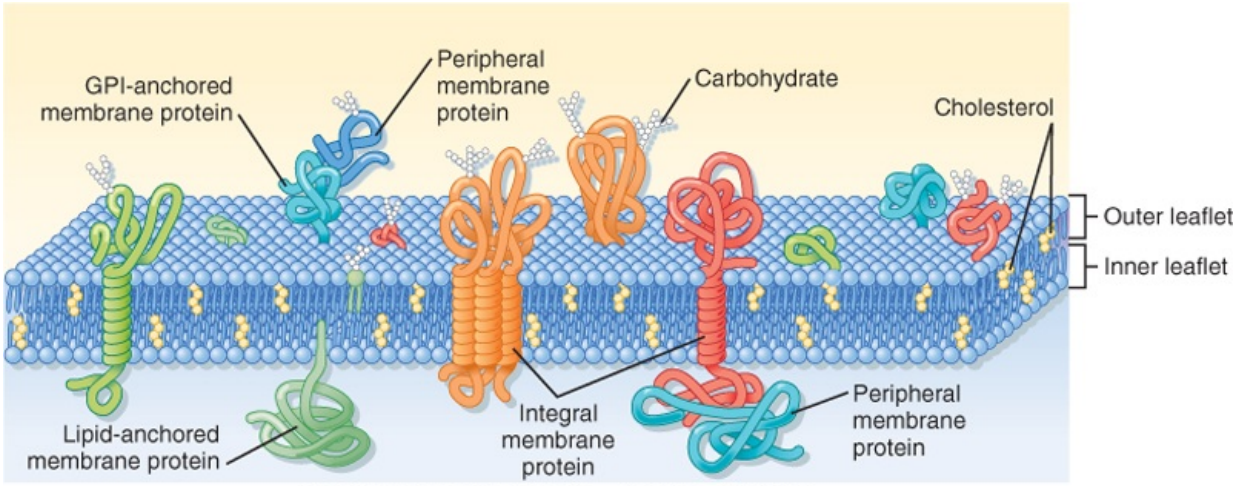

Figure 1-2 Schematic diagram of the cell plasma membrane. Not shown are lipid rafts. See text for details. (Modified from Figure 12-3 in Cooper GM: The Cell-A Molecular Approach, 2nd ed. Washington DC, Sinauer, 2000.)

