A continuación encontrarán 3 fragmentos de diferentes secciones del libro Animal Phyisiology de Hill y Wyse, de los capítulos 12, 15 y 16. Hay una versión anterior en español en Biblioteca de Facultad.

CHAPTER
12

Neurons

Locomotion in a squid, whether for capturing a meal or to avoid becoming one, depends on jet propulsion: The contraction of muscles in the squid's outer mantle expels seawater through a moveable siphon, propelling the animal in the opposite direction. As is true in all animals, feeding, escape, and similar behaviors in the squid are controlled by nervous-system signals, which travel rapidly in a point-to-point manner, from one specific cell to another. These signals arise from properties of nerve cells—termed *neurons*—which have long cablelike processes—termed *axons*—that convey electrical signals rapidly and faithfully from place to place in the body, even over long distances. In the squid, sensory neurons such as those in the eyes encode information about the squid's environment and convey signals to the brain. There, the signals are integrated into a decision to attack or retreat. The brain then sends commands to the mantle muscles, in part through a set of large neurons with large ("giant"), rapidly conducting axons.

As you will discover in this chapter, squid giant axons have played an important role in our understanding of neuronal functions. The diameter of these giant axons can be as large as 1 mm (1000 micrometers [μm]), and for more than half a century investigators have taken advantage of this prodigious cellular size to perform noteworthy experiments that have revealed the mechanisms of neuronal signaling. Sir Alan Hodgkin (1914–1998), who received the Nobel Prize in 1963 for his work on squid axons, recalled that a colleague had remarked (not, he thought, with the greatest tact) that it was the squid that really ought to be awarded the prize!

This chapter describes the electrical basis of neuronal function—the ability of neurons to generate electrical signals and propagate them over relatively large distances. The cellular mechanisms of neuronal signaling are similar in all animals, whether we examine neurons of squid, cockroaches, jellyfish, or humans. Before we turn to neuronal function, however, it is important to take a broader look at the challenges of integration and control. Doing so will clarify the range of physiological control processes and the contrasting functions of neuronal and hormonal modes of integration.

The Physiology of Control: Neurons and Endocrine Cells Compared

An animal needs to function like a coherent organism, not like a loose collection of cells and intracellular mechanisms. **Integration** is a general term that refers to processes—such as summation and coordination—that produce coherency and result in harmonious function. *Cellular integration* refers to processes within cells. *Whole-animal integration* refers to the selective combination and processing of sensory, endocrine, and central nervous system (CNS) information in ways that promote the harmonious functioning of the whole organism—including all its cells, tissues, and organs—within its environment. Just as some cells are specialized to produce movements, secrete acid, or carry oxygen, nerve cells and endocrine cells are spe-

Squid axons are important to physiologists—and to the squid

cialized for control and coordination. Whole-animal integration is carried out by the nerve and endocrine cells. The integrative functions carried out by those cells ensure that an animal's responses are smooth and coordinated, rather than clashing or disjointed.

Control systems, initially described in Boxes 1.1 and 10.2, occupy a central place in the achievement of integration. In the abstract, a **control system** is a system that sets the level of a particular variable (temperature, blood pressure, muscle force, and so on) that is being controlled. To do so, it uses information from sensors to determine signals it sends to effectors that can modify the controlled variable. Control systems often (but not always) operate on negative feedback principles (see Box 1.1) and are stabilizing: When the controlled variable deviates from a desired level, the control system activates effectors to reverse the deviation.

The nervous and endocrine systems are also often described as *control systems* because nerve cells and endocrine cells control the ways in which other cells function. This use of the concept of control systems is complementary to the use discussed in the previous paragraph. To see the relations, consider that control systems of the sort discussed in the previous paragraph are present in inanimate objects such as cars and computers, where the physical entities that implement control functions are made of materials such as copper and silicon. In animals, control functions are mostly carried out by nerve cells and endocrine cells.

The nervous system and the endocrine system work in systematically different ways to control and coordinate the cells of an animal. As shown in **Figure 12.1*a***, a signal in a neuron travels electrically along a cell process all the way to its target cell; transmission along the cell process is very fast and spatially highly defined (a signal travels only along the cell process in which it was initiated). When the electrical signal arrives at the end of the neuron process, it causes the release of a chemical substance—a neurotransmitter—that diffuses quickly across the minute gap between the neuron process and the target cell. When this chemical substance arrives at the target cell, it binds (noncovalently) with specific receptor molecules on the cell, activating target-cell responses. In contrast, as shown in **Figure 12.1*b***, when an endocrine cell emits a signal, it does so by secreting a chemical substance—termed a **hormone**—into the general blood circulation. The signal travels more slowly than a neuronal signal because it is carried by blood flow, but instead of being spatially highly circumscribed, the signal is transmitted to all cells in the body. The target cells—the cells that respond—are the subset of cells that have receptor proteins for the hormone in their cell membranes. In the ensuing paragraphs, we will discuss the broad features of neural and endocrine control at greater length. Then, in the remainder of this chapter and in Chapters 13–15, we will consider aspects of neural control in detail (neurons, synapses, sensory functions, and the organization of whole systems of neurons). We will discuss endocrine control in detail in Chapter 16.

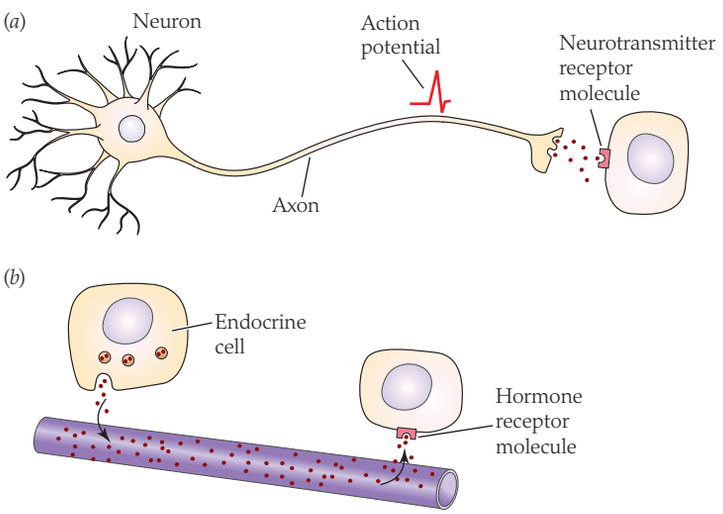


FIGURE 12.1 Neuronal and hormonal signaling both convey information over long distances Red dots are signaling molecules: neurotransmitter molecules in (*a*) and hormone molecules in (*b*). (*a*) Neurons have long axons that rapidly propagate action potentials, and also use short-distance chemical neurotransmitter signaling to communicate from cell to cell. (*b*) Endocrine cells release chemical hormones into circulatory fluids that carry the hormonal message over long distances to activate hormone receptors on other cells.

Neurons transmit electrical signals to target cells

Because neurons are commonly likened to the wires in a telephone or computer network, most people have an intuitive understanding of what these cells do. A **neuron** is a cell that is specially adapted to generate an electrical signal—most often in the form of a brief, self-propagating impulse called an *action potential*—that travels from place to place in the cell. As **Figure 12.2** reveals, a neuron has four parts—dendrites, cell body, axon, and presynaptic terminals—that generally correspond to its four functions—input, integration, conduction, and output—as a controller cell within an animal's body.

A neuron receives input—signals from other neurons or sensory cells—at specialized cell–cell contact points called **synapses**. Usually, the synaptic input occurs along branching *processes* known as **dendrites**, although synapses may occur on the cell body as well. Impulses arriving at a synapse from a *presynaptic* cell cause the release of a chemical substance called a **neurotransmitter** into the synaptic cleft, or space between the cells. The chemical neurotransmitter exerts specific physiological effects on the postsynaptic cell by binding to neurotransmitter receptors. These changes can result in a new electrical impulse in the target neuron. Thus a synapse allows for transmission of information between neurons through conversion of a signal from electrical to chemical to electrical.

The **cell body** (also called the *soma*) is commonly the part of a neuron where signal integration and impulse generation occur. A single neuron may receive thousands of synaptic contacts from other neurons. The neurotransmitters released across some synapses excite the neuron; those released across other synapses inhibit it. From moment to moment, the cell membrane of the cell body combines the inhibitory and excitatory synaptic inputs, and if excitatory inputs surpass inhibitory inputs, the neuron may respond by generating one or more action potentials.

The long slender **axon** is the conduction component of a neuron, serving to propagate action potentials along its length. The axon typically arises from the soma via a conical **axon hillock**, which leads to the **axon initial segment**, a specialized area that is commonly the site of action potential initiation. The microscopic axons from individual neurons sometimes collect together in long macroscopically visible bundles that are called *tracts* in the CNS and *nerves* in the peripheral nervous system.

Where an axon ends, it usually divides into several **presynaptic terminals**, which constitute the places where neuronal output occurs.

