

PRINCIPLES OF NEURAL SCIENCE

THIRD EDITION

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Information coming from peripheral receptors that sense the environment is analyzed by the brain into components that give rise to perceptions, some of which are stored in memory. On the basis of this information, the brain gives commands for the coordinated movements of muscles. The brain does all this with nerve cells and the connections between them. Despite the simplicity of the basic units, the complexity of behavior—evident in our capability for perception, information storage, and action—is achieved by the concerted signaling of an enormous number of neurons. The best estimate is that the human brain contains about 10^{11} neurons. Although nerve cells can be classified into perhaps as many as 10,000 different types, they share many common features. A key discovery in the organization of the brain is that nerve cells with basically similar properties are able to produce very different actions because of precise connections with each other and with sensory receptors and muscle.

Since only a few principles of organization give rise to considerable complexity, it is possible to learn a great deal about how the nervous system works by paying attention to four general features:

1. The mechanisms by which neurons produce their relatively stereotyped signals.
2. The ways in which neurons are connected.
3. The relationship of different patterns of interconnections to different types of behavior.
4. The means by which neurons and their connections are modified by experience.

In this chapter we shall introduce the basic features of neuronal signaling by considering some structural and functional properties of neurons and their surrounding

glial support cells. We shall examine how the interconnections between nerve cells produce a simple behavior, the knee jerk, and then briefly describe the location and function of the various signaling mechanisms, and how signaling is transformed within the neural circuit to mediate the behavior.

The Nervous System Has Two Classes of Cells

There are two distinct classes of cells in the nervous system: nerve cells (or neurons) and glial cells (or glia). We shall first consider nerve cells.

Nerve Cells

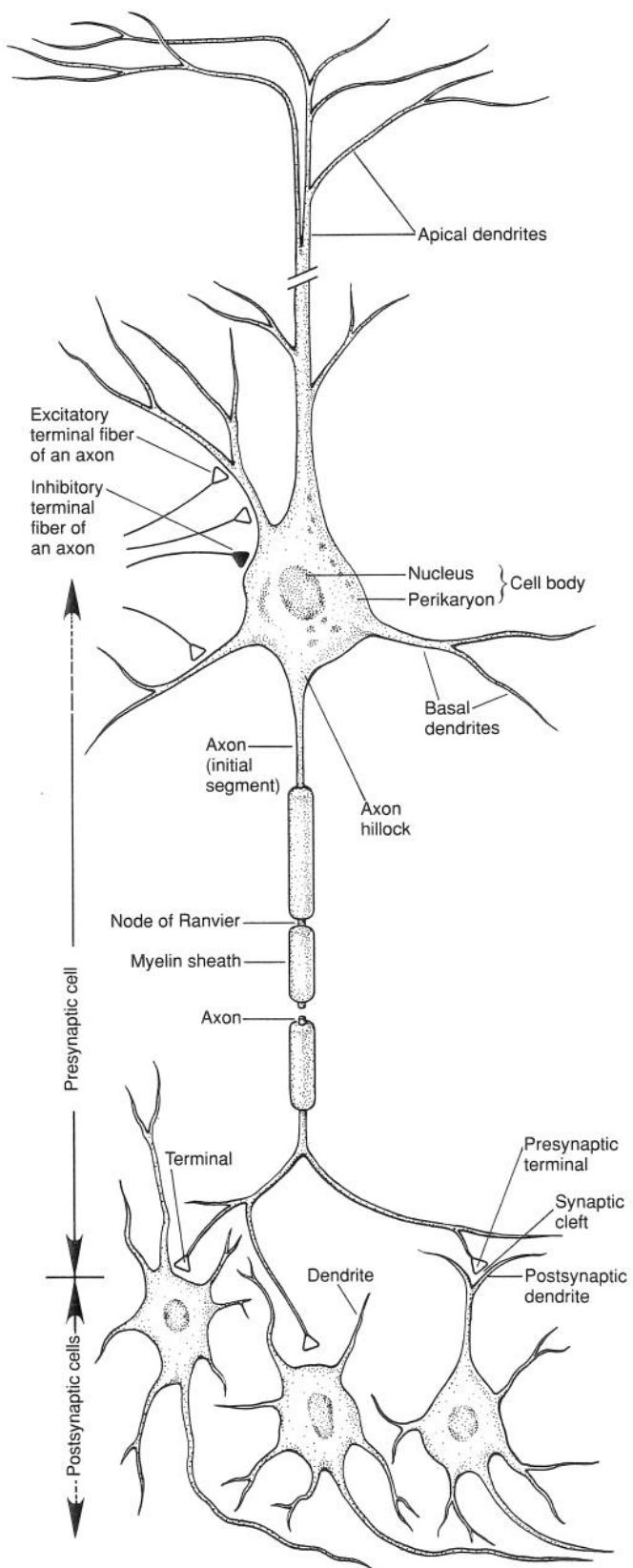
A typical neuron has four morphologically defined regions (Figure 2–1): the cell body (also called the soma, consisting of the nucleus and perikaryon), dendrites, axon, and pre-synaptic terminals. As we shall see later, each of these regions has a distinct function in the generation of signals.

The *cell body* is the metabolic center of the neuron. The cell body usually gives rise to two types of processes called the *dendrites* and the *axon*. A neuron usually has several dendrites; these branch out in tree-like fashion and serve as the main apparatus for receiving the input to the neuron from other nerve cells. Often the cell body is triangular or pyramidal in shape. Pyramidal-shaped cells typically have two sets of dendrites—a long slender set of *apical* dendrites emerging from the apex of the cell body and two or more sets of stubbier *basal* dendrites emerging from the base.

The cell body also gives rise to one axon, a tubular process with a diameter ranging from 0.2 to 20 μm that can ramify and extend for up to 1 meter. The axon is the main conducting unit of the neuron; it is capable of conveying information great distances by propagating in an all-or-none way a transient electrical signal called the *action potential*. The axon arises from a specialized region of the cell body called the *axon hillock*, where the action potential is initiated once a critical threshold is reached.

FIGURE 2–1

The main features of a typical vertebrate neuron. This neuron is drawn to illustrate its various regions and its points of contact with other nerve cells. The cell body contains the nucleus and perikaryon. The cell body gives rise to two types of processes—dendrites (both apical and basal) and axons. The axon is the transmitting element of the neuron. Axons vary greatly in length, with some extending more than 1 meter. Most axons in the central nervous system are very thin (between 0.2 and 20 μm) compared with the diameter of the cell body (up to 50 μm or more in diameter). The axon hillock, the region of the cell body where the axon emerges, is where the action potential is initiated. Many axons are insulated by a fatty myelin sheath, which is interrupted at regular intervals by regions known as the nodes of Ranvier. Branches of the axon of one neuron (the presynaptic neuron) form synaptic connections with the dendrites or cell body of another neuron (the postsynaptic cell). The branches of the axon of one neuron may form synapses with as many as 1000 other neurons.



The axon hillock and the axon lack ribosomes and cannot synthesize proteins. Newly synthesized macromolecules are assembled into organelles within the cell body and moved along the axon to presynaptic terminals by a process called axoplasmic transport, which we shall consider in Chapter 4. When severed from the cell body, the axon degenerates and dies (a topic we shall consider in Chapter 18). Large axons are surrounded by a fatty insulating sheath called *myelin*, which is essential for high-speed conduction of action potentials. The myelin sheath is formed not by the axon but by neighboring glial cells. The sheath is interrupted at regular intervals by *nodes of Ranvier*, named after the neuroanatomist Louis Antoine Ranvier, who first described them toward the end of the nineteenth century. We shall learn more about myelination in Chapter 3.

Near its end the axon divides into fine branches that have specialized swellings called *presynaptic terminals*; these are the transmitting elements of the neuron. By means of its terminals, one neuron transmits information about its own activity to the receptive surfaces (the dendrites and cell bodies) of other neurons. The point of contact is known as a *synapse*. The cell sending out the information, therefore, is called the *presynaptic cell*; the cell receiving the information is called the *postsynaptic cell*. The space separating the presynaptic from the postsynaptic cell at the synapse is called the *synaptic cleft*; it communicates freely with the extracellular space. Most presynaptic neurons terminate near the postsynaptic neuron's dendrites, but communication may occur with the cell body or, less often, with the initial segment or terminal portions of axons.

As we saw in Chapter 1, Ramón y Cajal provided much of the evidence for the *neuron doctrine*, which holds that neurons are the basic signaling units of the nervous system and that each neuron is a discretely bounded cell whose several processes arise from its cell body. In retrospect, it is hard to appreciate how difficult it was for Ramón y Cajal and others to obtain the evidence for this elementary idea. After Jacob Schleiden and Theodor Schwann put forward the cell theory in the early 1830s, the idea that cells are the structural units of all living matter became the central dogma for studying tissues and organs. For years, however, most anatomists believed that the cell theory did not apply to the brain. Unlike other tissues, whose cells are simple in shape and fit into a single field of the compound microscope, the cells of the nervous system are large and have complex shapes with processes that appear to extend endlessly and were therefore thought to be unrelated to the cell body.

