PHARMACY EDUCATION SERIES

ESSENTIALS OF HUMAN PHYSIOLOGY AND PATHOPHYSIOLOGY FOR PHARMACY AND ALLIED HEALTH

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ROUTLEDGE

Essentials of Human Physiology and Pathophysiology for Pharmacy and Allied Health

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Contents

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Preface

The presentation of material within the chapters was designed to maximize clarity and facilitate conveyance of key points to the students. Numerous subheadings, bulleted lists, tables, and definitions of key terms are included in each chapter along with study objectives that are designed to focus students on important concepts within each chapter. The word "pathophysiology" is derived from the Greek word "pathos" which means "suffering, disease" and "physiology" which is the science of the normal function of living things." Pathophysiology content in this text is specifically designed to build upon the information provided in the sections related to the normal physiology. We also believe that pathophysiology is a bridge between physiology and pharmacology. As a result of the authors' experience in teaching both pathophysiology and pharmacology it has become clear that the time to introduce health science students to therapeutics is in pathophysiology where the mechanism and effects of disease are explored in detail and the application of the drugs makes the most sense. A rationale for drug therapy section is therefore included in each chapter to allow students to correlate information they have learned on selected diseases to the clinical application of drugs.

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Authors

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chapter one

The cell

Study objectives

- Describe the function of each of the components of the plasma membrane
- Understand the physiological importance of the permeability barrier created by the plasma membrane
- Describe the factors that affect diffusion
- Explain how osmosis takes place
- Understand the clinical significance of the osmotic pressures of solutions
- Describe the factors that affect mediated transport
- Compare and contrast facilitated diffusion and active transport
- Define membrane potential
- Compare the distribution and permeability differences of ions across the cell membrane
- Describe how differences in ion distribution and permeability contribute to the resting membrane potential
- Describe how a cell's resting membrane potential is developed and maintained
- Explain the role of the Na^+-K^+-ATPase pump in the process of ion exchange across the cell membrane
- Distinguish between depolarization, hyperpolarization, and repolarization
- Compare and contrast graded potentials and action potentials
- Describe the process of local current flow
- Explain the mechanism by which action potentials are generated
- Understand the function of sodium and potassium voltage-gated channels
- Distinguish between the absolute refractory period and the relative refractory period
- Describe the process of saltatory conduction
- Explain the functional significance of myelin
- Explain why the conduction of the action potential is unidirectional
- Describe the mechanism by which chemical synapses function
- Describe the effects of a neurotransmitter binding to its receptors on the postsynaptic neuron
- Compare and contrast excitatory synapses and inhibitory synapses
- Distinguish between an EPSP and an IPSP
- Describe how neurotransmitters are removed from the synaptic cleft
- Explain how temporal summation and spatial summation take place
- Distinguish between convergence and divergence

- Understand how pH and hypoxia affect synaptic transmission
- Describe the potential mechanisms by which drugs, toxins and diseases affect synaptic transmission
- Explain why synaptic transmission is unidirectional
- Distinguish between an agonist and an antagonist
- Compare and contrast the various forms of cellular adaptation. What is the purpose of these adaptive changes?
- Discuss the underlying mechanisms by which cellular injury can occur
- Describe the major manifestations that present when cells are injured. Why does each of these manifestations occur?
- Define apoptosis and necrotic cell death. How do they differ?
- List the specific types of cellular necrosis that may occur and their distinct characteristics
- Define gangrene and gas gangrene
- Discuss the two mechanisms by which tissue repair occurs. Give examples of specific cell types that will utilize each repair mechanism
- List the steps involved in wound repair along with the key features of each step
- List various factors that can impair wound healing
- What is a keloid scar? Why does it occur?

1.1 *Plasma membrane*

Each cell is enclosed within a plasma membrane that separates the cytoplasmic contents of the cell, or the intracellular fluid (ICF), from the fluid outside of the cell, the extracellular fluid (ECF). An important homeostatic function of this plasma membrane is to serve as a *permeability barrier* that insulates or protects the cytoplasm from immediate changes in the surrounding environment. Furthermore, it allows the cell to maintain a cytoplasmic composition that is very different from that of the ECF. The functions of neurons (nerve cells) and muscle cells depend on this difference. The plasma membrane also contains many enzymes and other components such as antigens and receptors. These structures allow cells to interact with other cells, neurotransmitters, blood-borne substances such as hormones, and various other chemical substances, such as drugs.