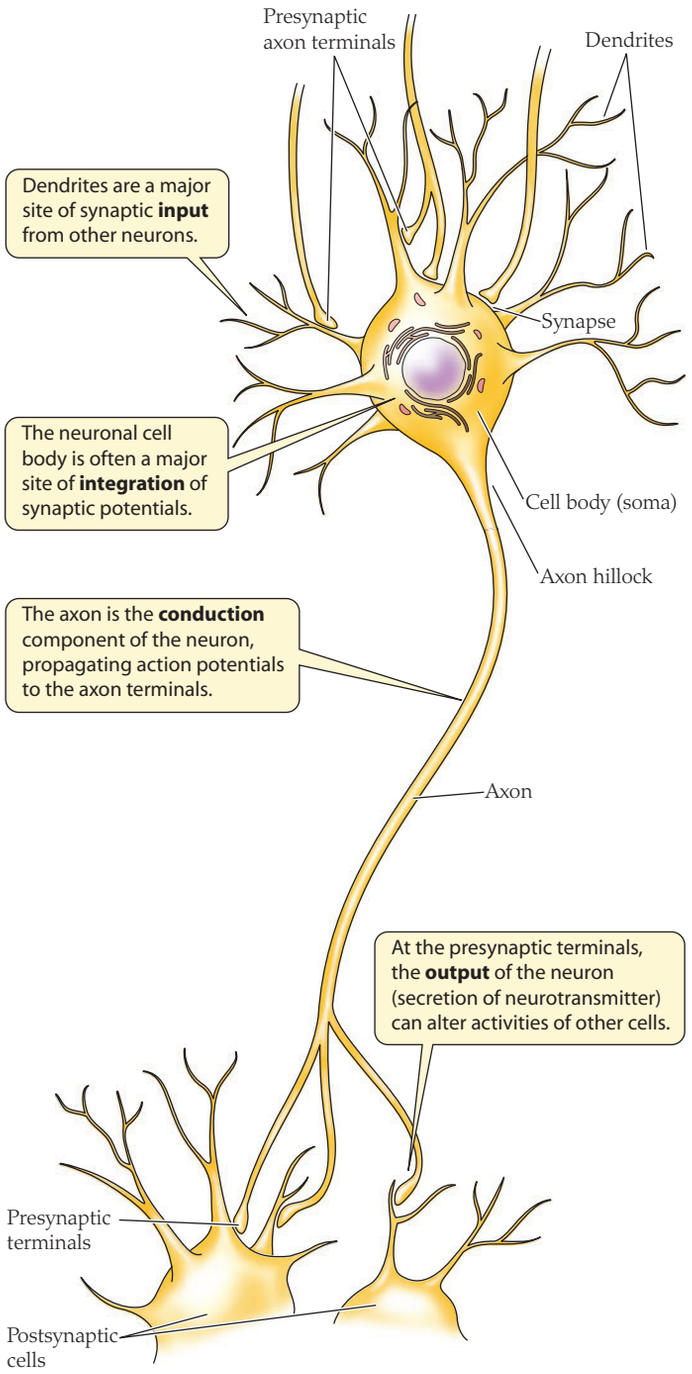


FIGURE 12.2 Neurons have four functional regions that typically correspond to their four major structural regions The descriptions in the figure provide a functional model of a neuron, showing typical functional properties that it mediates. The labels identify the structural parts of a neuron that are associated with these functions. The correlation between structures and functional properties is imperfect: Synaptic input often occurs at the cell body as well as the dendrites, for example, and some dendrites can generate action potentials. In contrast, some local neurons generate no action potentials at all, and thus lack a separate function of active conduction.

The presynaptic terminals form synapses with other neurons or other types of cells, such as muscle fibers (muscle cells). An action potential arriving at the presynaptic terminals triggers the release of molecules of neurotransmitter across the synapses to exert a specific physiological effect—excitatory or inhibitory—on the target cell. Neurons that form synaptic endings on a cell are said to **innervate** that cell.

The extended networks of neurons in an animal's body (along with supporting cells, described later) constitute its *nervous system*. Neurons perform various roles in the nervous system. Some neurons perform sensory functions by initiating signals in response to physical or chemical stimuli. As we have just described, other neurons integrate signals arriving from other neurons, generate nerve impulses of their own, and transmit these signals over distances that can be very long, at least on a cellular scale. As we will discuss in Chapter 15, animals have a *central nervous system* (CNS) (brain and spinal cord in vertebrates) and a *peripheral nervous system*. Neurons that relay sensory signals to integrative centers of the CNS are called **afferent neurons** (*afferent*, "to bring toward"). Other neurons, called **efferent neurons** (*efferent*, "to carry off"), relay control signals (instructions) from the CNS to target cells that are under nervous control, such as muscle cells or secretory cells. Neurons that are entirely within the CNS are called **interneurons**.

Neural control has two essential features: It is fast and addressed. Neuronal signals are *fast* in that they travel very rapidly and begin and end abruptly. A mammalian neuronal axon, for example, might conduct impulses along its length at 20 to 100 meters per second (m/s), and it might be capable of transmitting 100 or more impulses in a second. The connections of neurons are said to be *addressed* because they provide highly discrete lines of communication (like a letter or a telephone call). A neuron normally must make synaptic contact with another cell to exert control, and it typically innervates multiple, but relatively few, cells that are its potential targets. Neuronal lines of communication therefore provide opportunities for fine control of other cells both *temporally* and *spatially*, sending fast, rapidly changing signals to some potential targets and not to others.

Endocrine cells broadcast hormones

In contrast to the signals of the neurons in nervous systems—which are precisely targeted—the signals produced by the *endocrine system* are broadly distributed throughout the animal's body. Endocrine cells release *hormones* into the blood (or sometimes just into other extracellular fluids). These chemicals are carried throughout the body by the blood, bathing the tissues and organs at large. For a hormone to elicit a specific response from a cell, the cell must possess *receptor proteins* for that hormone (see Chapter 2, page 58). Thus cells of only certain tissues or organs respond to a hormone and are called *target cells*. The responsiveness of target cells is under control of gene expression; that is, the tissues that respond to a hormone are tissues that express the genes encoding its receptor proteins.

Endocrine control has two essential features: It is slow and broadcast. Individual hormonal signals are relatively *slow* because they operate on much longer timescales than individual neuronal signals. Initiation of hormonal effects requires at least several seconds or minutes because a hormone, once released into the blood, must circulate to target tissues and diffuse to effective concentrations within the tissues before it can elicit responses. After a hormone has entered the blood, it may act on targets for a substantial amount of time before metabolic destruction and excretion decrease its concentration to ineffective levels. In the human bloodstream, for example, the hormones vasopressin, cortisol, and thyroxine display half-lives of about 15 minutes (min), 1 hour (h), and nearly 1 week, respectively. Thus a single release of hormone may have protracted effects on target tissues.

Unlike addressed neural control, endocrine control is said to be *broadcast*. Once a hormone is released into the blood, all cells in the body are potentially bathed by it. The specificity of hormone action depends on which cells have receptor molecules for the hormone. Many types of cells may respond to the hormone, perhaps with different types responding in different ways. Alternatively, a hormone may affect only one type of target cell, because only those target cells have the kind of receptor to which the hormone attaches. Although in principle hormones may exert either limited or widespread effects, in practice they commonly affect at least a whole tissue, and often multiple tissues.

Nervous systems and endocrine systems tend to control different processes

Neural lines of communication are capable of much finer control—both temporal and spatial—than is possible for endocrine systems. Not surprisingly, the two systems tend to be used to control different functions in the body. *Whereas the nervous system controls predominantly the fine, rapid movements of discrete muscles, the endocrine system typically controls more widespread, prolonged activities* such as metabolic changes.

Consider, for example, running to catch a fly ball in baseball. It requires rapid computation and very specific control of discrete muscles in split-second time, functions that can be mediated only by the nervous system. In contrast, the control of metabolism or growth requires the modulation of many tissues over a protracted period. In principle, an animal's nervous system *could* carry out a coordination task of this sort. To do so, however, the nervous system would need thousands of discrete axons between integrating centers and controlled cells, and would need to send trains of impulses along all these axons for as long as the modulation is required. In contrast, an endocrine gland can accomplish this task with greater economy, by secreting a single long-lasting chemical into the blood. For this reason, control of metabolism is often under primarily hormonal control, as are other processes (growth, development, reproductive cycles, etc.) that involve many tissues and occur on timescales of days, months, or years.

Most tissues in an animal's body are under dual control of the nervous and endocrine systems. Skeletal muscle illustrates the relationship of this dual control. A typical vertebrate muscle contains thousands of muscle cells (muscle fibers) and is innervated by more than 100 motor neurons. Each motor neuron innervates a separate set of muscle fibers, controlling the contraction of just these fibers. The nervous system can selectively activate a few, many, or all of the motor neurons, to rapidly and precisely control the amount of force the muscle generates. At the same time that the nervous system controls the contractile activity of the muscle cells, the hormone insulin provides endocrine control of their metabolic activity. Insulin facilitates the muscle fibers' uptake of glucose from the blood and their rate of glycogen synthesis. This example emphasizes the spatial and temporal distinctions between the two types of control: The nervous system controls moment-to-moment, differential contractile actions of the muscle cells in a muscle, whereas the endocrine system provides simultaneous long-term metabolic control of all the muscle cells en masse.

Nervous and endocrine systems can exert control over each other, as well as over other targets. *Interaction between the nervous and endocrine systems occurs in both directions.* Nervous systems can affect the function of endocrine cells, as in innervated endocrine glands. Likewise, hormones can modulate nervous system function; for example, sex steroid hormones affect certain neurons in mammalian brains.

SUMMARY **The Physiology of Control: Neurons and Endocrine Cells Compared**

- Control by a nervous system involves neurons that send axons to discrete postsynaptic cells. Neurons generate rapidly conducting action potentials to control the specific targets on which they end. They exert fast, specific control by releasing neurotransmitters at synapses.
- Endocrine cells release hormones into the bloodstream to mediate endocrine control. All body cells are potential targets of a hormone, but only those with specific receptors for the hormone actually respond. Hormonal control is slower, longer lasting, and less specific than neural control.

Neurons Are Organized into Functional Circuits in Nervous Systems

The functions of a nervous system depend on "wiring"—the anatomical organization by which neurons are connected into circuits. Any behavioral activity (such as swimming, in the squid with which we opened the chapter) is a property of the neural circuit that mediates it. We will discuss nervous system organization in Chapter 15, but here we provide a simple illustrative example. Suppose you walk into the kitchen and surprise a cockroach. The cockroach jumps, exhibiting a *startle response* in which it turns away from the disturbance and prepares to run. This simple behavioral act is mediated by electrical signals and chemical synapses within the cockroach's nervous system.

The cockroach's jump is a **reflex**, a simple, stereotyped behavioral response to a distinct stimulus. Air currents or airborne sound waves vibrate filiform hairs that act as wind receptors at the cockroach's posterior end (**Figure 12.3**, ❶), providing the stimulus that evokes the reflex. This stimulus initiates a brief series of action potentials in sensory neurons ❷ located at the bases of the hairs. The action potentials travel along the conducting afferent processes (axons) of the sensory neurons toward the CNS, where the sensory neurons contact other neurons in the CNS. In the cockroach, the sensory axons make synaptic contacts with a few large *interneurons* (neurons that do not extend outside the CNS). These synapses are excitatory, so the barrage of action potentials from the sensory neurons excites the interneurons ❸, which generate their own action potentials.

The interneuron axons extend anteriorly in the ventral nerve cord (part of the CNS). They in turn make synaptic contact with efferent **motor neurons**, whose outgoing axons exit the CNS and innervate a muscle. The interneurons synaptically excite the motor neurons ❹, which in turn excite the extensor muscles of the legs ❺ that produce the jump. At the same time, the interneurons inhibit motor neurons that excite the antagonist flexor muscles of the cockroach's legs.