The coherent structure of the neuron did not become clear until late in the nineteenth century, following the introduction of a special histological technique in 1873 by Camillo Golgi. Golgi's silver impregnation method, which is still used today, has two advantages: (1) for unknown reasons the silver solution stains, in a random manner, only about 1% of the cells in any particular region of the brain, making it possible to study a single nerve cell in relative anatomical isolation from its neigh-

bors, and (2) the neurons that do take up the stain are delineated in their entire extent, including cell body, axon, and full dendritic tree.

Ramón y Cajal applied Golgi's method to the embryonic nervous systems of many organisms, including the human brain. By carefully examining the structure of nerve cells and their contacts with other cells in histological sections of almost every region of the nervous system, Ramón y Cajal described the differences between classes of nerve cells and delineated the precise connections between many of them. He thereby gained important insights not only into neuronal structure but also into neuronal function. In addition to the fundamental principles of the neuron doctrine, Ramón y Cajal grasped two other principles that proved particularly important and form the cellular basis of the modern connectionist approach to the brain that we discussed in Chapter 1.

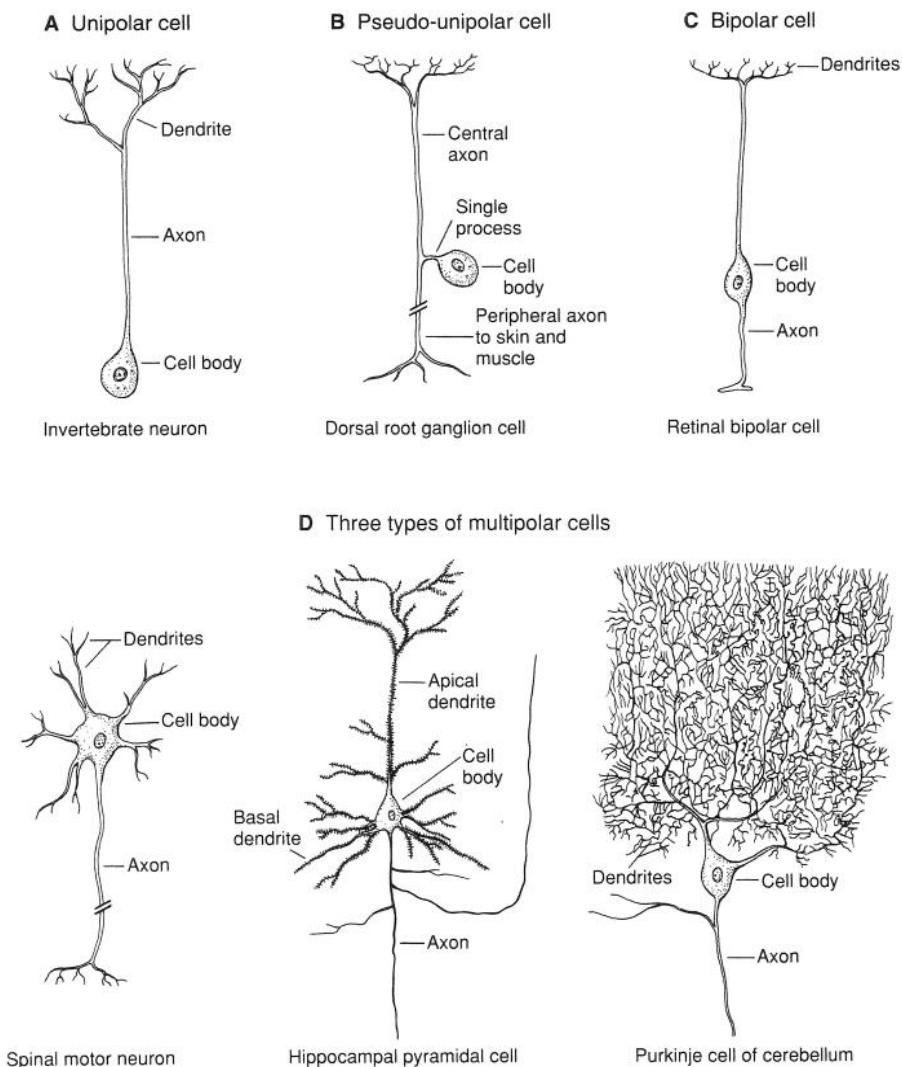
First, the *principle of dynamic polarization* states that information flows in a predictable and consistent direction within each nerve cell. The flow is from the receiving sites of the neuron (usually the dendrites and cell body) to the trigger zone at the axon hillock. There the action potential is initiated and propagated unidirectionally along the axon to the presynaptic release sites in the axon terminal. Although neurons vary greatly in shape and function, most adhere to this pattern of information flow.

Second, the *principle of connectional specificity* entails three important considerations: (1) there is no cytoplasmic continuity between nerve cells (even at the synapse, a synaptic cleft separates the presynaptic terminal from the postsynaptic cell); (2) nerve cells do not connect indiscriminately to one another to form random networks; rather (3) each cell makes specific connections at precise and specialized points of synaptic contacts—with some postsynaptic target cells but not with others.

Ramón y Cajal and the neuroanatomists who followed him also found that the feature that most dramatically distinguishes one neuron from another is shape, specifically the number and form of a neuron's processes. On the basis of the number of processes that arise from the cell body, neurons are classified into three large groups: unipolar, bipolar, and multipolar (Figure 2–2).

Unipolar cells have one primary process that may give rise to many branches. One branch is the axon and other branches serve as dendritic receiving structures. Unipolar cells have no dendrites emerging from the soma. These cells predominate in the nervous systems of invertebrates (Figure 2–2A), but they also occur in certain ganglia of the vertebrate autonomic nervous system.

Bipolar neurons have an ovoid soma that gives rise to two processes: a peripheral process or dendrite, which conveys information from the periphery, and a central process or axon, which carries information toward the central nervous system. Many bipolar neurons are sensory, such as the bipolar cells of the retina and of the olfactory epithelium (Figure 2–2C). The sensory cells of spinal ganglia—that carry information about touch, pressure, and pain—are special examples of bipolar cells. They initially develop as bipolar cells, but the two processes fuse to form

**FIGURE 2–2**

Neurons can be classified as unipolar, bipolar, or multipolar according to the number of processes that originate from the cell body. (Adapted from Ramón y Cajal, 1933.)

A. Unipolar cells, which have a single process, are characteristic of the invertebrate nervous system. In invertebrates different segments of a single axon serve as receptive surfaces or releasing terminals.

B, C. Bipolar cells have two processes: the dendrite, which carries information toward the cell, and the axon, which transmits information away from the cell. Neurons in the dorsal root ganglia of the spinal cord (**B**), which carry sensory information to the central nervous system, belong to a subclass of bipolar cells called pseudo-unipolar. As such cells develop, the two processes of the embryonic bipolar cell become fused and emerge from the cell body as a single process. This process then splits into

a single process that emerges from the cell body and splits into two processes; one runs to the periphery (to skin and muscle), the other to the spinal cord. As a result, sensory cells are called *pseudo-unipolar* (Figure 2–2B).

two processes, both of which function as axons, one going peripherally to skin or muscle, the other going centrally to the spinal cord. Bipolar cells of the retina (**C**) or of the olfactory epithelium represent typical bipolar cells.

D. Multipolar cells, which have an axon and many dendritic processes, are the most common type of neuron in the mammalian nervous system. Three examples show the large diversity of shape and organization. The spinal motor neuron innervates skeletal muscle fibers. The pyramidal cell has a pyramid shaped cell body. Dendrites emerge from both the apex (the apical dendrite) and base (the basal dendrites). Pyramidal cells are found in the hippocampus and throughout the cerebral cortex. The Purkinje cell of the cerebellum is characterized by its rich and extensive dendritic tree in one plane. This structure is designed to accommodate an enormous synaptic input.

Multipolar neurons predominate in the vertebrate nervous system. These cells have a single axon and one or more dendritic branches that typically emerge from all parts of the cell body (Figure 2–2D). Even within the cat-

egory of multipolar neurons, the size and shape of cells vary greatly. Multipolar cells vary in the number and length of their dendrites and the length of their axons. The number and extent of dendritic processes in a given cell correlate with the number of synaptic contacts that other neurons make onto it. A spinal motor cell, whose dendrites are moderate in both number and extent, receives about 10,000 contacts—2000 on the cell body and 8000 on the dendrites. The larger dendritic tree of the Purkinje cell of the cerebellum receives approximately 150,000 contacts!