1.1.1 *Structure and function of the plasma membrane*

The major components of the plasma membrane include:

- Phospholipids
- Cholesterol
- Proteins
- Carbohydrates

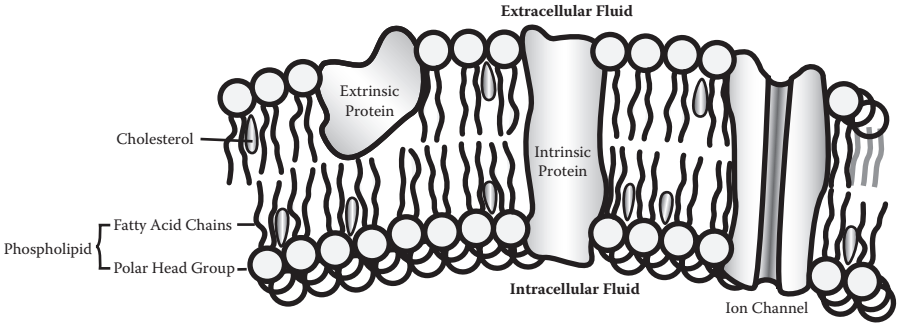

Figure 1.1 Structure of the plasma membrane. The plasma membrane is composed of a bilayer of phospholipid molecules. Associated with this bilayer are intrinsic proteins, which are embedded within and span the membrane, and extrinsic proteins, which are found on the external or internal surface of the membrane. Molecules of cholesterol are found in the inner, nonpolar region of the membrane.

The basic structure of the plasma membrane is formed by *phospholipids* (see Figure 1.1). These molecules are one of the more abundant of the membrane components. Phospholipids are *amphipathic* molecules that have both polar (water-soluble) and nonpolar (water-insoluble) regions. They are composed of a phosphorylated glycerol backbone, which forms a polar head group that is hydrophilic, and a nonpolar region containing two hydrophobic fatty acid chains. In an aqueous environment, such as the body, these molecules are arranged in a formation referred to as the *lipid bilayer* consisting of two layers of phospholipids. The polar region of the molecule is oriented toward the outer surface of the membrane where it can interact with water; and the nonpolar, hydrophobic fatty acids are in the center of the membrane away from the water. The functional significance of this lipid bilayer is that it creates a *semipermeable barrier*. Lipophilic, or non-water-soluble, substances can readily cross the membrane by simply passing through its lipid core. Important examples of these substances include gases, such as oxygen and carbon dioxide, and fatty acid molecules, which are used to form energy within muscle cells.

Most hydrophilic, or water-soluble, substances are repelled by this hydrophobic interior and cannot simply diffuse through the membrane. Instead, these substances must cross the membrane using specialized transport mechanisms. Examples of lipid-insoluble substances that require such mechanisms include proteins, nutrient molecules such as glucose and amino acids, and all species of ions (Na^+, Ca^{++}, H^+, Cl^-, and HCO_3^-). Therefore, the plasma membrane plays a very important role in determining the composition of the ICF by selectively permitting substances to move in and out of the cell.

PHARMACY APPLICATION:
LIPID SOLUBILITY AND DRUG ELIMINATION

The lipid solubility of many substances can change when physiological conditions vary. For example, the surrounding pH can determine whether a molecule is in a protonated form (positively charged, lipid-insoluble) or in an unprotonated form (uncharged, lipid-soluble). As discussed, charged substances do not readily cross the membrane, as do uncharged substances. This principle regarding lipid solubility is used in the treatment of an overdose of phenobarbital, a barbiturate used for sedation and seizure disorders. Phenobarbital is normally 30% removed by urinary excretion. In the case of an overdose, it would be advantageous to enhance urinary excretion. Alkalization of the urine to a pH of 7.5–8 helps to promote excretion. In fact, by alkalinizing the urine, the amount of phenobarbital excreted increases 5- to 10-fold. After alkalization, more phenobarbital would be ionized in the urine and, therefore, become lipid-insoluble and, therefore, the drug would not be reabsorbed from the kidney, but would instead be eliminated in the urine.

Another important aspect of the lipid bilayer is that the phospholipids are not held together by chemical bonds. This enables the molecules to move about freely within the membrane, resulting in a structure that is not rigid in nature, but instead, is very fluid and pliable. Another substance contributing to membrane fluidity is *cholesterol*. Cholesterol has a steroid nucleus that is lipid-soluble. Therefore, these molecules are found in the interior of the membrane lying parallel to the fatty acid chains of the phospholipids (see Figure 1.1). As such, they prevent the fatty acid chains from packing together and crystallizing, which would decrease membrane fluidity.

Membrane fluidity is very important in terms of function in many cell types. For example, skeletal muscle activity involves the shortening and lengthening of the muscle fibers. Furthermore, as white blood cells leave the blood vessels and enter the tissue spaces to fight infection, they must squeeze through tiny pores in the wall of the capillary, requiring significant deformation of the cell and its membrane. Finally, in all cells, many processes that transport substances across the plasma membrane require the embedded proteins to change their conformation and move about within the bilayer. In each case, for the cell membrane, or the entire cell, to change its shape, the membrane must be very fluid and flexible.

