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SECTION IV Physiology of Synaptic Transmission

SECTION V Physiology of Muscle Contraction

1

Introduction: Homeostasis and Cellular Physiology

OBJECTIVES

1. Recognize the need to maintain the constancy of the internal environment of the body and the concept of homeostasis.
2. Describe the hierarchical view of the body as an ensemble of distinct compartments.
3. Describe the composition and structure of the lipid bilayer membranes that encompass cells and organelles.
4. Explain why the protein-mediated transport processes that regulate the flow of water and solutes across biomembranes are essential to all physiological functions.

HOMEOSTASIS ENABLES THE BODY TO SURVIVE IN DIVERSE ENVIRONMENTS

Humans are independent, free-living animals who can move about and survive in vastly diverse physical environments. Thus we find human habitats ranging from the frozen tundra of Siberia and the mountains of Nepal[a] to the jungles of the Amazon and the deserts of the Middle East. Nevertheless, the elemental constituents of the body are cells, whose survival and function are possible only within a narrow range of physical and chemical conditions, such as temperature, oxygen concentration, osmolarity, and pH. Therefore the whole body can survive under diverse external conditions only by maintaining the conditions around its constituent cells within narrow limits. In this sense the body has an **internal environment,** which is kept constant to ensure survival and proper functioning of the body's cellular constituents. The process whereby the body maintains constancy of this internal environment is referred to as **homeostasis.**[b] When homeostatic mechanisms are severely impaired, as in a patient in an intensive care unit, artificial life support systems become necessary for maintaining the internal environment.

Achieving homeostasis requires various component physiological systems in the body to function coordinately. The musculoskeletal system enables the body to be motile and to acquire food and water. The gastrointestinal system extracts nutrients (sources of both chemical energy, such as sugars, and essential minerals, such as sodium, potassium, and calcium) from food. The respiratory (pulmonary) system absorbs oxygen, which is required in oxidative metabolic processes that "burn" food to release energy. The circulatory system transports nutrients and oxygen to cells while carrying metabolic waste away from cells. Metabolic waste products are eliminated from the body by the renal and respiratory systems. The complex operations of all

[a]The adaptability of humans is remarkable: humans can survive on Mount Everest, which, at 29,028 feet above sea level, is at the cruising altitude of jet airplanes. At the summit the temperature is approximately −40° Celsius (same as −40° Fahrenheit), the thin atmosphere supplies only about one third of the oxygen at sea level, and the relative humidity is zero.

[b]The concept of the internal environment was first advanced by the 19th-century pioneer of physiology Claude Bernard, who discussed it in his book, *Introduction à l'étude de la médecine expérimentale* in 1865. Bernard's often-quoted dictum is: "The constancy of the internal environment is the prerequisite for a free life." ("*La fixeté du milieu intérieur est la condition de la vie libre.*" from *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux,* 1878.) The term "homeostasis" was introduced by Walter B. Cannon in his physiology text, *The Wisdom of the Body* (1932).

the component systems of the body are coordinated and regulated through **biochemical signals** released by the endocrine system and disseminated by the circulation, as well as through electrical signals generated by the nervous system.

THE BODY IS AN ENSEMBLE OF FUNCTIONALLY AND SPATIALLY DISTINCT COMPARTMENTS

The organization of the body may be viewed hierarchically (Fig. 1.1). The various systems of the body not only constitute functionally distinct entities, but also comprise spatially and structurally distinct compartments. Thus the lungs, the kidneys, the various endocrine glands, the blood, and so on are distinct compartments within the body. Each compartment has its own local environment that is maintained homeostatically to permit optimal performance of different physiological functions.

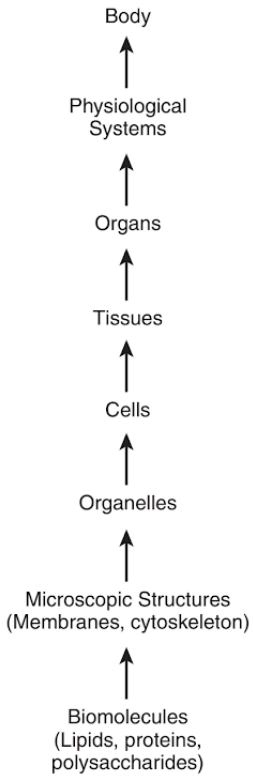

Fig. 1.1 Hierarchical View of the Organization of the Body. (Modified from Eckert, R., & Randall, D. (1983). *Animal physiology: mechanisms and adaptations* (2nd ed.). San Francisco: W.H. Freeman.)