The neurons of the brain can be classified functionally into three major groups: afferent, motor, and interneuronal. Afferent or sensory neurons carry information into the nervous system both for conscious perception and for motor coordination.¹ Motor neurons carry commands to muscles and glands. Interneurons constitute by far the largest class and consist of all the remaining cells in the nervous system that are not specifically sensory or motor. Interneurons process information locally or convey information from one site within the nervous system to another. The distinction between these two signaling functions of interneurons is in part determined by the length of their axon. Interneurons with long axons (sometimes called *Golgi type I cells*) relay information over great distances, from one brain region to another; they are therefore called *relay* or *projection interneurons*. Interneurons with short axons (*Golgi type II cells*) process information within specific regions of the brain; they are therefore called *local interneurons*.

Glial Cells

Nerve cell bodies and axons are surrounded by glial cells (Greek *glia*, "glue"). There are between 10 and 50 times more glial cells than neurons in the central nervous system of vertebrates. Glial cells are probably not essential for processing information, but they are thought to have several other roles:

1. They serve as supporting elements, providing firmness and structure to the brain. They also separate and occasionally insulate groups of neurons from each other.
2. Two types of glial cells, the oligodendrocyte in the central nervous system and the related Schwann cell in the peripheral nervous system, form myelin, the insulating sheath that covers most large axons.
3. Some glial cells are scavengers, removing debris after injury or neuronal death.
4. Glial cells buffer the K⁺ ion concentration in the extracellular space and some take up and remove chemical transmitters released by neurons during synaptic transmission.

¹Afferent neurons are also commonly called primary sensory neurons, and we use these two terms interchangeably in this chapter. The term afferent (carried toward the nervous system) applies to all information reaching the central nervous system from the periphery, whether or not this information leads to conscious sensation. The term sensory should, strictly speaking, be applied only to that component of afferent input that enters the brain to generate a conscious perception.

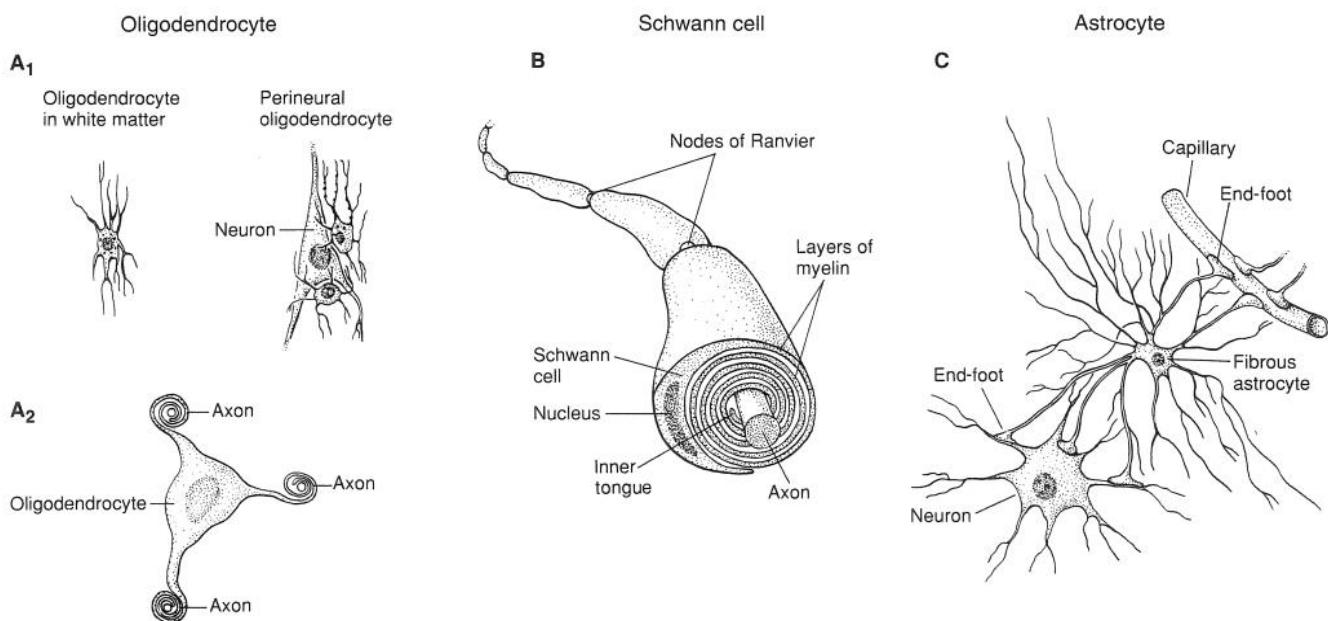
5. During development certain classes of glial cells guide the migration of neurons and direct the outgrowth of axons.
6. Certain glial cells induce formation of the impermeable tight junctions in endothelial cells that line the capillaries and venules of the brain, causing the lining of these vessels to create the *blood-brain barrier*.
7. There is suggestive evidence that some glial cells have nutritive functions for nerve cells, although this has been difficult to demonstrate conclusively.

Glial cells in the vertebrate nervous system are divided into two major classes: *microglia* and *macrogliia*. Microglia are phagocytes that are mobilized after injury, infection, or disease. They arise from macrophages and are physiologically and embryologically unrelated to the other cell types of the nervous system. We shall therefore not consider the microglia further. The macrogliia consist of three predominant types: oligodendrocytes, Schwann cells, and astrocytes (Figure 2–3).

Oligodendrocytes and *Schwann cells* are small cells with relatively few processes (Figure 2–3A, B). These cells insulate axons by forming a myelin sheath, which greatly enhances the conduction of electrical signals. They form this sheath by wrapping their membranous processes concentrically around the axon in a tight spiral. Oligodendrocytes, which occur in the central nervous system, may envelop several axons (on average 15). Schwann cells, which occur in the peripheral nervous system, envelop only one axon (Figure 2–3B). Oligodendrocytes and Schwann cells also differ to some degree in their chemical makeup. Myelination is considered in greater detail in Chapter 3.

Astrocytes, the third major class of glial cell, are the most numerous and, at the same time, the most enigmatic. They have irregularly shaped cell bodies and often relatively long processes (Figure 2–3C). In the optic nerve, astrocytes extend two sets of processes. Some of them form *end-feet* on the surface of the nerve, brain, and spinal cord, giving rise to the *glial membrane* (or *limiting sheath*) that surrounds the central nervous system as a protective covering. Others contact blood vessels and cause the endothelial cells to form tight junctions. This impenetrable seal between cells lining the capillaries forms the blood-brain barrier that protects the brain by preventing toxic substances in the blood from entering the brain (Figure 2–4).

Astrocytes also serve additional functions. First, astrocytes that surround synaptic regions take up certain neurotransmitters with high affinity, thus removing them from the synaptic cleft. Second, the fact that astrocytes have end-feet that contact both blood capillaries and neurons has led to the suggestion that astrocytes have a nutritive function. Third, astrocytes may, along with microglia, remove neuronal debris and help seal off damaged brain tissue after injury. Finally, as first shown by Stephen Kuffler, John Nicholls, and their colleagues, the resting potential of astrocytes is exclusively determined by their high permeability to K⁺. As a result, astrocytes take up and buffer the excess K⁺ released by neurons when their activity is high.

**FIGURE 2–3**

The principal types of macroglia in the nervous system are the astrocytes and oligodendrocytes in the central nervous system and the Schwann cells in the peripheral nervous system.

A. Oligodendrocytes are small cells with many processes and are found in the central nervous system. 1. In white matter (left) they participate in myelination; in gray matter (right) they surround the cell bodies of neurons. 2. A single oligodendrocyte forms myelin sheaths around many axons by wrapping its plasma membrane around the axons. (Adapted from Penfield, 1932.)

B. Schwann cells are found in the peripheral nervous system. Each of several Schwann cells lined up along the length of a

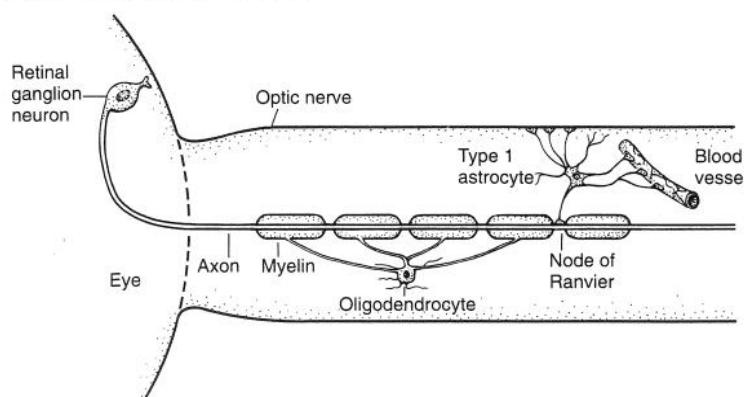
single axon at regular intervals forms a segment of myelin sheath about 1 mm long. The intervals between the segments of myelin become the nodes of Ranvier. The myelin sheath is formed when the inner tongue of the Schwann cell turns around the axon several times, thereby adding concentric layers of membrane to the axon. In reality, the layers of myelin are more compact than shown here. (Adapted from Alberts et al., 1989.)