As the barrage of action potentials in Figure 12.3 indicates, this startle response happens very quickly: It is less than 150 milliseconds (ms) from stimulus to jump! This rapid and selective activation of

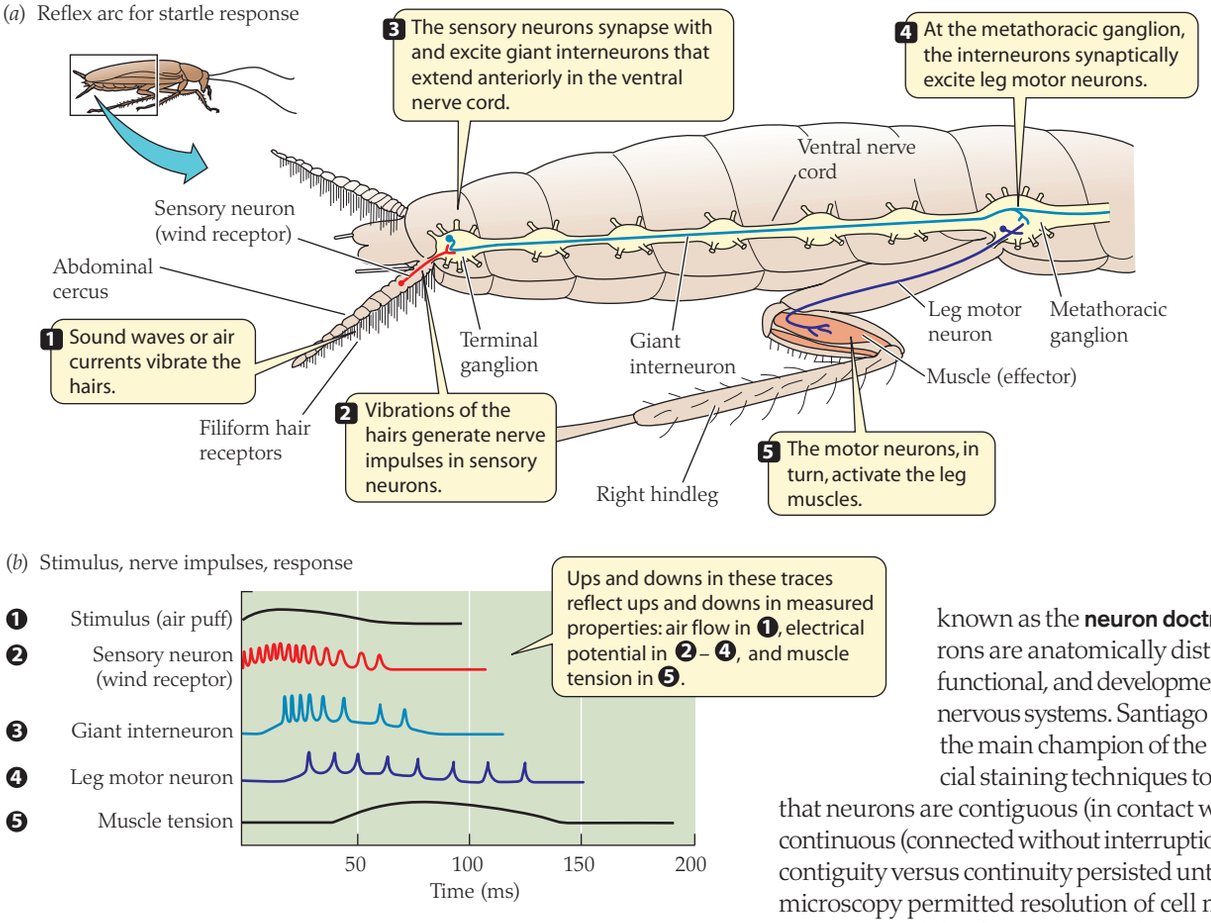


FIGURE 12.3 The neural circuit mediating the startle response in the cockroach *Periplaneta americana* (*a*) Hairlike wind receptors located on an abdominal cercus trigger this reflex. (*b*) Nerve and muscle cells in the reflex circuit respond to a controlled puff of air lasting 50 ms. The action potentials in successive neurons in the circuit lead to contraction (tension) in the muscle of the leg. (After Camhi 1984.)

particular muscles to generate a behavioral response is the essential element of neural control.

The Cellular Organization of Neural Tissue

Nervous systems are composed primarily of neural tissue, which in turn is composed of discrete cells: neurons and glial cells (see page 300), as well as connective tissue cells and cells of the circulatory system. The cellular organization of nervous systems is a corollary of the **cell theory**, which states that organisms are composed of cells, that these cells are the structural and functional units of organization of the organism, and that all cells come from preexisting cells as a result of cell division. Matthias Schleiden (1804–1881) and Theodor Schwann (1810–1882) formulated the cell theory in 1839.

The cell theory gained widespread and rather rapid acceptance—except as applied to nervous systems. Instead, the dominant view of the organization of nervous systems in the latter half of the nineteenth century was the **reticular theory**, most strongly argued by Joseph von Gerlach (1820–1896) and Camillo Golgi (1843–1926). The reticular theory held that nervous systems were composed of complex, continuous meshworks of cells and processes in protoplasmic continuity with each other (i.e., the cells ran together without any boundaries).

The reticular theory was supplanted only gradually, over the first third of the twentieth century, by an outgrowth of the cell theory known as the **neuron doctrine**, which states that neurons are anatomically distinct and are the structural, functional, and developmental units of organization of nervous systems. Santiago Ramón y Cajal (1852–1934), the main champion of the neuron doctrine, used special staining techniques to demonstrate convincingly that neurons are contiguous (in contact with each other) but are not continuous (connected without interruption). However, the debate on contiguity versus continuity persisted until the 1950s, when electron microscopy permitted resolution of cell membranes and rigorously demonstrated the discontinuity of neurons in contact.

Neurons are structurally adapted to transmit action potentials

Neurons, as seen earlier, are cells that are specialized for generating electrical impulses and transmitting those impulses from place to place within the body, sometimes over considerable distances. They have long processes, which relate to their functions—acting, for example, as the conduits for long-distance transmission. As you will recall, a neuron consists of a *cell body*, or *soma* (plural *somata*) (also called the *perikaryon*), which is the region that contains the nucleus, and one or more *processes* arising from it (Figure 12.4).

The cytology of a neuronal soma is broadly similar to that of nonneuronal cells. It contains a nucleus and most of the organelles and cytoskeletal elements familiar to cytologists: mitochondria, Golgi apparatus, smooth endoplasmic reticulum (ER), rough ER, microtubules, neurofilaments, and actin microfilaments. Neurons are very active in protein synthesis and thus have extensive, well-developed rough ER, aggregates of which can be stained to appear in light microscopy as *Nissl substance*.

Neurons can be classified according to the number of processes emanating from the soma. Neurons may be unipolar (having one process), bipolar (two processes), or multipolar (three or more processes). Unipolar neurons predominate in the CNS of most invertebrates, multipolar neurons predominate in the vertebrate CNS, and many sensory neurons are bipolar in various taxa. The neuronal processes themselves exhibit a bewildering geometric variety and complexity. Early anatomists attempted to bring order to this variety by classifying processes as *axons* and *dendrites*. Their classifications were usually based on vertebrate CNS neurons (see Figure 12.4) and are useful for cells resembling vertebrate central

neurons in form. Definitions of dendrites and axons, however, are based on a mixture of functional and morphological criteria that do not always coincide in a single neuron. Functionally (as we noted previously) a *dendrite* is considered to be a *receptive element* of a neuron that conveys information toward the soma (see Figure 12.2). An *axon*, by contrast, is the *output element* of a neuron, carrying information away from the cell body to other cells. This functional classification applies to most, but not all, neurons.

The dendrites of spinal motor neurons are relatively short and branch repeatedly (*dendrite* is Greek for "branch"). Dendrites of most neurons have continuously varying diameters and lack myelin sheaths (which we'll discuss shortly). In general, the broader dendritic trunks resemble the soma in fine structure; they contain rough ER, mitochondria, microtubules, neurofilaments, and an occasional Golgi apparatus. Thinner dendritic branches may lack Golgi apparatus and rough ER. The dendrites of many vertebrate neurons bear numerous short, thin protrusions termed *dendritic spines* that, when present, are important sites of synaptic input.

The axon of a neuron is classically single and long, with a relatively constant diameter and few collateral branches. The larger vertebrate axons are surrounded by **myelin** sheaths—multiple wrappings of insulating glial cell membranes (see below) that increase the speed of impulse transmission. Not all axons are myelinated; the smaller axons of vertebrate neurons and nearly all invertebrate axons lack myelin and are termed *unmyelinated*. At the fine structural level, axons contain microtubules, neurofilaments, elongated mitochondria, and sparse smooth endoplasmic reticulum (see Figure 12.4). Axons generally lack rough ER and Golgi apparatuses. Functionally, the axon is usually the portion of the neuron that supports action potentials, which *propagate* or conduct along the axon without decrement, carrying information away from the cell body to the axon terminals.

Glial cells support neurons physically and metabolically

Cells that are referred to collectively as **glial cells** or **neuroglia** ("nerve glue") surround the neurons (Figure 12.5). Rudolf Virchow (1821–1902) discovered and named the neuroglial cells in 1846 and thought that their primary function was to bind the neurons together and maintain the form and structural organization of the nervous system. The ratio of glial cells to neurons increases with increasing evolutionary complexity, from brains of fish to mammals. Glial cells are estimated to make up half the volume of the mammalian brain and to outnumber neurons by ten to one. These measures suggest that glial cells are important in nervous system function, perhaps in ways that are not yet fully understood.

Different types of glial cells play diverse functional roles in nervous systems. Vertebrate nervous systems have two kinds of ensheathing glial cells, called **Schwann cells** (in the peripheral nervous system, or PNS) and **oligodendrocytes** (in the CNS). Ensheathing glia envelop the axons of neurons (see Figure 12.5). The glial sheath can be a simple encircling of an *unmyelinated* axon or a group of axons, or a *myelin sheath* consisting of multiple concentrically wrapped layers of glial membrane that insulate the axon and increase the velocity of nerve-impulse propagation (discussed in detail later in this chapter). Other glial cells called **astrocytes** line