Compartmentation is an organizing principle that applies not just to macroscopic structures in the body, but to the constituent cells as well. Each cell is a compartment distinct from the extracellular environment and separated from that environment by a membrane (the *plasma membrane*). The intracellular space of each cell is further divided into subcellular compartments (cytoplasm, mitochondria, endoplasmic reticulum, etc.). Each of these subcellular compartments is encompassed within its own membrane, and each has a different microscopic internal environment to allow different cellular functions to be carried out optimally (e.g., protein synthesis in the cytoplasm and oxidative metabolism in the mitochondria).

The Biological Membranes That Surround Cells and Subcellular Organelles Are Lipid Bilayers

Diverse "integral" membrane proteins are inserted into the **lipid bilayer membranes** that separate cells and subcellular compartments from the surrounding environment. Many of these proteins are **transmembrane proteins** that mediate the transport of various solutes or water across the bilayers. Ion channels and ion pumps are examples of such transport proteins. Other transmembrane proteins have signaling functions and transmit information from one side of the membrane to the other. Receptors for neurotransmitters, peptide hormones, and growth factors are examples of signaling proteins.

Biomembranes Are Formed Primarily From Phospholipids but Can Also Contain Cholesterol and Sphingolipids

Most of the lipids that make up biomembranes are *phospholipids.* These **amphiphilic** (or **amphipathic**) **phospholipids** consist of a **hydrophilic** (water-loving), or **polar,** phosphate-containing head group attached to two **hydrophobic** (water-fearing), or **nonpolar,** fatty acid chains. The phospholipids assemble into a sheet or *leaflet.* The polar head groups pack together to form the hydrophilic surface of the leaflet, and the nonpolar hydrocarbon fatty acid chains pack together to form the hydrophobic surface of the leaflet. Two leaflets combine at their hydrophobic surfaces to form a bilayer membrane.

The bilayer presents its two hydrophilic surfaces to the aqueous environment, whereas the hydrophobic fatty acid chains remain sequestered within the interior of the membrane (Fig. 1.2). The individual lipid molecules within the bilayer are free to move and are not rigidly packed. Therefore the lipid bilayer membrane behaves in part like a two-dimensional fluid and is frequently referred to as a **fluid mosaic.**

Biomembranes typically also contain other lipids such as cholesterol and sphingolipids. In animals, biomembranes usually contain significant amounts of cholesterol,

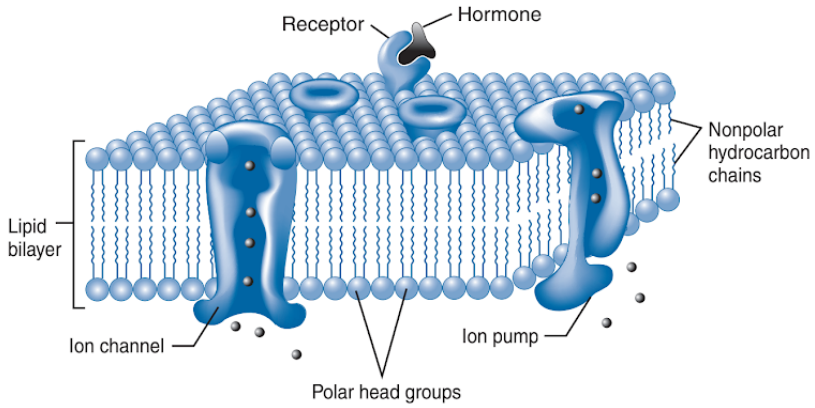

Fig. 1.2 Lipid Bilayer of the Plasma Membrane, With Various Membrane Proteins That Serve Transport and Signaling Functions. The locations of the polar head groups and nonpolar hydrocarbon chains of the phospholipids in the bilayer are shown. Also represented are a hormone receptor, an ion channel, and an ion pump.

a nonphospholipid whose presence modifies the fluidity of the membrane.

Biomembranes Are Not Uniform Structures

Different biomembranes vary in their lipid composition. For example, the plasma membrane is rich in cholesterol but contains almost no cardiolipin (a structurally complex phospholipid); the reverse is true for the mitochondrial membranes. Even the lipid compositions of the two leaflets constituting a single bilayer membrane can differ. For example, whereas phosphatidyl choline is most abundant in the outer leaflet of the plasma membrane, phosphatidyl serine is found almost exclusively in the inner leaflet. Such asymmetry can be maintained because flip-flop of lipid molecules from one leaflet to the other occurs naturally at an extremely slow rate.