C. Astrocytes are star shaped. They have end-feet that contact both capillaries and neurons and are therefore thought to have a nutritive role as well as a role in inducing endothelial cells to form the blood-brain barrier.

FIGURE 2–4

The optic nerve of the adult rat contains two types of glial cells: oligodendrocytes and astrocytes. The nerve is composed of the axons of many ganglion cells (the optic nerve fibers). Oligodendrocytes form the myelin sheath for the axons of ganglion cells. Astrocytes form the glial membrane at the surface of the nerve and have processes that terminate on blood vessels. The astrocytes also serve to buffer high extracellular K⁺ (which re-

sults from the extrusion of K⁺ with high rates of neuronal activity) by taking it up and extruding it in regions of low K⁺ concentration. In cultures of optic nerve, two types of astrocytes are apparent. Only type 1 astrocytes are illustrated in the figure; type 2 are discussed in Chapter 57. (Adapted from Raff, 1989.)



When neurons fire repeatedly, K^+ accumulates in the extracellular space. Because of their high permeability, astrocytes can take up the excess K^+ and store it so as to protect the neighboring neurons from the depolarization that might result if the K^+ accumulated. To maintain electrical neutrality, astrocytes can gain an amount of Cl^- equal to that of K^+ . The movement of Cl^- will therefore neutralize the charge.

In addition, since astrocytes are connected to each other through cytoplasmic bridges (electrical synapses we shall learn more about later), they form large syncytia—sheets of interconnected cells—and therefore can also lose the K^+ they gain at one site to a distal site. Eric Newman has found that the K^+ conductance is not uniformly distributed along the surface of astrocytes. The end-feet of astrocytes that contact blood vessels and the pial membrane, the surface covering that surrounds and protects the brain, have a much higher K^+ conductance than the remainder of the astrocyte cell surface. The astrocytes therefore extrude from their end-feet the excess K^+ they have taken up anywhere along their surface. Depending upon neuronal activity, the K^+ concentration in the extracellular space can vary from 3 to 10 mM. This is the range of K^+ concentration that is critical for controlling the diameter of the arteries and arterioles of the cerebral vasculature, on which the astrocytes end. When neuronal activity drives the K^+ concentration to 10 mM, the diameter of the ves-

sels increase by 50%! The siphoning capabilities of astrocyte end-feet and the sensitivity of the cerebral vessels to K^+ therefore provide a mechanism for autoregulation of the vasculature, so that blood flow and oxygen consumption can keep pace with neuronal activity. When neural activity increases, K^+ accumulates, the vessels dilate, and blood flow increases.

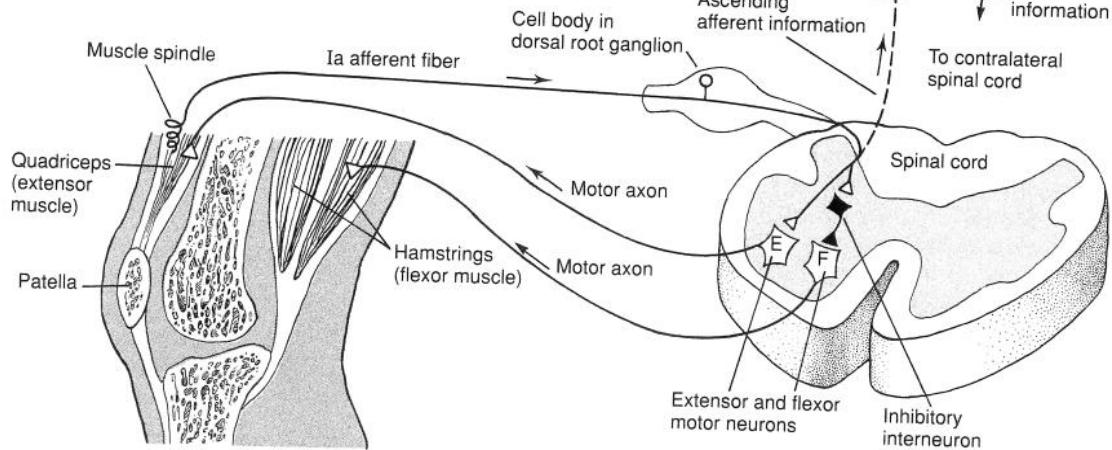
Although the electrical properties of some glial cells can be altered by changes in external K^+ concentration, and even though many glia have a variety of ion channels in their plasma membranes that can be affected by voltage and even by chemical transmitters, there is no evidence that glia are directly involved in electrical signaling. Signaling is the function of nerve cells.

Nerve Cells Are the Signaling Units of Behavioral Responses

The critical signaling functions of the brain—the processing of sensory information, the programming of motor and emotional responses, learning and memory—are carried out by interconnected sets of neurons. We shall examine in general terms how these interconnections produce a behavior by considering a simple involuntary stretch reflex, the knee jerk. We shall use this behavior to illustrate the two basic principles of neuronal functioning delin-

FIGURE 2–5

The knee jerk reflex is an example of a monosynaptic reflex system. Each extensor and flexor motor neuron in the drawing represents a population of many cells. Tapping the knee pulls on the tendon of the quadriceps femoris muscle, an extensor muscle that extends the lower leg. When the muscle stretches in response to the pull of the tendon, information regarding this change in the muscle is conveyed by afferent (sensory) neurons to the central nervous system. In the spinal cord the sensory neurons act directly on motor neurons that contract the quadriceps. In addition, they act indirectly, through interneurons, to inhibit motor neurons that contract the antagonist muscle, the hamstring. These actions combine to produce the reflex behavior. Other signals convey information about the reflex to higher regions of the brain.



eated by Ramón y Cajal: dynamic polarization and connectional specificity.

The patella (kneecap) is the site of attachment for the tendon of the quadriceps femoris, an extensor muscle that moves the lower leg. By tapping the patellar tendon, the quadriceps femoris is pulled by the tendon and briefly stretched. This initiates a kick, a reflex contraction of the quadriceps femoris and the concomitant relaxation of the antagonist flexor muscles, the hamstrings (Figure 2–5). The stretch reflex changes the position of the body and limb by increasing the tension of selected groups of muscles. It also maintains muscle tone, a background level of tension.

The stretch reflex is called a *monosynaptic reflex* because it is mediated in large part by a single set of synaptic connections between two types of neurons in the spinal cord—sensory (afferent) neurons, which send information to the central nervous system, and motor neurons, which send information from the central nervous system to muscles. The cell bodies of the sensory neurons of this reflex are clustered near the spinal cord in the *dorsal root ganglia* (Figure 2–5). They are an example of a bipolar cell: one branch of the cell's axon goes out to the muscle and the other runs into the spinal cord (see Figure 2–2). The branch that innervates the muscle makes contact with receptors in the muscle, called *muscle spindles*, which are sensitive to stretch. The branch in the spinal cord forms excitatory connections both with the motor neurons that innervate the extensor muscles and control their contrac-

tion, and with local interneurons that inhibit the motor neurons that innervate the antagonist flexor muscles.

Although only two types of nerve cells are involved, the stretching of a single muscle activates several hundred sensory neurons, each of which innervates between 100 and 150 motor neurons. This type of connection, where a single neuron branches many times and terminates on many target cells, is common especially in the input stages of the nervous system and allows for *divergence* of information flow (Figure 2–6A). As a result of *neuronal divergence*, a single neuron can exert a widespread influence by distributing its signals to many target cells. Because there are usually five to ten times more sensory neurons than motor neurons, many sensory cells terminate on a single motor cell. This type of connection allows for *convergence* of information flow, common at the output of the nervous system (Figure 2–6B). *Neuronal convergence* allows a target cell to integrate diverse information from many sources.