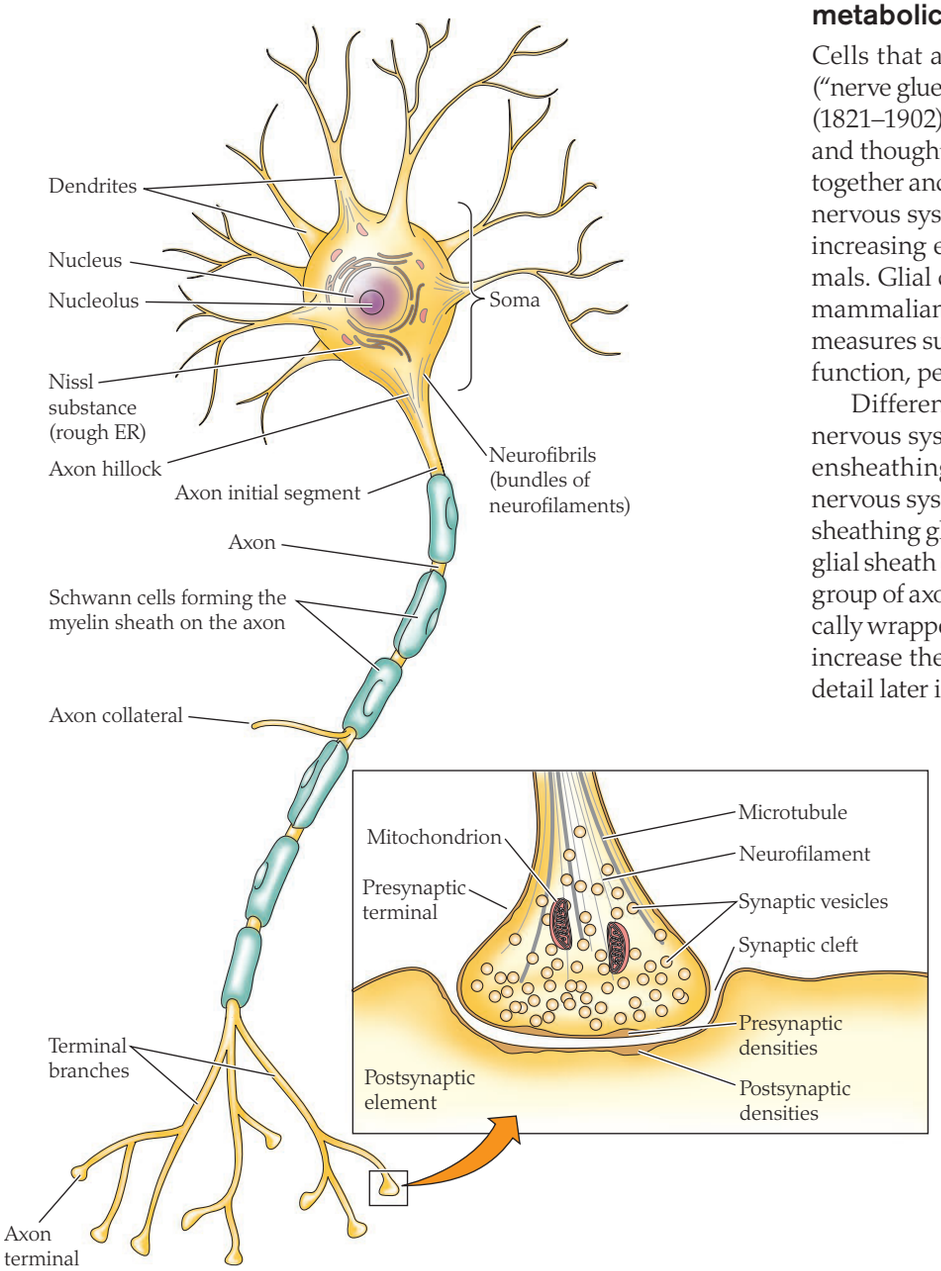


FIGURE 12.4 The cellular structure of neurons Every neuron has a cell body (soma or perikaryon) and processes usually classified as axons and dendrites. The inset shows the structure of the very end of the axon, the axon terminal. The soma contains organelles, including rough endoplasmic reticulum (ER), Golgi apparatus (not shown), and mitochondria. Stained aggregates of rough ER appear in light microscopy as Nissl substance. Cytoskeletal elements—microtubules and neurofilaments (see inset)—are present in the soma, dendrites, and axon. The axon of this neuron is myelinated, with periodic thickenings of myelin insulation around its axons. (The importance of the myelin sheath for the rate of propagation of nerve impulses is discussed later in this chapter; see page 323.) The axon ends in terminals, where synaptic vesicles (see inset) store molecules of neurotransmitter for synaptic transmission.

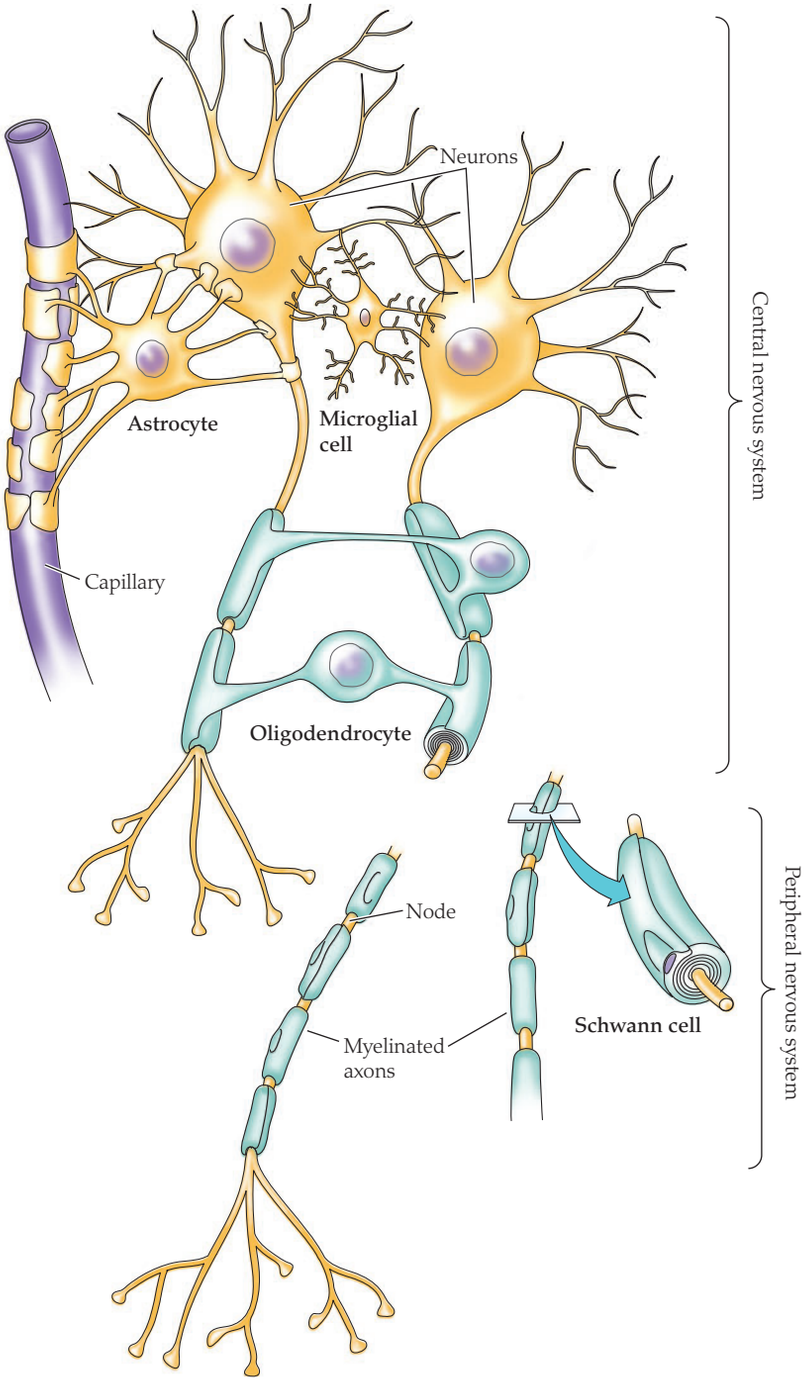


FIGURE 12.5 Glial cells There are four types of glial cells in vertebrate nervous systems. Schwann cells ensheathe axons (myelinated are shown; unmyelinated are not shown) in the peripheral nervous system. Oligodendrocytes ensheathe axons in the CNS. Astrocytes are metabolic support cells in the CNS. Microglial cells are phagocytes related to cells of the immune system.

the outside surfaces of capillaries in the vertebrate CNS and act as metabolic intermediaries between the capillaries and neurons. Astrocytes take up neurotransmitters from extracellular space and help supply metabolic substrates to neurons. They also regulate extracellular ion concentrations and play important roles in nervous system development. *Microglial cells* mediate immune responses in neural tissue and may act as phagocytes, consuming pathogens and cell debris in brain injury.

SUMMARY The Cellular Organization of Neural Tissue

- Neurons are the principal cells of nervous systems. They have long processes (dendrites and axons) that are specialized to receive signals from other neurons (via dendrites) and to generate and propagate action potentials (via axons).
- Glial cells are the support cells of the nervous system. Schwann cells (in the PNS) and oligodendrocytes (in the CNS) form sheaths around neuronal axons, including insulating myelin sheaths around myelinated axons. Astrocytes surround capillaries and act as metabolic intermediaries between neurons and their circulatory supply. Microglial cells serve immune and scavenging functions.

The Ionic Basis of Membrane Potentials

What are the properties of the electrical signals of neurons, and how are these signals generated? Let's begin with a brief review of basic electrical concepts. Protons and electrons have *electrical charge*, and **ions** are atoms or molecules that bear a net charge because they have unequal numbers of protons and electrons. The net movement of charges constitutes an **electric current** (I), which is analogous to the hydraulic current of fluids flowing in a system of pipes. The separation of positive and negative electrical charges constitutes a **voltage**, or electrical *potential difference* (V). This potential difference can do work when charges are allowed to flow as current. Voltage is analogous to a height difference or head of pressure in a hydraulic system, allowing water to flow downhill.

Figure 12.6 shows a simple electrical circuit, that of a flashlight. A battery provides voltage; closing the switch allows current to flow through the electrical circuit. The electric current in the flashlight is the flow of free electrons along metal wires. Current flows through the lightbulb filament, which acts as **resistance** (***R***) that limits the current flow. Consequently, the filament heats and glows, emitting light.

Electrical circuits in cells are similar to the circuit in a flashlight, but they differ in some important ways. In cells, both the inside and outside media are *aqueous* solutions in which the electrical charges are ions rather than free electrons. Furthermore, all currents in cells are carried by ions, and any voltage or potential difference results from local imbalances of ion charges. Recall from Chapter 5 (see Figure 5.4) that fluids farther than a few nanometers from a membrane are electrically neutral, with equal numbers of positive and negative charges.

Because of this *charge neutrality of bulk solutions*, the only portion of a cell that *directly* determines its electrical properties is its outer-limiting cell membrane. Any electrical activity of a nerve cell is a property of the cell membrane, and the electrical potentials observed are called *transmembrane* potentials. The only immediately important attribute of the rest of the cell is the concentration of ions in solution in the intracellular fluid.