Some cytoskeletal proteins bind to membrane proteins. These interactions enable the cytoskeleton to confer structural integrity on the membrane. Just as important, such interactions, by grouping and "tethering" membrane proteins, also organize membrane proteins into functional **membrane microdomains.** Such microdomains are compositionally and functionally different from other regions of the membrane. Thus it should be apparent that most biomembranes are not uniform either in composition or in architecture but are highly organized structures with different microdomains serving different functions.

TRANSPORT PROCESSES ARE ESSENTIAL TO PHYSIOLOGICAL FUNCTION

Each compartment within the body, whether microscopic or macroscopic, has the optimal biochemical composition to enable a different set of physiological processes to take place. However, those very physiological processes tend to alter the composition within the compartments. In this light, homeostasis within each compartment implies that transport processes must operate continuously to adjust and maintain the internal environment of each compartment, including microscopic compartments such as those within subcellular organelles. Therefore transport mechanisms are central to homeostasis. Moreover, coordinated regulation of the physiological functions that occur in distinct compartments implies communication, that is, the transmission and reception of signals, between different compartments. At the subcellular level this is achieved through the generation and movement of biochemical signals, including **second messengers** such as inositol trisphosphate (IP_3), cyclic adenosine monophosphate (cAMP), or calcium ions (Ca^{2+}).

Extracellular (or intercellular) communication is mediated by biochemical signals and by electrical signals. Many biochemical signals (e.g., hormones and growth factors) are secreted by specialized cells and are disseminated through the circulation to distant targets. Other biochemical signals (e.g., neurotransmitters; see Section IV) mediate local intercellular communication. The electrical signals are generated and propagated through the transport of certain ions across the membranes of "excitable" cells (Chapters 5 to 7). By their nature, the signaling mechanisms themselves alter the composition of the cells from which they originate. Thus the composition of those cells, too, must be continually restored. Therefore transport processes are also fundamental to the coordinated regulation of physiological processes in the body. Indeed, when membrane transport processes go awry, as may occur with mutations in transporter proteins,

homeostatic mechanisms are disrupted and physiology is adversely affected (this is referred to as **pathophysiology**). Examples of pathophysiological mechanisms are presented throughout this book.

CELLULAR PHYSIOLOGY FOCUSES ON MEMBRANE-MEDIATED PROCESSES AND ON MUSCLE FUNCTION

The foregoing description implies that homeostasis and its regulation depend on transport and signaling processes that occur at or through biological membranes. For this reason such **membrane-mediated processes** are essential to physiology and are a central theme of this text (Chapters 2 to 13). Of these membrane-mediated processes, passive diffusion and osmosis are fundamental physical processes that can occur *directly* through any lipid bilayer membrane and are the topics of Chapters 2 and 3, respectively. Most of the membrane-mediated processes can occur only through the agency of diverse protein machinery (e.g., ion channels, solute transporters, and transport ATPases or "pumps") residing in cellular membranes. These membrane protein–dependent processes are the subject of Chapters 4 to 13. A schematic representation of a cellular (plasma) membrane and some of the transport and signaling processes it mediates is shown in Fig. 1.2.

Although processes mediated by cellular membranes are fundamental to physiological function, they take place on a microscopic scale. The maintenance of life also requires action on a macroscopic scale. Thus acquisition of food and water requires body mobility; nutrient extraction requires maceration of food and its passage through the gastrointestinal tract; intake of oxygen and expulsion of carbon dioxide require expansion and contraction of air sacs in the lungs; and distribution of nutrients and dissemination of endocrine signals to various tissues require rapid transport of material through circulation. All these processes require movement on a macroscopic scale. The evolutionary solution to the problem of large-scale movements is *muscle*. For this reason the cellular mechanisms underlying muscle function constitute the other major theme of this text (Section V).

SUMMARY

1. To survive under extremely diverse conditions, the body must be able to maintain a constant internal environment. This process is referred to as *homeostasis*.
2. Homeostasis requires the coordination and regulation of numerous complex activities in all the component systems of the body.
3. The body can be viewed in terms of a hierarchical organization in which compartmentation is a major organizing principle.
4. Cells and subcellular organelles are compartments that are encompassed within biomembranes, which are lipid bilayer membranes.
5. Biomembranes are composed primarily of phospholipids and integral membrane proteins; the membranes may also contain other lipids such as cholesterol and sphingolipids.
6. Most of the integral membrane proteins span the membrane (i.e., they are transmembrane proteins) and are involved in signaling or in the transport of water and solutes across the membrane. These processes are essential for homeostasis.
7. Biomembranes are usually nonuniform structures: the inner and outer leaflets often have different composition. Many integral membrane proteins bind to elements of the cytoskeleton and may be organized into microdomains with specialized functions.
8. The transport processes mediated by integral membrane proteins such as channels, carriers, and pumps in cell and organelle membranes are essential for physiological function.
9. The maintenance of life also depends on movement on a macroscopic scale. Such movements are mediated by muscle.