In summary, the stretch reflex is mediated by a simple, direct connection between sensory and motor neurons. Sensory neurons are excited when an extensor muscle is stretched. In turn, the sensory neurons excite motor neurons, which cause the extensor muscle to contract. Concurrently, the sensory neurons end on projection interneurons that transmit information about the local neural activity to higher regions of the brain concerned with movement. Thus, the electrical signals that produce the stretch reflex convey four kinds of information: (1) sen-

FIGURE 2–6

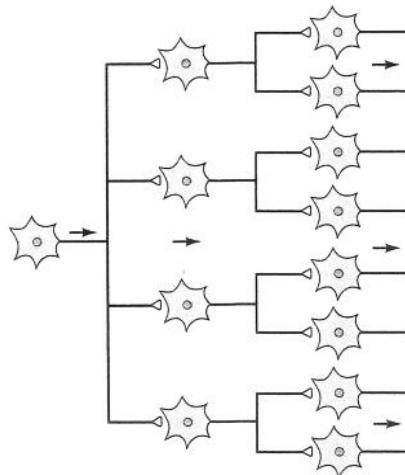
Divergence and convergence of neuronal connections illustrate a key principle in the organization of the brain. In the sensory systems, the neurons at the input stages usually branch and make divergent connections with the second stage of processing, and this divergence is carried forward to the third and subsequent stages. In turn, the motor neurons at the output of the nervous system receive a progressive convergence of connections.

This convergence induces not only excitatory influences as illustrated here, but inhibitory influences as illustrated in Figure 2–10.

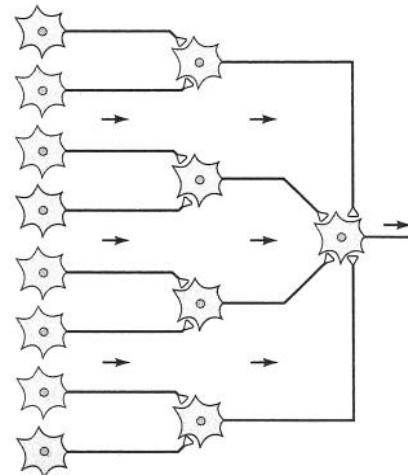
A. Divergence Two consecutive stages of divergence illustrate how the divergence of a single cell can exert influence on many target cells.

B. Convergence Two stages of convergence illustrate the focusing on one target cell of the influence of many presynaptic neurons.

A Divergence



B Convergence



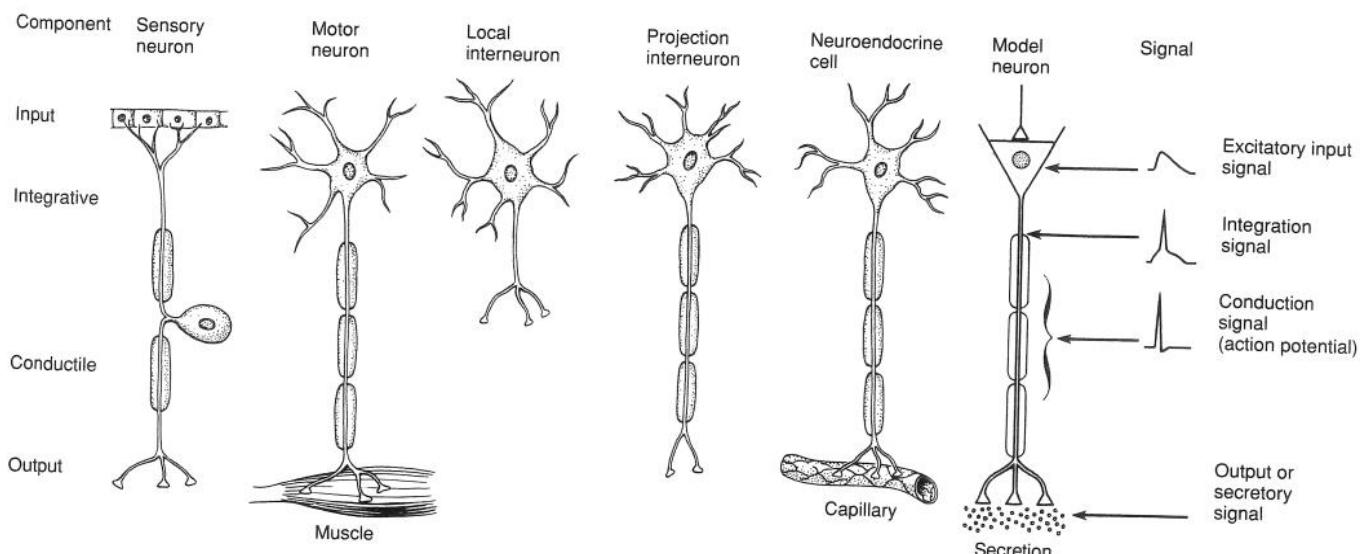


FIGURE 2–7

Most neurons, whether they are sensory, motor, interneuronal, or neuroendocrine, have four functional components in common: an input component, an integrative component, a conductile component, and an output component. On the basis of these common features, the functional organization of neurons in

sensory information from the body surface to the central nervous system (the spinal cord), (2) motor commands from the central nervous system to muscles, the end organs of effector behavior, (3) complementary motor commands (excitation and inhibition of different motor neurons) leading to coordinated muscle action, and (4) sensory information about local neuronal activity related to behavior to other parts of the central nervous system. In our example a transient imbalance of the body produces sensory information that is conveyed to motor cells, which convey commands to the muscles to contract so that balance will be restored.

Signaling Is Organized in the Same Way in All Nerve Cells

To produce a behavior, each participating sensory and motor nerve cell generates, in sequence, four types of signals at four different sites within the neuron: an *input signal* (called a *receptor potential* in the sensory neuron, and a *synaptic potential* in the interneuron or motor neuron), an *integration signal*, a *conducting signal*, and an *output signal*. Indeed, regardless of size, shape, transmitter biochemistry, or behavioral function, almost all neurons can be described by a generalized model neuron that has four components: an input or receptive component, an integrative or summing component, a long-range signaling or conductile component, and an output or secretory component (Figure 2–7). Each component is located at a particular region in the neuron and carries out a special function in signaling. All of these signals depend on the electrical properties of the cell membrane.

This model neuron is a modern restatement of Ramón

general can be represented by a model neuron. The functional components of the neuron are represented in distinct regions, with unique shapes and properties, and each produces a characteristic signal. Not all neurons share all of these features; for example, local interneurons often lack conductile components.

y Cajal's principle of dynamic polarization. The type of message conveyed by a neuron is determined not so much by the properties of the signal but by the neuron's specific connections. To understand the mechanism by which neurons produce signals and how these signals are transformed by one component after another, it is first necessary to understand the electrical properties of the cell membrane.

Signals Represent Changes in the Electrical Properties of Neurons

Neurons, like other cells of the body, maintain a potential difference of about 65 mV across their external membrane. This potential is called the *resting membrane potential*. It results from an unequal distribution of Na^+ , K^+ , Cl^- , and organic anions across the membrane of cells, which leaves the inside of the nerve cell membrane negative in relation to the outside. Because the outside of the membrane is arbitrarily defined as zero, we say the resting membrane potential is -65 mV. In different nerve cells the resting membrane potential may range from -40 to -80 mV. In muscle cells the resting potential is higher still, about -90 mV.

The unequal distribution of ions is maintained by a metabolically driven pump, the Na^+-K^+ pump, which we shall learn more about in Chapter 6. The pump establishes the ionic gradients for Na^+ and K^+ that characterize the nerve cell. By transporting Na^+ out of the cell and K^+ into it, this pump keeps the Na^+ concentration low within the cell (about 10 times lower than outside) and the K^+ concentration within the cell high (about 50 times higher than outside). The resting membrane potential results

from two properties of the cell: (1) the concentration gradients established by the $\text{Na}^+–\text{K}^+$ pump, and (2) the membrane's high leakiness (permeability) to K^+ and relatively low permeability to Na^+ in its resting state. Because of its high concentration inside the cell, K^+ tends to be driven out of the cell under the influence of the concentration gradient. As K^+ moves out of the cell, it leaves behind a cloud of unneutralized negative charge on the inside surface of the membrane, which makes the membrane more negative on the inside (by about 65 mV) than on the outside (see Figure 6–1).

Excitable cells, such as nerve and muscle cells, are different from most other cells in the body in that their resting membrane potential can be significantly altered and therefore can serve as a signaling mechanism. When the membrane potential of a nerve cell is reduced by 10 mV (from about –65 to –55 mV), an all-or-none action potential is initiated. During the action potential the permeability characteristics of the resting nerve cell membrane suddenly reverse—the membrane becomes highly permeable to Na^+ and, after a delay, returns to its resting state permeability to K^+ . We shall learn more about the mechanisms underlying the resting and action potential in Chapters 6 and 8.

Other types of neuronal signaling, such as receptor potentials and synaptic potentials, also involve changes in potential across the membrane. The resting membrane potential therefore provides the baseline against which *all* other signals are expressed. These signals result from perturbations of the membrane, which cause the membrane potential either to increase or decrease with respect to the resting potential. An increase in membrane potential (e.g., from –65 to –75 mV) is called *hyperpolarization*. A reduction in membrane potential (e.g., from –65 to –55 mV) is called *depolarization*. As we shall see later, hyperpolarization decreases a cell's ability to generate an action potential (the conducting signal transmitted along the axon) and is therefore *inhibitory*. Depolarization increases a cell's ability to generate a transmittable signal and is therefore *excitatory*.