CHAPTER

15

Nervous System Organization and Biological Clocks

Pictured here is a star-nosed mole (*Condylura cristata*). Star-nosed moles, like other moles, are *fossorial*: they live underground and dig for their food, which consists of small invertebrates. Moles have greatly reduced visual systems and are often considered blind, but some are sensitive at least to light levels. Star-nosed moles have evolved a stellate array of fleshy fingerlike structures (shown in the photograph). The function of this "star" is tactile; it contacts the ground as many as 10–15 times per second and enables the mole to forage efficiently on small prey. The star-nosed mole may seem like an odd animal with which to introduce the integrative functions of nervous systems. But it illustrates two general points. First, the activities of the many cells in the mole's body must be controlled and coordinated in order for the mole to function and behave as a mole, rather than as just a mass of cells. In Chapter 2 we introduced controls *within* cells, mediated by cell-membrane receptors, second messengers, enzymes, transcription factors, and the like. Our focus here is control, coordination, and integration of activities *among* cells—that is, *inter*cellular control. Such control is the major functional role of the nervous system, and of the endocrine system. In the last three chapters we considered the cellular elements of nervous systems, the synaptic interactions of neurons, and the ways in which environmental information is acquired by sensory processes. In this chapter we consider how entire nervous systems are organized for the specific and adaptive control of sets of cells. (Endocrine control is treated separately, in Chapter 16.)

The second point that the star-nosed mole illustrates is that control systems such as the nervous system are not only reactive, but also proactive. That is, although a nervous system functions to respond to changes in the outside world—stimuli in the animal's environment—it also coordinates its own activities without waiting for stimuli. Animals have *intrinsic* or *endogenous* functions such as daily rhythms of activity. Even if an animal cannot see day and night in its environment, its behavioral and physiological activities continue to cycle on a daily basis that anticipates the day–night cycle. This anticipatory activity is controlled by a *biological clock*—an endogenous, physiological timekeeping mechanism—that allows the animal to know when day will start, whether the animal sees light or not. Anticipation of this sort can be highly advantageous to an animal because it permits the animal to prepare physiologically and behaviorally for the new day, rather than merely waiting in a state of total ignorance about when the day will arrive. That this intrinsic rhythm persists without environmental cues doesn't diminish their importance, however. Environmental cues are necessary to reset the clock, *entraining* it to the outside world so that it does not drift earlier or later. In this chapter, in addition to discussing nervous systems in general, we will examine the biological clocks that control endogenous rhythms, as an example of the intrinsic, anticipatory functions of nervous systems.

How does this star-nosed mole control and integrate the functions of all the cells in its body?

The Organization and Evolution of Nervous Systems

The organization of neurons into functional nervous systems is what allows for the complexity of the neural control of animal physiology and behavior. We can define a **nervous system** as an organized constellation of cells (neurons and support cells) specialized for the repeated conduction of electrical signals within and between cells. These signals pass from sensory cells and neurons to other neurons and then to muscles, glands, or other organs that carry out actions. Nervous systems integrate the signals of converging neurons, generate new signals, and modify the properties of neurons based on their interactions. Nearly all animals have nervous systems. All nervous systems share similar characteristics, although they vary in the complexity of their organization and of their behavioral output.

Before we proceed to a closer look at the organization and evolution of nervous systems, we need to develop a framework of basic terms and organizational concepts that will facilitate our discussion. Some of these terms and concepts, although initially presented here, will be revisited and refined later in the chapter as well.

The nervous system in most types of animals consists of two major divisions: the *central nervous system* and the *peripheral nervous system*. The **central nervous system** (**CNS**) consists of relatively large structures such as the brain and spinal cord in which large numbers of neurons and support cells are anatomically juxtaposed and interact to achieve integrative functions. The CNS is rich with the cell bodies and processes (axons and dendrites) of neurons. Some neurons, called **interneurons**, are confined to the CNS. Other neurons are at least partially outside the CNS: Those that convey information to the CNS are **sensory neurons**, and those that convey information out of the CNS to control muscles or other effectors are **motor neurons**. An **effector** is an organ, tissue, or cell that *acts*—that carries out functions such as motion or secretion—under the direction of the nervous system (or endocrine system). Muscles and glands are examples of effectors. The **peripheral nervous system** (**PNS**), then, consists of all the processes and cell bodies of sensory and motor neurons that are present outside the CNS (including autonomic ganglia and the enteric nervous system, considered later).

In the PNS, a **nerve** consists of the axons of multiple neurons bundled together into a structure resembling a cable of telephone wires. Although individual axons are too minute to be seen without a microscope, a nerve is macroscopically visible because it consists of many axons. If one transects a nerve and looks at either stump under a microscope, one sees many axons in cross section, just as one sees the cross sections of many wires when one cuts a wire cable. Axons of multiple neurons are often bundled together in the CNS as well as in the PNS. Such bundles in the CNS are not called *nerves*, however. Instead they are called *tracts*, *commissures*, or *connectives*, as we will discuss later. Another term of importance in describing the anatomy of nervous systems is *ganglion*. A ganglion, speaking macroscopically, is a swelling positioned along a nerve or connective. Because further details of ganglion structure and function differ in different groups of animals, we will postpone a closer look at them until later in this chapter.

Physiologists recognize two primary divisions of the vertebrate PNS: the *somatic* and the *autonomic nervous systems*. These same divisions are sometimes recognized in the PNSs of invertebrates. The **somatic nervous system** is the part of the PNS that controls the skeletal (striated) muscles that generally produce voluntary movements; skeletal muscles are thus called **somatic effectors**. Sensory reception of external stimuli and transmission of this sensory information are also functions of the somatic nervous system. The **autonomic nervous system**, by contrast, is the part of the PNS that controls **autonomic effectors** (or **internal effectors**), defined to include all neuron-controlled effectors other than the striated muscles, such as cardiac muscle, smooth (nonstriated) muscles, and glands. The autonomic nervous system also has sensory neurons that convey information to the CNS about the internal organs. The somatic nervous system controls most observable behavior and therefore is the part of the PNS with which we are most familiar. Autonomic effectors exert most of their effects on visceral organs, internally and invisibly.

Nervous systems consist of neurons organized into functional circuits

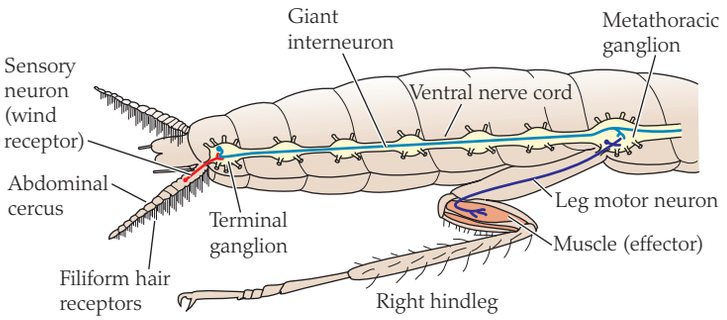
A good way to start a discussion of the cellular organization of nervous systems is to recall the example of the cockroach in Chapter 12 (page 299). As is typical of nervous systems in general, in the nervous system of the cockroach, cellular elements sense the environment, send signals to other cells (neurons) in the CNS, and ultimately control and coordinate cells of effectors to generate physiological or behavioral outputs. In the specific case we discussed (see Figure 12.3), wind-receptor sensory neurons were excited by an environmental mechanical stimulus, and those sensory neurons in turn synaptically stimulated interneurons that excited motor neurons to induce contraction of muscle cells, producing a reflexive behavioral response—a jump. **Figure 15.1** represents the cockroach's neural circuit as a block diagram, simplified to illustrate how this simple reflex in a cockroach exemplifies the general functional features of nervous systems:

- Neurons are organized in circuits in such a way that they can elicit a coordinated, adaptive response of effectors.
- Sensory receptor cells (which, like neurons, are excitable cells) transform environmental stimuli into electrical signals.
- Central interneurons integrate signals from sensory receptors and other signals arising within the animal, generating an integrated pattern of impulses.
- Motor commands are sent out from the CNS to effectors.

Many types of animals have evolved complex nervous systems

We have little direct knowledge of the evolution of nervous systems, which are rarely preserved in the fossil record. Theories of nervous system evolution are based on interpretations of the anatomy and the molecular genetics of living groups, a risky proposition because all groups alive today are highly evolved and none can be taken as representing a primitive condition. Comparative studies of living animals show that the *neurons* of the nervous systems of all animals, although diverse in form, are quite similar in their functional properties. For example, the neurons of all phyla have common molecular bases for their excitability and intercellular communication, with homologous voltage-gated channels and

(*a*) The startle response circuit of the cockroach



(*b*) Simplified diagram of the response circuit

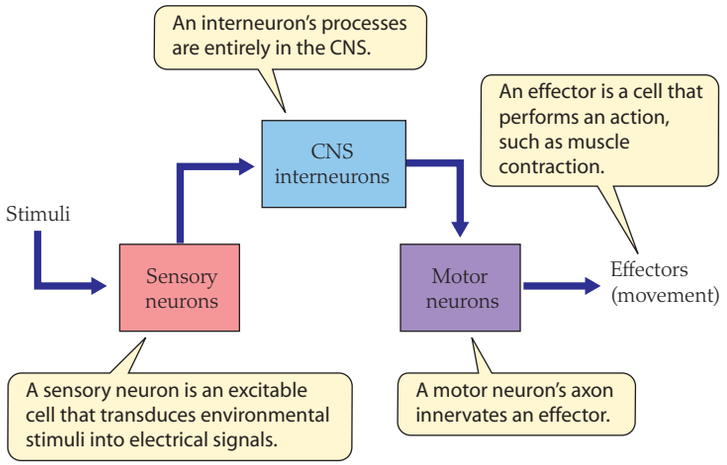


FIGURE 15.1 Neuronal elements in a nervous system: a neural circuit mediating the cockroach startle response (*a*) The startle response circuit (introduced in Figure 12.3) involves three neuronal elements: sensory neurons, interneurons, and motor neurons. (*b*) A simplified diagram of this circuit shows the basic functions of neural circuits in nervous systems. Sensory neurons convey signals about environmental stimuli to the central nervous system. These signals are integrated by central neurons and can trigger or modulate output signals of motor neurons to control effectors such as contracting muscle cells.

synaptic mechanisms. Moreover, the genetic controls of nervous system development show striking homologies in a wide range of phyla. The major changes in the evolutionary history of nervous systems appear to have involved changes in the *complexity of organization* of neurons into systems, rather than changes in the neurons themselves.

Two major trends characterize the evolution of nervous systems in the bilaterally symmetrical phyla of animals: centralization and cephalization. **Centralization** of nervous systems refers to a structural organization in which integrating neurons are collected into central integrating areas rather than being randomly dispersed. **Cephalization** is the concentration of nervous structures and functions at one end of the body, in the head. **Box 15.1** further discusses the evolution of diverse nervous systems; here we consider two major types of relatively complex nervous systems, those of arthropods and of vertebrates.