KEY WORDS AND CONCEPTS

- Internal environment
- Homeostasis
- Biochemical signals
- Compartmentation
- Lipid bilayer membranes
- Transmembrane proteins
- Amphiphilic (or amphipathic) phospholipids
- Hydrophilic (polar)
- Hydrophobic (nonpolar)
- Fluid mosaic
- Membrane microdomains
- Second messengers
- Pathophysiology
- Membrane-mediated processes

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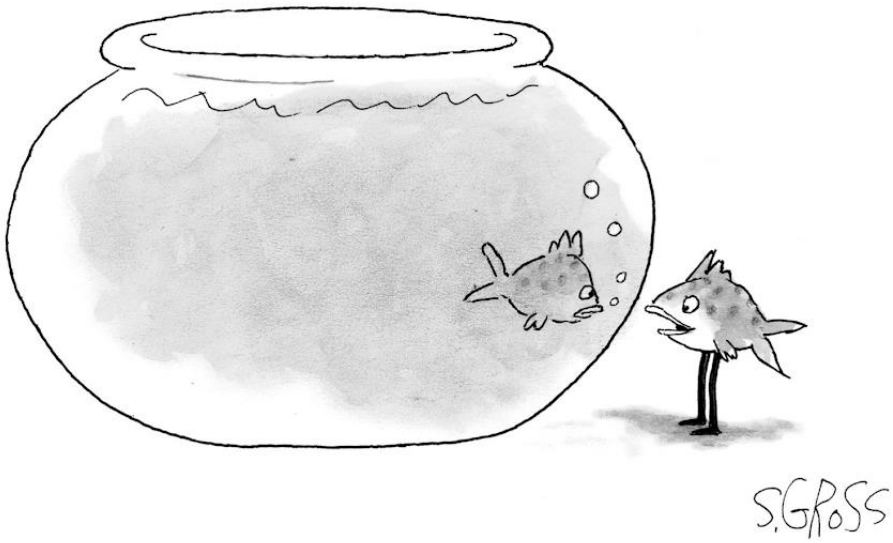

"In order to be free I had to make certain adjustments."

2

Diffusion and Permeability

OBJECTIVES

1. Define diffusion as the migration of molecules *down* a concentration gradient.
2. Recognize that diffusion is the result of the purely *random* movement of molecules.
3. Define the concepts of *flux* and membrane *permeability* and the relationship between them.

DIFFUSION IS THE MIGRATION OF MOLECULES DOWN A CONCENTRATION GRADIENT

Experience tells us that molecules always move spontaneously from a region where they are more concentrated to a region where they are less concentrated. As a result, concentration differences between regions gradually diminish as the movement proceeds. **Diffusion** always transports molecules from a region of high concentration to a region of low concentration, because the underlying molecular movements are completely *random*. That is, any given molecule has no preference for moving in any particular direction. The effect is easy to illustrate. Imagine two adjacent regions of comparable volume in a solution (Fig. 2.1). There are 5200 molecules in the left-hand region and 5000 molecules in the right-hand region. For simplicity, assume that the molecules may move only to the left or to the right. Because the movements are random, at any given moment approximately half of all molecules would move to the right and approximately half would move to the left. This means that, on average, roughly 2600 would leave the left side and enter the right side, whereas 2500 would leave the right and enter the left. Therefore a net movement of approximately 100 molecules would occur across the boundary going from left to right. This net transfer of molecules caused by **random movements** is indeed from a region of higher concentration into a region of lower concentration.

FICK'S FIRST LAW OF DIFFUSION SUMMARIZES OUR INTUITIVE UNDERSTANDING OF DIFFUSION

The preceding discussion indicates that the larger the difference in the number of molecules between adjacent compartments, the greater the net movement of molecules from one compartment into the next. In other words, the *rate* at which molecules move from one region to the next depends on the concentration difference between the two regions. The following definitions can be used to obtain a more explicit and quantitative representation of this observation:

1. **Concentration gradient** is the change of concentration, ΔC, with a change in distance, Δx (i.e., $\Delta C/\Delta x$).
2. **Flux** (symbol J) is the amount of material passing through a certain cross-sectional area in a certain amount of time.