Proteins are also associated with the lipid bilayer and essentially float within it. Intrinsic, or transmembrane, proteins are embedded within and span the membrane. These proteins are like phospholipids in that they

are amphipathic with the polar regions of the molecule extending beyond the lipid bilayer and the nonpolar region embedded within it. Extrinsic, or peripheral, proteins are found on either the internal or the external surface of the membrane (see Figure 1.1). These proteins are not amphipathic and do not associate with the internal region of the membrane. The membrane proteins provide a variety of important cellular functions by forming the following structures:

- Channels
- Carrier molecules
- Enzymes
- Chemical receptors
- Antigens

Some proteins may form *channels* through the cell membrane, which allow small water-soluble substances, such as ions, to enter or leave the cell. These channels are quite specific and allow only one type of ion to pass through it (e.g., sodium channels, calcium channels). Other proteins may serve as *carrier molecules* that selectively transport larger water-soluble molecules, such as glucose or cellular products, across the membrane. *Enzymes*, which regulate specific chemical reactions, are extrinsic proteins and are found on either the internal (e.g., adenylate cyclase) or the external (e.g., acetylcholinesterase) surfaces of the membrane. *Chemical receptors* are found on the outer surface of the cell membrane and selectively bind with various endogenous molecules such as neurotransmitters and hormones as well as drugs. Many substances that are unable to enter the cell and cause a direct intracellular effect may indirectly influence intracellular activity without crossing the membrane through receptor activation. Other proteins found on the external surface of the plasma membrane are *antigens*. These molecules serve as cell "markers" that allow the body's immune system to distinguish between our own cells and foreign cells or organisms, such as bacteria and viruses.

The plasma membrane contains a small amount of *carbohydrate* (2%–10% of the mass of the membrane) found predominantly on the outer surface. This carbohydrate is found attached to most of the protein molecules, forming glycoproteins, and to some of the phospholipid molecules (<10%), forming glycolipids. Consequently, the external surface of the cell has a carbohydrate coat, or glycocalyx.

These carbohydrate moieties have several important functions including the following:

- *Repel negatively charged substances*: many of the carbohydrates are negatively charged creating an overall negative charge on the surface of the cell that repels negatively charged extracellular molecules and helps to keep red blood cells apart from each other

- *Cell-to-cell attachment*: the glycocalyx of one cell may attach to the glycocalyx of another cell, which causes the cells themselves to become attached
- *Receptors*: carbohydrates may also serve as specific membrane receptors for extracellular substances, such as hormones
- *Immune reactions*: carbohydrates play a role in the ability of cells to distinguish between "self" cells and foreign cells

PHARMACY APPLICATION:
HYDROPHILIC DRUGS BIND TO RECEPTORS

Many substances within the body, including neurotransmitters and hormones, are hydrophilic and, therefore, are incapable of entering the cells to carry out their effects directly. Instead, they bind to their specific receptors on the cell surface. This receptor binding then elicits a series of intracellular events that alter cell function and cell metabolism. As such, there are many instances where it would be clinically advantageous to either enhance or inhibit these activities. Therefore, drugs may be designed to bind to these specific receptors. A drug that binds to and stimulates a receptor, mimicking the action of the endogenous chemical substance, is referred to as a receptor *agonist*. An example is albuterol sulfate, a selective β_2-adrenergic receptor agonist. Stimulation of β_2-adrenergic receptors on airway smooth muscle causes dilation of the airways in a patient experiencing an asthmatic attack and relieves the patient's wheezing. Conversely, a drug that binds to and blocks a receptor, preventing the action of the endogenous substance, is referred to as a receptor *antagonist*. An example in this case is cimetidine hydrochloride, which inhibits histamine H_2 receptors on parietal cells in the stomach. Because histamine H_2 receptor stimulation leads to gastric acid secretion, blockade of these receptors with an antagonist reduces acid secretion. While cimetidine hydrochloride is the active ingredient in Pepcid®, ranitidine hydrochloride, another histamine H_2 receptor antagonist, is found in Zantac® and works in much the same way. These drugs may be used to treat patients with a peptic ulcer or gastroesophageal reflux disease (GERD).

1.1.2 Membrane transport

The lipid bilayer arrangement of the plasma membrane renders it semipermeable. Uncharged or nonpolar molecules, such as oxygen, carbon dioxide and fatty acids, are lipid soluble and may permeate through the membrane quite readily. Charged or polar molecules, such as glucose, proteins, and ions, are water soluble and are impermeable and unable to cross the membrane unassisted. These substances require protein channels or carrier molecules to enter or leave the cell.