Using the sensory and motor neurons involved in the simple knee jerk as an example, we shall now examine how neural information is generated and transformed both within and between neurons by the four components essential for signaling.

The Input Component Produces Graded Local Signals

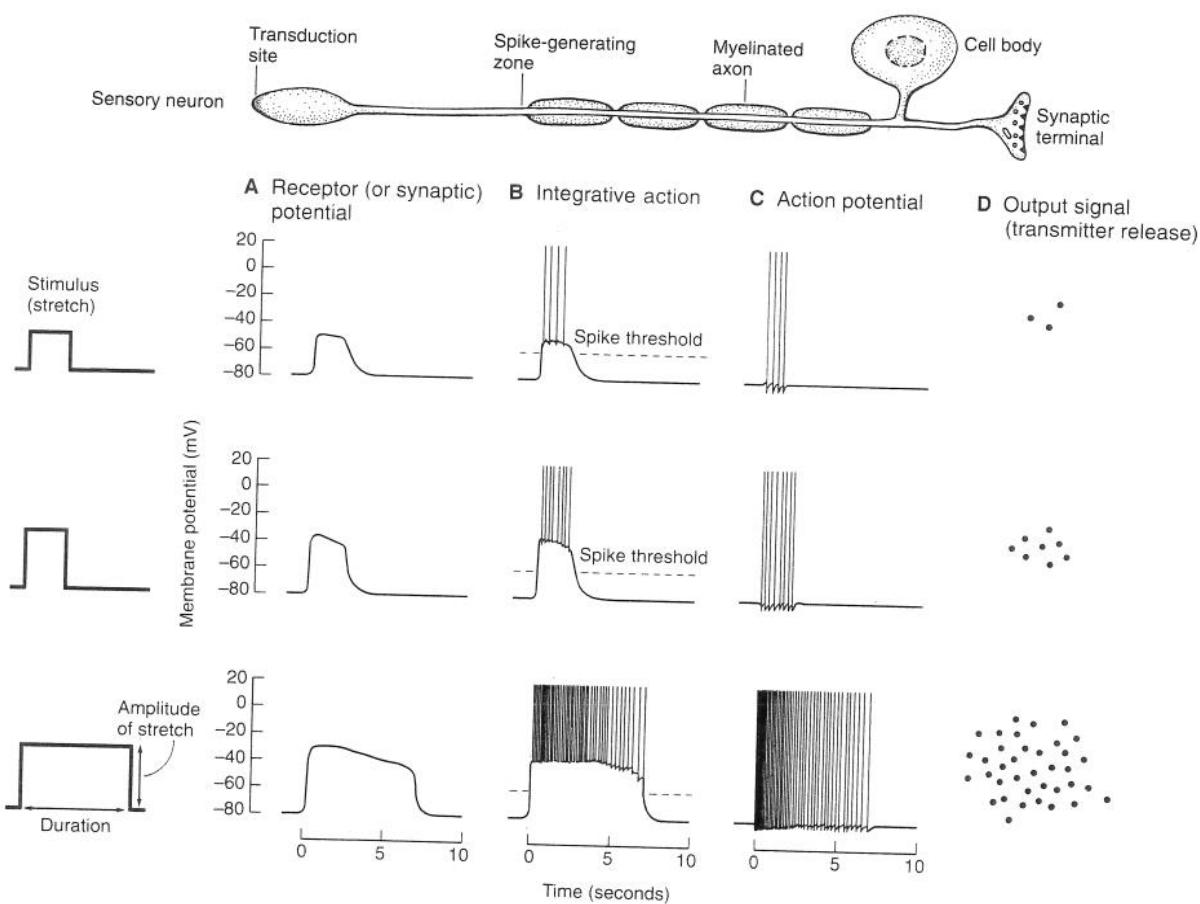
In most neurons the resting potential is the same throughout the cell, so that no current flows from one part of the neuron to another in the resting state. Typically, current flow is initiated at the input component of the neuron, where appropriate sensory or chemical stimuli activate special protein molecules, thereby giving rise to an input signal—a change in membrane potential. In sensory neurons the protein molecules are called *transducing receptor proteins*; in motor or interneurons they are called *synaptic receptor proteins*.

The input signal of sensory neurons, the receptor potential, is generated at a specialized region of the sensory cell called the receptive surface. In the example of the stretch reflex the transducing proteins are stretch-sensitive ion channels we shall learn more about in Chapter 23. These transducing proteins transform the sensory stimulus into a flow of ionic current that produces a change in the resting potential of the cell membrane: the receptor potential. The magnitude of the receptor potential is graded in both amplitude and duration. The larger or longer-lasting the stretch of the muscle, the larger and longer-lasting are the resulting receptor potentials (Figure 2–8A). Most receptor potentials are depolarizing. As we shall learn later in considering vision, however, some receptor potentials are hyperpolarizing.

The receptor potential is the first representation of stretch to be coded in the nervous system, but it alone would not cause any signals to appear in the rest of the nervous system. This is because the transducing proteins are restricted to the receptive surface of the sensory neurons and the receptor potential is a purely local signal that spreads only passively along the axon. It decreases in amplitude with distance and cannot be conveyed much farther than 1 or 2 mm. At about 1 mm down the axon the amplitude of the signal is only about one-third what it was at the site of generation. For the signal to be conveyed to the rest of the nervous system, it must be further amplified.

The input signal of motor neurons (or interneurons), the synaptic potential, has properties that are similar to those of the receptor potential. Synaptic potentials are the perturbations of membrane potential in one neuron (the postsynaptic neuron) caused by the output of another cell (the presynaptic neuron). They are the means by which one cell influences the activity of another. The presynaptic sensory neuron releases a chemical transmitter that interacts with synaptic receptor molecules at the surface of the postsynaptic motor cell. In the postsynaptic cell the synaptic receptor molecule transforms chemical potential energy into an electrical signal: the synaptic potential. Like the receptor potential, the synaptic potential is graded; its amplitude and duration are functions of the amount of transmitter and the time period over which it is released. The synaptic potential can be either depolarizing (excitatory) or hyperpolarizing (inhibitory), depending on the receptor molecule.

Receptor molecules for transmitters also are typically highly localized. For example, the receptors for inhibitory synapses are often segregated from those for excitatory synapses. Inhibitory synapses are often located on the cell body of the neuron, whereas excitatory synapses are often located on the dendrites or on dendritic specializations called *spines* (see below). Synapses are not usually found along the main portion of the axon, but some neurons have synaptic receptors on their presynaptic terminals and occasionally at nodes of Ranvier. Synaptic potentials, like receptor potentials, spread passively from one region of the neuron to another. The features of receptor and synaptic potentials are summarized in Table 2–1.

**FIGURE 2–8**

Transformation of information within a neuron. Each of the four components of an afferent neuron produces a characteristic signal.

A. The input signal, the receptor potential, is graded in amplitude and duration, proportional to the amplitude and duration of the stimulus.

B. The integrative action transforms the information in the input signal into action potentials that are actively propagated down the axon. An action potential is generated only if the receptor (or synaptic) potential is greater than a certain threshold. Once the receptor potential surpasses this threshold, any further increase in amplitude increases the frequency with which the action potentials are generated. The graded nature of input signals is translated into a frequency code of action potential at the trigger zone. The *duration* of the input signal determines the duration of the train of action potentials.

C. Action potentials are all-or-none: Every potential has the same shape, amplitude, and duration. These action potentials are conducted without fail along the full length of the axon, which can be 1–2 meters. The information in the signal therefore continues to be coded in the frequency and number of spikes. The greater the amplitude of the stimulus, the greater the frequency of spikes. The greater the duration of the stimulus, the longer the burst of potentials and therefore the greater the number of spikes.

D. The output signal, the release of transmitter substance onto the postsynaptic cell, results when the action potential reaches the synaptic terminal. The total number of action potentials per unit time determines exactly how much transmitter (black dots) will be released.