With these definitions, the earlier observation can be simply restated as "flux is proportional to concentration gradient," or

$$J \propto \frac{\Delta C}{\Delta x} \qquad \textbf{(2.1)}$$

By inserting a proportionality constant, D, we can write the foregoing expression as an equation:

$$J = -D\frac{\Delta C}{\Delta x} \qquad \textbf{(2.2)}$$

The proportionality constant, D, is referred to as the **diffusion coefficient** or **diffusion constant**. The minus

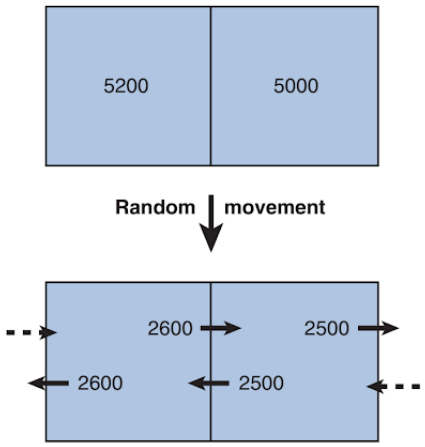

Fig. 2.1 Two Adjacent Compartments of Comparable Volume in a Solution. The left compartment contains 5200 molecules, and the right compartment contains 5000 molecules. If the molecules can only move randomly to the left or to the right, approximately half of all molecules would move to the right and approximately half would move to the left. This means that, on average, roughly 2600 would leave the left side and enter the right side, whereas 2500 would leave the right and enter the left. Thus about 100 molecules would spontaneously move from left to right.

sign accounts for the fact that the diffusional flux, or movement of molecules, is always *down* the concentration gradient (i.e., flux is from a region of high concentration to a region of low concentration). The graphs in Fig. 2.2 illustrate this sign convention.

Equation 2.2 applies to the case in which the concentration gradient is linear, that is, a change in concentration, ΔC, for a given change in distance, Δx. For cases in which the concentration gradient may not be linear, the equation can be generalized by replacing the linear concentration gradient, $\Delta C/\Delta x$, with the more general expression for concentration gradient, dC/dx (a derivative). The diffusion equation now takes the form

$$J = -D\frac{dC}{dx} \tag{2.3}$$

This equation is also known as **Fick's First Law of Diffusion**. It is named after Adolf Fick, a physician who first analyzed this problem in 1855.

To complete the discussion of Fick's First Law, we should examine the dimensions (or units) associated with each parameter appearing in Equation 2.3. Because flux, J, is the quantity of molecules passing through unit area per unit time, it has the dimensions of "moles per square centimeter per second" ($= [\text{mol/cm}^2]/\text{sec} = \text{mol}\cdot\text{cm}^{-2}\cdot\text{sec}^{-1}$). Similarly, the concentration gradient, dC/dx, being the rate

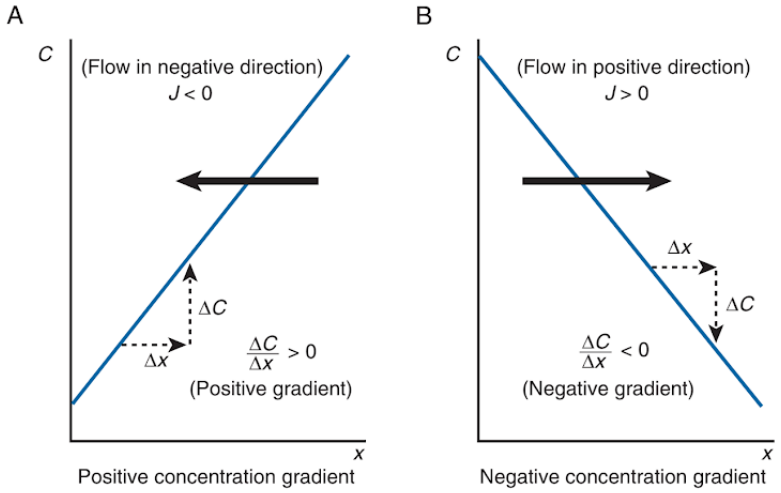

Fig. 2.2 The Direction (Sign) of the Concentration Gradients is Opposite to the Direction (Sign) of the Flux. (A) A positive concentration gradient: the concentration increases as we move in the positive direction along the x-axis ($\Delta C/\Delta x > 0$). The flux being driven by this positive gradient is in the negative direction. The concentration increases from left to right, but the flux is going from right to left. **(B)** A negative concentration gradient: the concentration decreases as we move in the positive direction along the x-axis ($\Delta C/\Delta x < 0$). The flux being driven by this negative gradient is in the positive direction. The concentration increases from right to left, but the flux is going from left to right.