ARTHROPOD CENTRAL NERVOUS SYSTEMS ARE ORGANIZED AS CHAINS OF SEGMENTAL GANGLIA Animals with relatively complex central nervous systems exhibit two different major forms of CNS organization: *ganglionic* central nervous systems characteristic of protostomes, and *columnar* nervous systems characteristic of vertebrates and other deuterostomes (see the back endpapers for the protostome/deuterostome distinction). To see the features of ganglionic nervous system organization, we focus here on arthropods. Aspects of the organization of a ganglionic nervous system are also present in annelids and molluscs.

In arthropods, the CNS consists of a chain of segmental ganglia. **Ganglia** (singular *ganglion*) are swellings containing discrete aggregations of nerve cell bodies and processes. The chained ganglia are linked by paired bundles of axons called **connectives** (**Figure 15.2**). The CNS of an arthropod such as a cockroach consists of an anterior *brain* and a *ventral nerve cord* that is linked to the brain by connectives encircling the esophagus. The ventral nerve cord is a chain of ganglia linked by connectives—one ganglion for each thoracic and abdominal body segment. (Some arthropods show secondary fusion of some of these segmental ganglia.)

Each ganglion in the CNS of an arthropod consists of an outer *rind* and an inner *core*. The rind consists mostly of cell bodies of neurons and is devoid of axons and synapses. Indeed, nearly all neuronal cell bodies of arthropods are confined to the rinds of the central ganglia, the major exceptions being cell bodies of sensory neurons, many of which are located in the PNS. The inner core of each ganglion contains two regions: a region of synaptic contacts between axons and dendrites that is termed the **neuropil** (or *neuropile*) and a region of **tracts** (bundles) of axonal processes within the ganglion.

In arthropod or other ganglionic nervous systems, there are four terms for a bundle of nerve axons, depending on where the bundle is located. In the PNS a bundle of axons is a *nerve*, between ganglia in the CNS it is a *connective*, within a ganglion it is a *tract*,

BOX 15.1 EVOLUTION OF NERVOUS SYSTEMS

All multicellular animals except sponges have neurons and nervous systems. Sponges are primitive multicellular animals without organs and organized tissues. Although they lack neurons and synapses, they possess genes for many of the proteins that make up synaptic structures. In fact, genomic analyses have found many genes important for nervous system organization to be present in primitive, unicellular choanoflagellate protists. **Box Extension 15.1** describes the organization and evolution of nervous systems in different animal groups.

Azure vase sponge (*Callyspongia plicifera*)

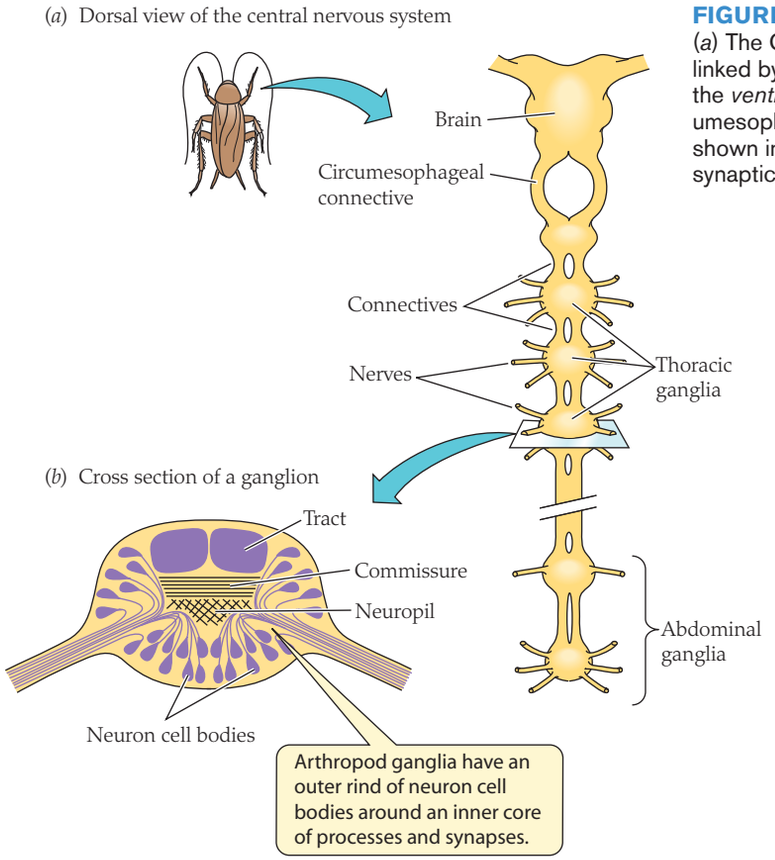


FIGURE 15.2 The organization of an arthropod central nervous system (*a*) The CNS, shown here in a dorsal view, consists of a chain of segmental ganglia linked by connectives. The circumesophageal connectives link the anterior *brain* to the *ventral nerve cord*, which consists of the linked ganglia posterior to the circumesophageal connectives. (Some abdominal ganglia are omitted.) (*b*) A ganglion, shown in cross section, contains an outer rind of cell bodies and an inner core of synaptic neuropil and of axons (tracts and commissures).

and between right and left sides of a bilaterally symmetrical ganglion it is a **commissure**. The terms *nerve*, *tract*, and *commissure* have the same meanings for vertebrate nervous systems, but vertebrate central nervous systems do not have connectives.

THE VERTEBRATE CENTRAL NERVOUS SYSTEM IS A CONTINUOUS COLUMN Vertebrate central nervous systems, in contrast to those of arthropods, are classed as columnar because they consist of a continuous column of neural tissue, with cell bodies and synaptic areas intermingled. The CNS of vertebrates consists of a brain and a spinal cord (Figure 15.3). It differs from the ganglionic CNSs of arthropods (and other protostomes) in several respects, some of which have already been mentioned. The vertebrate CNS is dorsal and hollow, and it develops from a neural tube that invaginates from the dorsal surface of the embryo. The nerve cords of arthropods, in contrast, are ventral and solid, do not arise by invagination, and have connectives between central ganglia. The vertebrate CNS, reflecting its origin as a continuous tube, is not clearly divided into ganglia and connectives, as is the arthropod CNS (compare Figure 15.3*a* with Figure 15.2*a*).

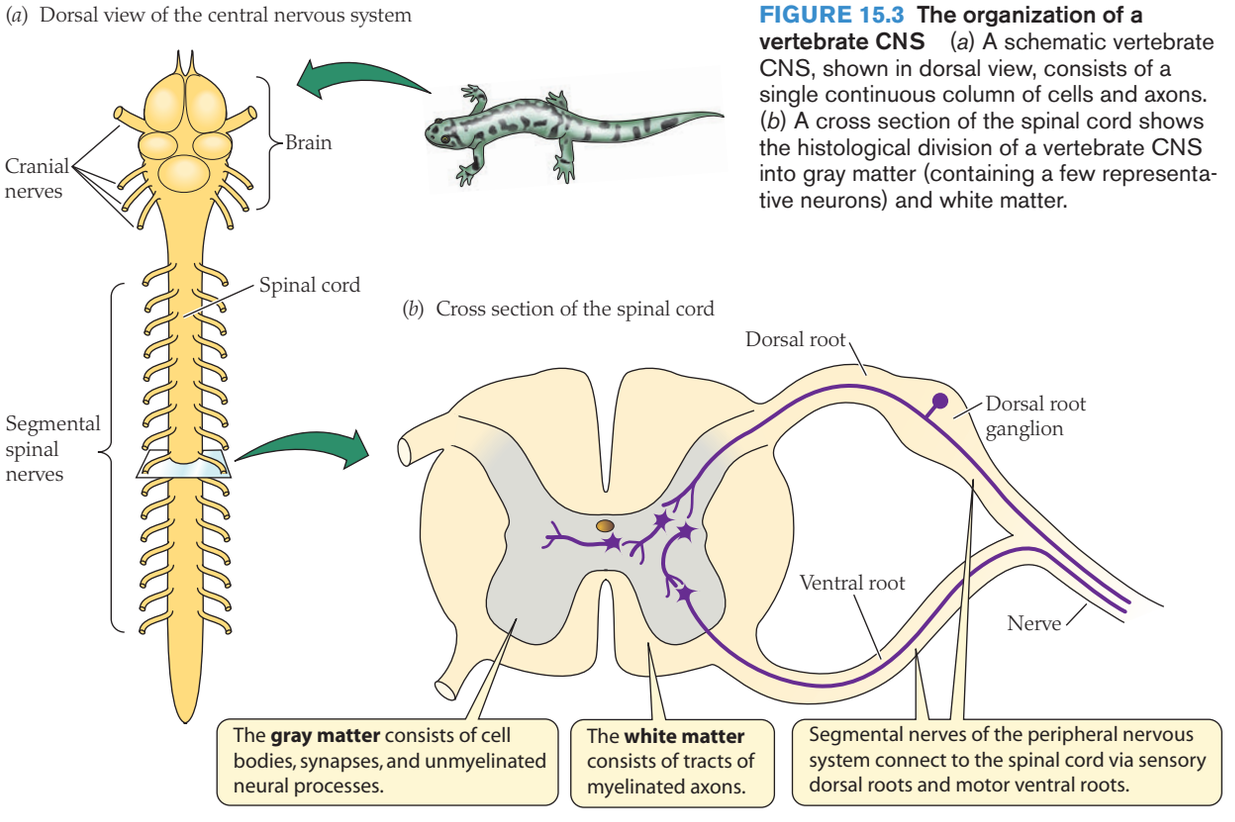


FIGURE 15.3 The organization of a vertebrate CNS (*a*) A schematic vertebrate CNS, shown in dorsal view, consists of a single continuous column of cells and axons. (*b*) A cross section of the spinal cord shows the histological division of a vertebrate CNS into gray matter (containing a few representative neurons) and white matter.

Despite the differences in organization between ganglionic and columnar CNSs, there is good evidence that the centralized organization of nervous systems in bilaterally symmetrical animals is an ancient characteristic that evolved once. In 1822, the French biologist Étienne Geoffroy Saint-Hilaire suggested that vertebrates were related to other Bilateria (animal phyla with bilateral symmetry) such as worms and arthropods, but that vertebrates were inverted, so that what had been a ventral nervous system in other groups became dorsal in the inversion. Anton Dohrn and others championed this idea in the later nineteenth century, but the idea was not taken very seriously until it received strong support from recent studies of expression of homologous patterning genes in the development of nervous systems in different phyla. Similarities in patterns of gene expression and control between vertebrates and protostomes (such as fruit flies and annelid worms) strongly suggest a common origin of CNS organization, with an inversion of the body axis of vertebrates as Saint-Hilaire envisioned.