The Integrative Component Makes the Decision to Generate an Action Potential

Action potentials, the conducting signals of neurons, are generated by a sudden inrush of Na^+ through voltage-sensitive Na^+ channels. These channels are absent in the input region of the neuron (the membrane of the receptor terminal of sensory neurons or the synaptic membrane of interneurons and motor neurons). In most neurons the

functional properties of the membrane change and the density of Na^+ channels increases dramatically within 1 mm of the input component. In sensory neurons these changes occur at the first node of Ranvier in the myelinated axon; in motor neurons or interneurons they occur at the axon hillock, the initial segment of the axon as it emerges from the cell body. These axon regions have the highest density of voltage-gated Na^+ channels in the neuron and therefore the lowest threshold for generating an

TABLE 2–1. Features of Receptor, Synaptic, and Action Potentials

Feature	Receptor potential	Synaptic potential	Action potential
Amplitude	Small (0.1–10 mV)	Small (0.1–10 mV)	Large (70–110 mV)
Duration	Brief (5–100 ms)	Brief to long (5 ms–20 min)	Brief (1–10 ms)
Summation	Graded	Graded	All-or-none
Signal	Hyperpolarizing or depolarizing	Hyperpolarizing or depolarizing	Depolarizing
Propagation	Passive	Passive	Active

action potential. When the input signal spreads passively to this region it will, if it is larger than the threshold, give rise to one or more action potentials. At the integrative component the activity of all receptor (or synaptic) potentials is summed and the decision is reached as to whether or not to generate an all-or-none signal (Figures 2–7 and 2–8). Consequently, this region in the axon is called the *trigger zone* or *integrative component*.

Many cell bodies also have the capability of generating action potentials, but the threshold of the cell body is usually higher than that of the initial segment of the axon. Some neurons also have a trigger zone in the dendrites, where the threshold for an action potential also is relatively low. Dendritic trigger zones serve to amplify the effectiveness of synapses distant from the cell body. The action potentials produced at these dendritic trigger zones then discharge the final common trigger zone in the initial segment of the axon.

The Conductile Component Propagates an All-or-None Action Potential

Once the threshold of the integrative component has been exceeded, an action potential is initiated. Unlike input potentials, which are graded, the conducting signal is *all-or-none*. This means that stimuli below the threshold will not produce a signal, whereas all stimuli above the threshold produce the same signal—the amplitude and duration of the signal are always the same regardless of variations in the stimuli. Moreover, unlike input potentials, which spread passively and thus decrease in amplitude with distance, the action potential does not decay as it travels the length of the axon from the initial segment to the terminal of the neuron, a distance that can be 1 meter or more in length (Table 2–1). The action potential is a large depolarizing signal up to 110 mV in amplitude (Figure 2–8C). It often lasts only 1 ms and can be conducted at rates that vary between about 1 and 100 meters per second.

The remarkable feature of action potential signaling is that it is so stereotyped that it varies only subtly (although in some cases importantly) from nerve cell to nerve cell. This feature was demonstrated by Edgar Adrian, who was the first to study the nervous system on the cellular level in the 1920s. Adrian, and subsequently Joseph Erlanger and Herbert Gasser, found that the shape of all action potentials is similar whatever their function and wherever

they occur in the nervous system. Indeed, action potentials carried into the nervous system by a sensory axon often are indistinguishable from those carried out of the nervous system by a motor axon. What determines the intensity of sensation or the speed of movement is not the magnitude or duration of individual action potentials, but their *frequency*. In turn, the duration of a sensation or movement is determined by the period during which action potentials are generated (Figure 2–8C).

Only two features of neuronal firing are critical for signaling in the axon: the number of action potentials and the time intervals between them. As Adrian put it in 1928, summarizing his work on sensory fibers: “... all impulses are very much alike, whether the message is destined to arouse the sensation of light, of touch, or of pain; if they are crowded together the sensation is intense, if they are separated by long intervals the sensation is correspondingly feeble.”

Adrian’s comments point to one of the deep questions on the organization of the brain. If the signaling mechanisms are stereotyped and do not reflect properties of the stimulus, how do neural messages carry specific meaning? How is a message that carries visual information distinguished from one that carries information about a bee sting, or both of these from message commands for voluntary movement? As we shall learn in later chapters, the *meaning* of a signal is determined entirely by the neural *pathway* activated by the stimulus. The pathways activated by photoreceptor cells responding to light are completely different from those activated by sensory cells that respond to touch. The meaning of the signal—be it visual or tactile, sensory or motor—is determined not by the signal itself, but by the specific pathway along which it travels.

The Output Component Releases Transmitter

When the action potential reaches the terminal region of the neuron, it stimulates the release of packets of chemical transmitter. Transmitters can be small molecules related to amino acids, such as L-glutamate or acetylcholine, or they can be peptides like enkephalin. These transmitter molecules are packaged in subcellular organelles called *vesicles*, and are loaded into specialized release sites in the presynaptic terminals called *active zones*. The transmitter is released at these sites from its vesicles by fusion of the

vesicle with the surface membrane, a process known as *exocytosis*. The release of chemical transmitter serves as the *output signal*. The amount of transmitter release is a graded function of the number and the frequency of the action potentials (Figure 2–8D). The transmitter released by the presynaptic neuron diffuses across the synaptic cleft to the postsynaptic cell, where it causes the postsynaptic cell to generate either an excitatory or an inhibitory synaptic potential, depending on the postsynaptic receptor and the current flow initiated by this protein.

The Information Carried by a Signal Is Transformed As It Passes from One Component to the Next

A critical feature of neuronal signaling is that the neural information is *transformed* as it passes from one component of the neuron to the next. The information is even more elaborately transformed as it passes from one neuron to the next. In the stretch reflex we can see aspects of these transformations in their most elementary form.

The particular features of the stimulus of a stretch of muscle—its amplitude and duration—are reflected in the graded amplitude and duration of the receptor potential in the afferent neuron. If the receptor potential exceeds the threshold for initiating an action potential, the graded signal is transformed at the initial segment of the afferent neuron into an all-or-none signal, a pattern of action potentials, or frequency code. The action potential guarantees that the signal will be propagated faithfully and without fail to the terminals of the neuron. Moreover, any

increase in the amplitude of the receptor potential beyond threshold increases the frequency of the action potentials, and any increase in the duration of the input signal increases the duration of the train of action potentials. The digitally coded information—the frequency and number of action potentials—is conveyed along the entire extent of the axon. At the presynaptic terminals of the sensory neurons the frequency of action potentials determines the amount of transmitter released. In this way the digital signal (frequency of action potentials) is retransformed into an analog signal (a graded amount of transmitter).

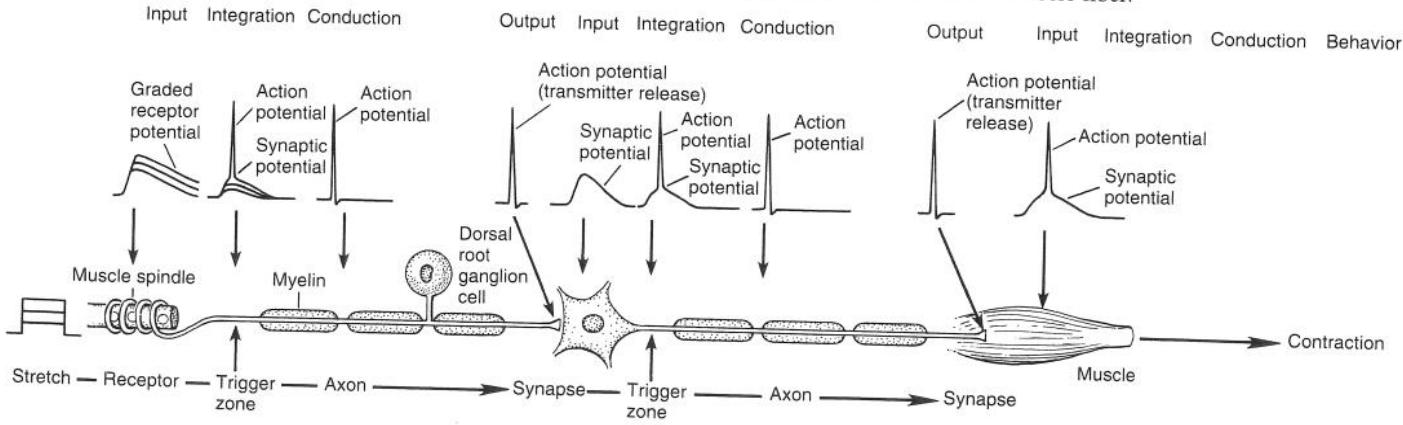
These sets of transformation are recapitulated in the motor neuron. The transmitter released by the sensory neurons interacts with receptor molecules on the motor neurons to initiate a graded synaptic potential, which spreads to the initial segment of the axon. There it can initiate an action potential, which propagates without fail to the motor cell's terminals, where it causes transmitter release. This then triggers a synaptic potential in the muscle. This synaptic potential in the muscle fiber produces an action potential that leads to the final transformation of this reflex—muscle contraction and the generation of a behavioral act. The sequence of signal transformations from sensory to motor neuron to muscle is illustrated in Figure 2–9.