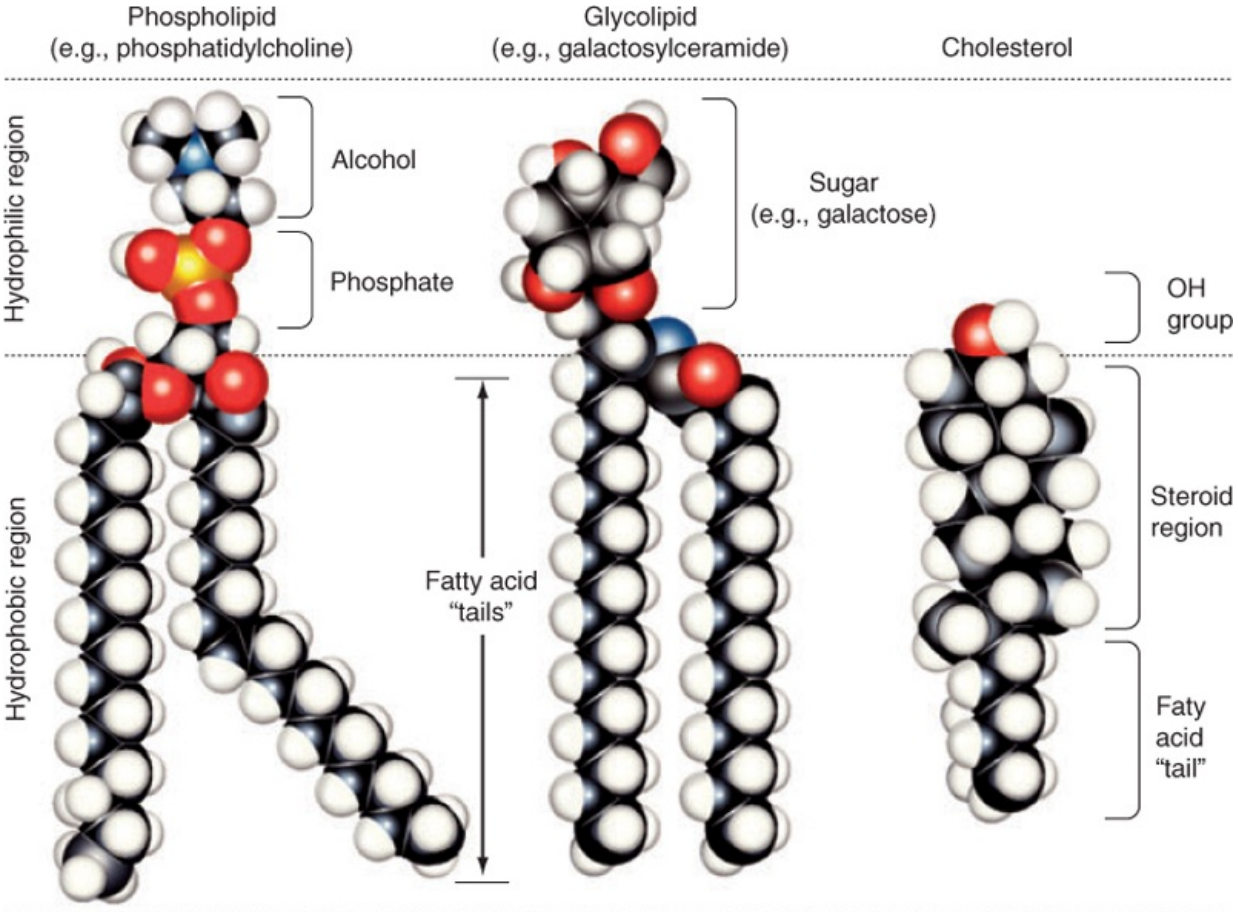

Figure 1-3 Models of the major classes of plasma membrane lipids depicting the hydrophilic and hydrophobic regions of the molecules. The molecules are arranged as they exist in one leaflet of the bilayer. The opposing leaflet is not shown. One of the fatty acyl chains in the phospholipid molecule is unsaturated. The presence of this double bond produces a "kink" in the fatty acyl chain that 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 1-1. Plasma Membrane Lipids

Phospholipid	Leaflet Location

Phosphatidylcholine	Outer
Sphingomyelin	Outer
Phosphatidylethanolamine	Inner
Phosphatidylserine	Inner
Phosphatidylinositol*	Inner

*Involved in signal transduction.

The majority of membrane phospholipids have a glycerol backbone to which are attached the fatty acyl chains, as well as an alcohol linked to glycerol via a phosphate group. The common alcohols are choline, ethanolamine, serine, inositol, and glycerol. Another important phospholipid, sphingomyelin, has the amino alcohol sphingosine as its backbone instead of glycerol. Table 1-1 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. As summarized in Table 1-1, 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.

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The sterol molecule **cholesterol** is also a critical component of the bilayer (Fig. 1-3). It is found in both leaflets and serves to stabilize the membrane at normal body temperature (37°C). Cholesterol can represent as much as 50% of the lipids found in the membrane. Another minor lipid component of the plasma membrane is **glycolipid.** These lipids, as their name indicates, contain two fatty acyl chains linked to polar head groups that consist of carbohydrates (Fig. 1-3). As discussed later, 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 orient with their polar groups on the outer surface of the leaflet in which they are located. Their hydrophobic portions are thus located within the interior of the bilayer.

The lipid bilayer is not a static structure. Lipids can freely 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 membrane becomes more fluid. The presence of unsaturated fatty acyl chains in 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 (Fig. 1-3). This kink prevents the molecule from closely associating with surrounding lipids, and as a result membrane fluidity is increased. Some membranes contain lipids (e.g., sphingomyelin and cholesterol) that aggregate into what are called **lipid rafts.** These lipid rafts often have specific proteins associated with them and 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 mechanisms and molecules.

Membrane Proteins

As much as 50% of the membrane is composed of protein. These membrane proteins are classified as either integral, lipid anchored, or peripheral (Fig. 1-2).

Integral membrane proteins are embedded 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 and are termed **transmembrane proteins.** Transmembrane proteins have both hydrophobic and hydrophilic regions. The hydrophobic region, often in the form of an α helix with the hydrophobic amino acids facing out, 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 extracellular portion of the protein contains the ligand binding site, 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.

Proteins 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. The glycolipid 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 associate with the polar head groups of the membrane lipids but more commonly bind to integral or lipid-anchored proteins. Peripheral proteins are easily removed from the membrane, whereas integral and lipid-anchored proteins require the use of detergents to isolate them from the membrane.

MECHANISMS OF MEMBRANE TRANSPORT

Intracellular and extracellular fluid is composed primarily of H_2O in which solutes (e.g., ions, glucose, amino acids) are dissolved. The normal function of cells requires continuous movement of water and solutes into and out of the cell. 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 movement of water across the membrane. With the exception of gases (e.g., O_2 and CO_2) and ethanol, which can diffuse across the lipid bilayer, movement of water and other solutes across the plasma membrane occurs via specific membrane transport proteins.

Membrane Transport Proteins

Table 1-2 lists the major classes of membrane transport proteins, their mode of transport, and the rate at which they transport molecules or ions across the membrane.

Water Channels

Table 1-2. Major Classes of Plasma Membrane Transporters

Class	Transport Mode	Transport Rate
Water channel	Gated*	Up to 10^9 molecules/second
Ion 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

*Water channels (i.e., aquaporins) may be continuously open and thus function similar to a pore, which is not gated (e.g., the porins found in the outer membrane of mitochondria). However, the permeability of a water channel can be modified and is therefore listed as gated.

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Water channels, or **aquaporins (AQPs),** are the main route for water movement into and out of the cell. They are widely distributed throughout the body, although different isoforms are found in different cell types. To date, 11 AQPs have been identified. The amount of H_2O that can enter or leave the cell via AQPs can be regulated by altering the number of AQPs in the membrane or by changing their permeability (i.e., gating). Changes in pH have been identified as one factor that can modulate the permeability of AQPs.

Ion Channels

AT THE CELLULAR LEVEL

AQPs are divided into two subgroups. One group is permeable only to water. The