SUMMARY **The Organization and Evolution of Nervous Systems**

- Animals have evolved nervous systems with varying degrees of centralization and complexity. There are homologies between the nervous systems of different animal groups.
- Most phyla of animals have bilateral symmetry and have evolved central nervous systems (CNSs) that centralize control functions. Sensory neurons convey information into the CNS, and motor neurons convey outward commands to effectors. CNSs usually have some degree of cephalization (concentration of neural structures into a clear anterior brain).
- Arthropods have a ganglionic nervous system, one major form of nervous system organization. The arthropod CNS is a ventral ladderlike chain of segmental paired ganglia joined by connectives. A vertebrate CNS, in contrast, is a continuous column of cells and axons.

The Vertebrate Nervous System: A Guide to the General Organizational Features of Nervous Systems

The nervous systems of most animals tend to share common organizational features. Here we discuss these organizational features using vertebrate nervous systems as examples. Keep in mind, however, that many of these organizational features apply to nervous systems in general. The vertebrate nervous system is organized into different regions that are discrete in gross structure, although neurons and their functions may cross these boundaries.

Nervous systems have central and peripheral divisions

The division of nervous systems into central and peripheral divisions was stressed earlier but deserves reiteration because it is of such pivotal importance. For a vertebrate, the CNS consists of the brain and spinal cord, and the PNS consists of nerves that connect the CNS to various parts of the body (Figure 15.4). Peripheral nerves contain axons of **afferent** neurons—neurons that carry nerve impulses *toward* the CNS (e.g., sensory neurons)—and axons of **efferent** neurons that carry nerve impulses *away* from the CNS (e.g., motor neurons). The vertebrate PNS also includes **peripheral ganglia**, which are collections of neuronal cell bodies associated with peripheral nerves. (These should not be confused with the *central* ganglia of arthropod nervous systems.) As in other animals, the vertebrate PNS conveys sensory input to the CNS, and it conveys motor output (to control muscles and other effectors) from the CNS to the periphery. Effector functions include contraction, secretion, emission of light and heat, electric organ discharge, and other actions.

The central nervous system controls physiology and behavior

The vertebrate CNS demonstrates the two general principles of organization of complex nervous systems: centralization and

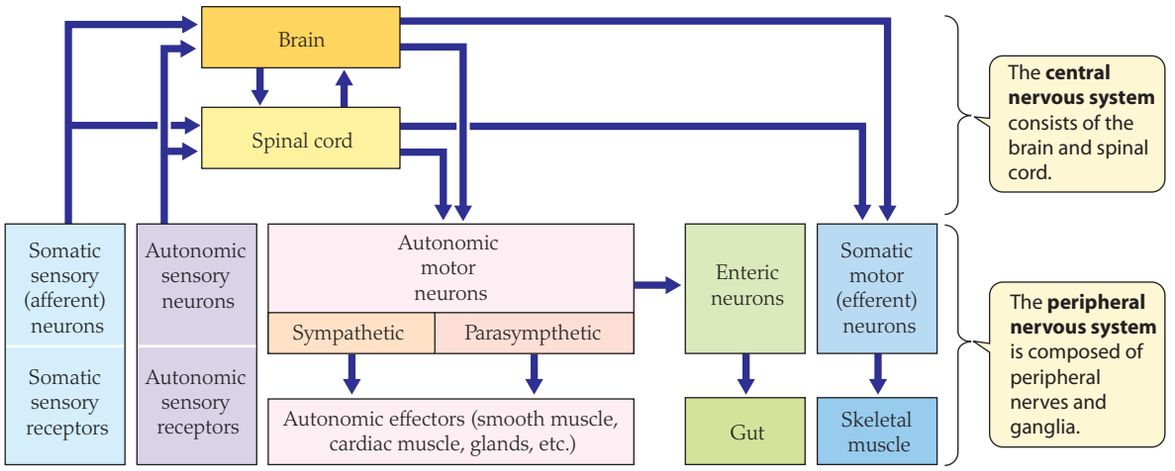


FIGURE 15.4 Divisions of the vertebrate nervous system are interconnected The most basic distinction is between the central nervous system (CNS) and the peripheral nervous system (PNS). The PNS has sensory and motor divisions. The somatic nervous system includes somatic receptors and afferent sensory neurons (these might be parts of the same sensory cell, or different cells), and efferent motor neurons controlling striated skeletal muscle. The autonomic nervous system includes autonomic sensory neurons and efferent neurons controlling internal autonomic effectors. The enteric division of the autonomic nervous system has some communication with the CNS but functions rather independently to control the gut.

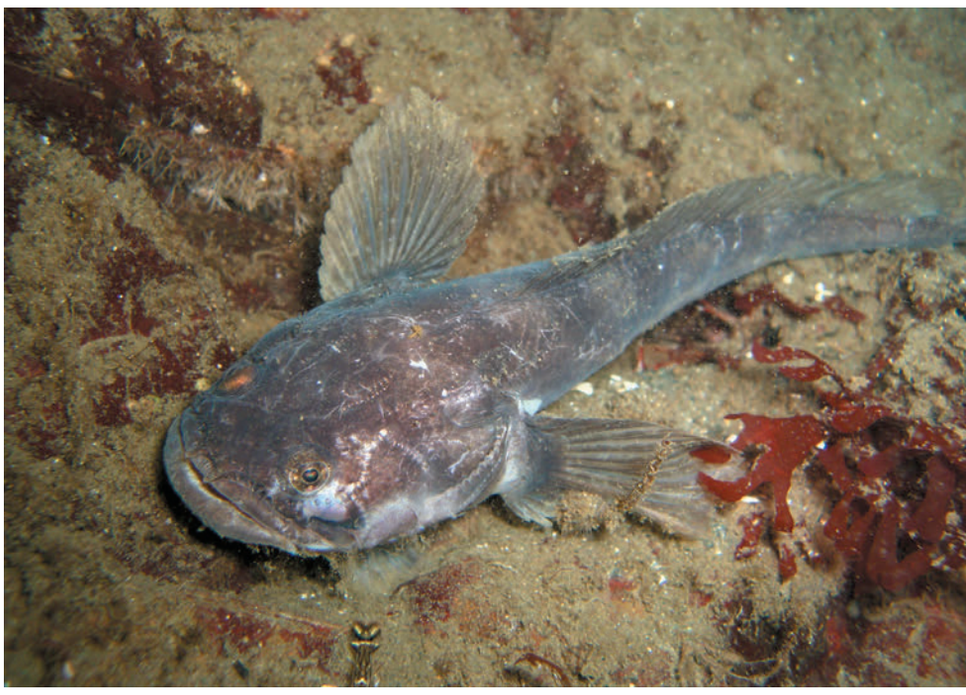
Endocrine and Neuroendocrine Physiology

CHAPTER 16

The plainfin midshipman (*Porichthys notatus*) is a bottom-dwelling fish that lives off the Pacific coast of North America. Males and females migrate to shallow waters of the intertidal zone to breed during summer nights. The swim bladder of males is larger than that of females, and its sonic muscles produce sounds used to court females. There are two types of males. During the breeding season, type I males build nests and make "singing" calls to attract females to the nest for spawning. After fertilization, the female returns to deeper waters. The type 1 male remains at the nest to court more females and to provide parental care to multiple clutches of embryos until they are free-swimming (~30–40 days). Type II males do not build nests, make courting sounds, or provide parental care. Instead, they sneak opportunities to fertilize eggs released at a nest of a type I male.

The midshipman reproductive cycle is tightly choreographed by sex steroids. In males, the blood level of 11-ketotestosterone rises in March at the beginning of the nesting period and is maintained through July. During this time the sonic muscles of the swim bladder grow, and the testes become filled with sperm. In females, estrogen and testosterone peak in April and are correlated with increased ovarian function and also increased sensitivity of the auditory system to detect the male's advertisement sounds. Investigators have found that nonreproductive females caught in deep waters during the winter are unresponsive to recordings of advertisement calls played underwater. However, when injected with estrogen or testosterone they are attracted to the speaker just like reproductive females are attracted to the type I male's nest in the summer. These experiments strongly suggest that steroid hormones promote the increased sensitivity of the female auditory system. These changes improve the plainfin midshipman fish's reproductive potential by ensuring that a female successfully detects and locates a nesting male in nighttime waters. The reproductive cycle of the plainfin midshipman is but one example of the powerful roles hormones play to influence physiological changes at multiple tissues and organs in order to optimize an animal's success.

In this chapter we examine the principles of hormonal regulation by focusing on a few well-studied examples. Our goal is to give you the tools to apply these principles in understanding the functions of hormones discussed in future chapters. As we explore endocrine physiology, we will see that hormones play essential and integral roles in maintaining homeostasis by changing physiology and behavior in response to demands imposed by both environmental conditions and stages in an animal's life history. Because hormones influence a broad range of physiological processes, essentially every cell in an animal participates in some endocrine function, and nearly every hormone participates in more than one physiological process.



The plainfin midshipman fish (*Porichthys notatus*)

Introduction to Endocrine Principles

In Chapter 12 we compared rapid, "addressed" neural control of physiological processes with slow, "broadcast" endocrine control. Chemical signals are used to achieve both types of control. However, in neural control, neurotransmitters released from axon terminals of neurons diffuse short distances to bind to receptor molecules on postsynaptic cells (**Figure 16.1*a***). Their short travel time to discrete sites ensures rapid, pinpointed control. Enzymes or reuptake mechanisms rapidly inactivate most neurotransmitters, so the neural signal is quickly terminated.

By contrast, hormones secreted from endocrine or neuroendocrine cells travel in the blood to distant target cells where they exert their effects (**Figure 16.1*b*,*c***). Whereas neurotransmitter molecules from an axon terminal typically reach a single postsynaptic cell, hormone molecules carried through the bloodstream can influence large populations of target cells, as long as the target cells express receptor molecules for the hormone. Therefore, transport of hormones over long distances permits widespread responses. These responses are initiated slowly, relative to responses to neural signals, because hormones require travel time to reach target cells. Further, some hormones are synthesized only when the endocrine cell is stimulated to secrete them, and this synthesis takes time. Finally, certain hormones control gene transcription and the synthesis of proteins by target cells, so the responses they initiate are exhibited only after a delay, when protein synthesis is accomplished. Responses to hormones may be brief or last as long as hours or days.

Processes controlled by endocrine systems in both vertebrates and invertebrates include water balance, metabolism, coping with a hostile environment, reproduction, and growth and development. Although researchers have accumulated a great deal of detailed knowledge regarding the functions and roles of hormones in vertebrates, our understanding of the endocrine systems of many invertebrate groups is still highly incomplete. Nevertheless, physiologists have found that the basic principles of endocrine function—our focus in this chapter—apply to both vertebrates and invertebrates.