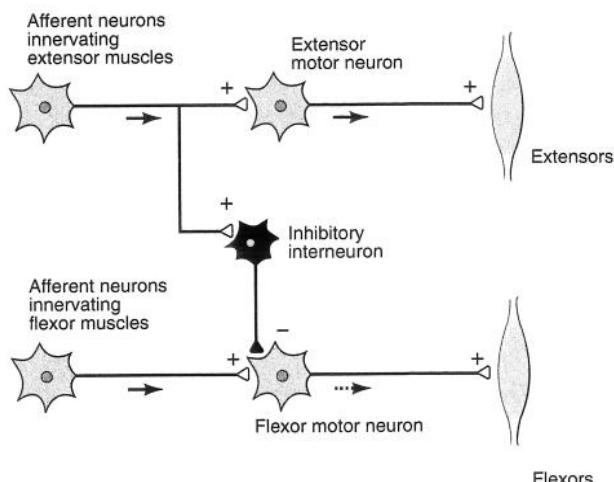
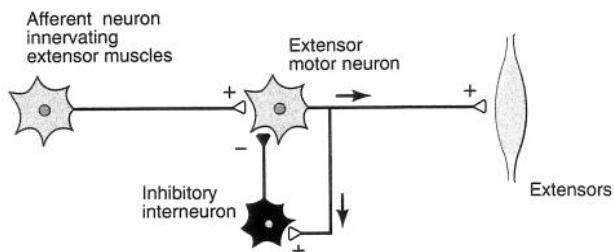
The stretch reflex is a very simple behavior, produced by two classes of neurons connected to each other through excitatory connections. Half the neurons of the brain are inhibitory, however. They release transmitter that hyperpolarizes the membrane potential of the postsynaptic cell and thus reduces the likelihood of firing. For example, in

FIGURE 2–9

This diagram summarizes the sequence of signals that produces a reflex action. Graded stretching of a muscle produces a graded (proportional) *receptor potential* in the terminal fibers of the sensory neuron (the dorsal root ganglion cell). This potential then spreads passively to the integrative segment, or trigger zone, at the first node of Ranvier. If the receptor potential is sufficiently large, it will trigger an *action potential* at the integrative segment, and the action potential will propagate actively and without change along the axon to the terminal region. At the terminal of the afferent neuron the action potential leads to an output signal: the release of a transmitter substance. The trans-

mitter diffuses across the synaptic cleft and interacts with receptor molecules on the external membranes of the motor neurons that innervate the stretched muscle. This interaction initiates a synaptic potential in the motor cell. The synaptic potential then spreads passively to the axon hillock or initial segment of the motor neuron axon, where it may initiate an action potential that propagates actively to the terminal of the motor neuron. At the terminal the action potential causes transmitter release, which triggers a synaptic potential in the muscle. This signal produces an action potential in the muscle, causing contraction of the muscle fiber.



A Feed-forward inhibition**B Feedback inhibition****FIGURE 2–10**

Inhibitory interneurons can make either feed-forward or feedback connections.

A. Feed-forward inhibition is common in monosynaptic reflex systems, such as the knee jerk reflex system (see Figure 2–5). Afferent neurons from extensor muscles excite not only the extensor motor neurons but also inhibitory neurons that inhibit the firing of the motor cells that innervate the antagonistic flexor muscles. Feed-forward inhibition enhances the activity of the active synergistic pathway by suppressing the activity of other antagonistic pathways.

B. In negative feedback (recurrent) inhibition the extensor motor neurons activate inhibitory interneurons that reduce the probability of firing in the extensor motor neurons themselves. Negative feedback is self-regulating and prevents activity within the active pathway from exceeding a certain critical maximum.

the knee jerk reflex the afferent neurons that contract the extensor muscles of the leg also activate inhibitory interneurons that prevent the antagonist flexor muscles from being brought into action. This type of inhibition is a form of *feed-forward* inhibition designed to suppress other competitive actions (Figure 2–10A). Inhibition can also be self regulating and of the *feedback* variety. In this type a neuron that excites a target cell also acts on an inhibitory interneuron that feeds back and inhibits the active neu-

ron, thereby limiting its ability to excite the target (Figure 2–10). We will repeatedly encounter both types of inhibitory arrangements when we examine more complex behaviors in later chapters.

Nerve Cells Differ Most at the Molecular Level

The four-component model we have outlined here, although applicable to the vast majority of neurons, is a simplification and is not accurate in detail for all neurons. For example, some neurons do not generate action potentials; typically, these are local interneurons that lack a conductile component—they have no axon or only a very short one. In these neurons the input signals are summed and spread passively to the terminal region, where they directly affect secretion. Other cells do not have a steady resting potential and consequently are spontaneously active. Even cells that appear similar can differ in important details at the molecular level. For example, different neurons use different combinations of ion channels in their membranes. As we shall learn in Chapter 8, the diversity of ion channels results in neurons having different thresholds, excitability properties, and firing patterns. For example, neurons with different ion channels can encode the same synaptic potential into different patterns of firing.

Neurons also differ in their chemical transmitters and receptors. These differences have physiological importance, but they also account for the fact that a disease may strike one class of neurons but not others. Certain diseases strike motor neurons only (for example, amyotrophic lateral sclerosis or poliomyelitis), whereas others, such as tabes dorsalis, affect primarily sensory neurons. A motor disorder called Parkinson's disease affects a particular population of interneurons, which are located in the substantia nigra of the basal ganglia and use dopamine as a chemical transmitter. Some diseases are selective even within the neuron: Some only affect the receptive elements, others the cell body, and still others the axon. Indeed, because there are so many cell types and each type has molecularly distinct molecular components, the nervous system is attacked by a greater number and variety of diseases, both neurological and psychiatric, than any other organ in the body.

Despite these differences, the basic electrical signaling properties of nerve cells are surprisingly similar. Given the large number of different nerve cells in the brain, this simplicity is fortunate. If we understand in detail the molecular mechanisms that produce signaling in any one kind of cell, we shall be well along the way to understanding these mechanisms in many other kinds of nerve cells.

Patterns of Interconnection Allow Relatively Stereotyped Nerve Cells to Convey Unique Information

We have seen how a limited number of nerve cells can interact to produce simple behaviors by activating certain movements and inhibiting others. But can more complex behaviors be related so specifically to individual neurons?

In invertebrate animals a single (command) cell can initiate a complex behavioral sequence. However, as far as we know, in the human brain no such complex functions are initiated by a single neuron. Rather, every behavior is generated by many cells. The neural mediation of behavior is subdivided into discrete aspects of sensory input, motor output, and intermediate processing. Each of these aspects is conveyed by a group of neurons, and even a single aspect can involve several groups of neurons. The deployment of several groups of neurons or several pathways to convey the same information is called *parallel processing*. This probably increases both the richness and the reliability of function within the central nervous system.

Subdivision and localization of function are key strategies in the nervous system. Specific aspects of information processing are restricted to particular regions within the brain. For example, each sensory modality is processed to a distinct region where the sensory connections represent precisely a map of the appropriate surface of the body—the skin, tendons and joints, retina, basilar membrane of the cochlea, or olfactory epithelium. Muscles and movements are also represented in an orderly arrangement of connections. Thus, the brain contains at least two classes of maps: one class for sensory perceptions and the other for motor commands. The two types of maps are interconnected in ways that we do not as yet fully understand.

Most neurons, whether motor, sensory, or interneuronal, do not differ greatly in their electrical properties. Neurons with similar properties carry out different functions because of the connections they make in the nervous system. These connections are established during development and determine the cell's role in behavior. In those regions of the brain in which we understand how the components of a mental process are represented, the logical operations performed by a group of neurons only becomes comprehensible when the flow of information through the interconnections of the network is specified.

A similar conclusion about the importance of connections has now been recognized by scientists attempting to construct computational models of brain function. Scientists working in this field, a branch of computer science called *artificial intelligence*, initially used serial processing models to simulate the higher-level cognitive processes of the brain—processes such as pattern recognition, the acquisition of new information, memory, and motor performance. They soon realized that although these serial models solved many problems rather well, including such difficult tasks as playing chess, they performed poorly and slowly on other computations that the brain does rapidly and well, such as the almost immediate recognition of faces or the comprehension of speech.

As a result, most modelers of neural function have turned from serial systems to parallel distributed systems, which they call *connectionistic models*. Connectionistic models use interconnected computational elements that, like neural circuits, process information simultaneously and in parallel. The preliminary insights that have emerged from such models are consistent with physiolog-

ical studies, and illustrate that individual elements in the model do not transmit large amounts of information. It is the connections between the many elements, not the contribution of individual components, which make complex information processing possible. Individual neurons can carry out important computations because they are wired together in organized and different ways. It is the distinctiveness of the wiring and the ability to modify this wiring through learning that create a brain in which relatively stereotyped units can endow us with individuality.

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