Defined specifically, a **hormone** is a chemical substance produced and released by nonneural endocrine cells or by neurons; it exerts regulatory influences on the function of other, distant cells reached via the blood; and it is effective at very low concentrations (as little as 10^{-12} *M*). Hormones released by neurons are often referred to as neurohormones, and the neurons as neuroendocrine or neurosecretory cells. The secretory cells that produce hormones secrete them into the surrounding extracellular fluid, from which they diffuse into capillaries.[1] The secre-

[1] In animals with open circulatory systems, the blood and extracellular fluid blend to form hemolymph (see Chapter 24). In these animals, hormones are released directly into, and circulated in, the hemolymph.

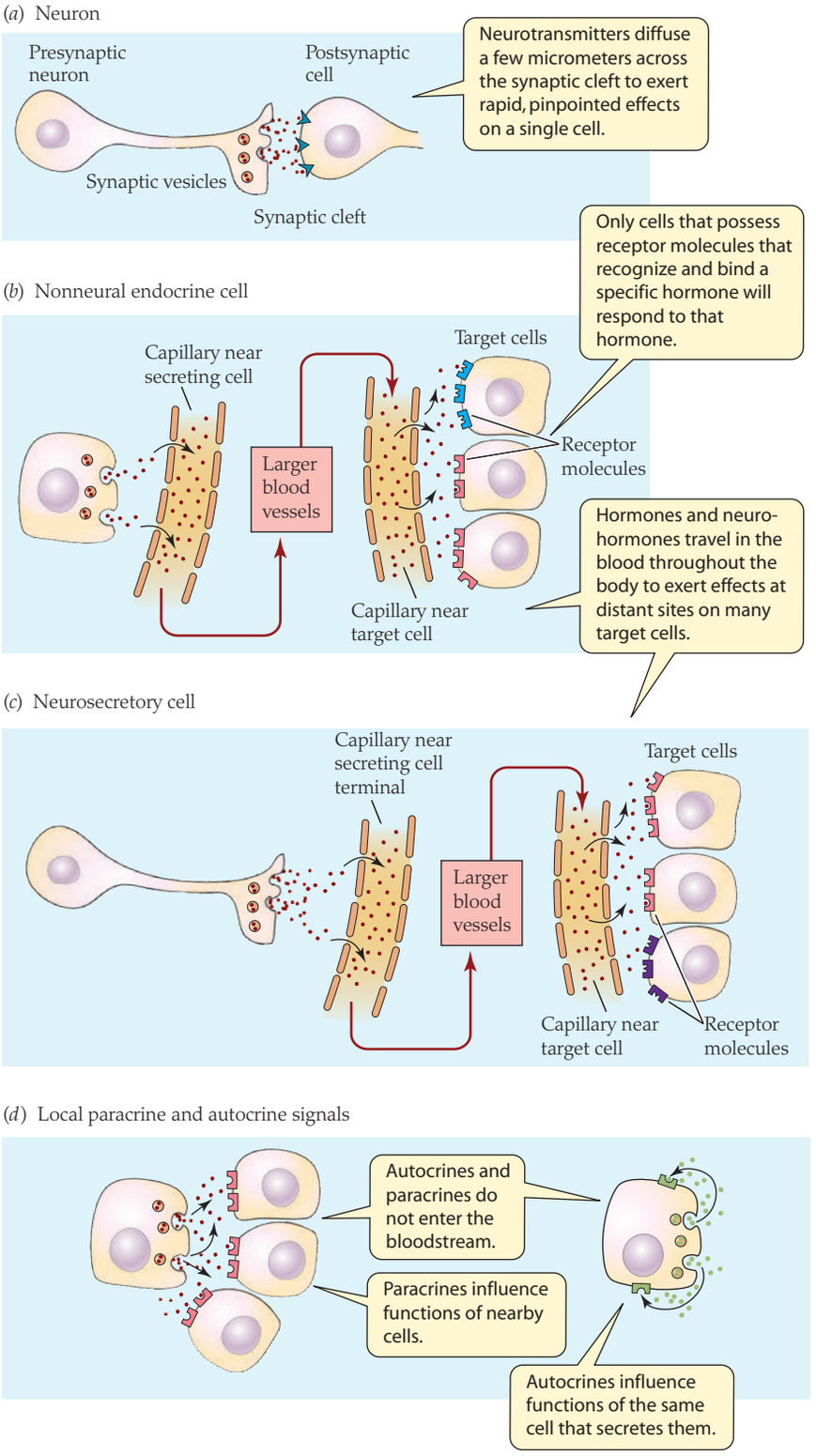


FIGURE 16.1 Chemical signals act over short and long distances within the body (*a*) A neuron releases neurotransmitter molecules that act on receptor molecules of the postsynaptic cell. (*b*) A nonneural endocrine cell secretes hormone molecules that enter a capillary (or hemolymph) and are carried throughout the bloodstream. Hormones enter and leave capillaries through spaces between the endothelial cells that make up the capillary wall. (*c*) A neurosecretory cell secretes hormone like a neuron releases neurotransmitter, and the hormone enters and leaves the blood in the same manner as a hormone from a nonneural endocrine cell. (*d*) Paracrine and autocrine signals diffuse locally to activate receptors on neighboring cells (paracrine) or on the same cell (autocrine). They do not enter the blood. Figure 16.19 illustrates long-distance chemical signals that act *outside* the body, such as pheromones.

tory cells may be organized into discrete organs termed **endocrine glands** (also called *ductless glands* because they lack outflow ducts), or they may be isolated cells or clusters of cells distributed among the cells of other tissues. A table of the major mammalian endocrine and neuroendocrine tissues, their secretions, and their main actions at target tissues can be found in Appendix K.

Some substances are unambiguously hormones, such as thyroid hormones (secreted by the thyroid gland) and gastrin (secreted by G cells in the gastric mucosa of the lower part of the mammalian stomach) (see Chapter 6). Many substances carried in the blood—CO_2, for example—may act as signals but are clearly not hormones. CO_2 is produced by metabolism and signals the respiratory centers of some animals to increase their breathing. However, CO_2 is not released primarily by specialized secretory cells, and it is found continuously in the blood at relatively high concentrations. Not all compounds, however, are so easily categorized. Many chemical signals affect the function of nearby cells located in the same organ or tissue but do not enter the circulatory system. These **autocrine** and **paracrine** substances act in many ways like hormones but are usually categorized separately (**Figure 16.1*d***). Furthermore, the same compound may be used both as a hormone and as another type of chemical signal in the same organism. In mammals, for example, cholecystokinin (CCK) is not only a hormone secreted by cells in the intestine, but also functions as a neurotransmitter or neuromodulator in the central nervous system (CNS). **Intracrines** are another example of signaling molecules. These peptide growth factors or hormones function *within* cells in addition to performing traditional hormonal, paracrine, or autocrine functions. Intracrines are either retained within the cell that synthesized them or internalized from the extracellular space.

Hormones bind to receptor molecules expressed by target cells

Although a hormone circulates past many cells, it interacts only with certain cells, called target cells, that respond to it. A target cell expresses *receptor molecules* that specifically bind the hormone. Consider thyroid hormones, for example. These hormones, secreted by the thyroid gland, exert a wide range of metabolic, structural, and developmental effects on many different tissues (see Appendix K). They have such widespread effects because many different cells of the body possess receptor molecules that recognize thyroid hormones. Typical target cells express thousands of receptor molecules for a particular hormone. In addition, many target cells express separate populations of different types of receptor molecules, so they are capable of responding to more than one hormone. The *sensitivity* of a target cell to a particular hormone depends on the number of functional receptor molecules the target cell expresses for that hormone. The sensitivity of a target cell to a particular hormone can change under different conditions because the number of receptor molecules that recognize that hormone can increase (by upregulation) or decrease (by downregulation). These variations in the types and numbers of receptor molecules expressed by target cells contribute to the immense versatility of hormonal regulation in animals. An additional consideration to keep in mind is that a target cell's response to a particular hormone at any moment in time depends not only on the number of receptor molecules it expresses for that hormone but also on the hormone's concentration in the blood.

Concentrations of hormones in the blood vary

For hormones to serve as physiological regulators, their rates of synthesis and secretion must be controlled. Often neurons or other hormones control these processes. Most endocrine cells synthesize and release some hormone all the time, but the rate of release is variable, depending on mechanisms of control. In general, the higher the rate at which a hormone is secreted, the higher its concentration in the blood, and the greater its effect on target cells. Because hormone molecules secreted into the blood are enzymatically degraded at their targets or by organs (such as the liver and kidneys in vertebrates), they do not circulate indefinitely. The blood concentration of a hormone represents a balance between the *rate of addition* of hormone to the blood (by secretion) and the *rate of removal* of hormone from the blood (by metabolic destruction and excretion). Hormone concentration depends primarily on the rate of addition to the blood, because the rate of removal is relatively constant. A hormone's half-life—the time required to reduce the concentration by one-half—indicates its rate of removal from the blood and thus the duration of its activity.

Some hormones may be converted to a more active form after secretion by a process termed **peripheral activation**. For example, thyroid hormone is secreted mainly as a four-iodine compound also known as tetraiodothyronine, or T_4. After T_4 is secreted, target and other tissues enzymatically remove one iodine to form triiodothyronine, or T_3, which is more physiologically active than T_4.

Most hormones fall into three chemical classes

Table 16.1 summarizes the characteristics of the following three chemical classes of hormones:

1. **Steroid hormones** are synthesized from cholesterol (**Figure 16.2**). In vertebrates, the gonads and the adrenal cortex secrete steroid hormones, as do the skin and, in pregnant mammals, the placenta. The molting hormones of arthropods (e.g., ecdysone) are also steroids. Steroid hormones are lipid-soluble, so they can pass through cell membranes to reach receptor molecules located inside their target cells. In some cells, lipid-soluble hormones (e.g., estrogen) are transported across the membrane. One transporter of these hormones is *megalin*, an integral protein receptor molecule of the target cell membrane that brings lipid-soluble hormones (often complexed with carrier molecules) into the cell by endocytosis.
2. **Peptide** and **protein hormones** are structured from chains of amino acids (**Figure 16.3**). In vertebrates, they include antidiuretic hormones, insulin, and growth hormone. Examples of peptide and protein hormones in invertebrates include the gamete-shedding hormone of sea stars and the diuretic hormones of insects. Peptide and protein hormones vary enormously in molecular size, from tripeptides (consisting of just 3 amino acid residues, such as thyrotropin-releasing hormone) to proteins containing nearly 200 amino acids (such as growth hormone). Often hormones consisting of assemblages of amino acids are simply called *peptide hormones* (blurring the size distinction), and we will usually follow that practice. Peptide hormones are soluble in aqueous solutions.