2

Nerve Cells and Behavior

Eric R. Kandel

HUMANS ARE VASTLY superior to other animals in their ability to exploit their physical environment. The remarkable range of human behavior—indeed, the complexity of the environment humans have been able to create for themselves—depends on a sophisticated array of sensory receptors connected to a highly flexible neural machine—a brain—that is able to discriminate an enormous variety of events in the environment. The continuous stream of information from these receptors is organized by the brain into perceptions (some of which are stored in memory for future reference) and then into appropriate behavioral responses. All of this is accomplished by the brain using nerve cells and the connections between them.

Individual nerve cells, the basic units of the brain, are relatively simple in their morphology. Although the human brain contains an extraordinary number of these cells (on the order of 10^{11} neurons), which can be classified into at least a thousand different types, all nerve cells share the same basic architecture. The complexity of human behavior depends less on the specialization of individual nerve cells and more on the fact that a great many of these cells form precise anatomical circuits. One of thekey organizational principles of the brain, therefore, is that nerve cellswith basically similar properties can nevertheless produce quite differentactions because of the way they are connected with each other and with sensory receptors and muscle.

Since relatively few principles of organization give rise to considerable complexity, it is possible to learn a great deal about how the nervous system produces behavior by focusing on four basic features of the nervous system:

- The mechanisms by which neurons produce signals.
- The patterns of connections between nerve cells.
- The relationship of different patterns of interconnection to different types of behavior.
- The means by which neurons and their connections are modified by experience.

In this chapter we introduce these four features by first considering the structural and functional properties

of neurons and the glial cells that surround and support them. We then examine how individual cells organize and transmit signals and how signaling between a few interconnected nerve cells produces a simple behavior, the knee jerk reflex. Finally, we consider how changes in the signaling ability of specific cells can modify behavior.

The Nervous System Has Two Classes of Cells

There are two main classes of cells in the nervous system: nerve cells (neurons) and glial cells (glia).

Glial Cells Are Support Cells

Glial cells far outnumber neurons—there are between 10 and 50 times more glia than neurons in the central nervous system of vertebrates. The name for these cells derives from the Greek for glue, although in actuality glia do not commonly hold nerve cells together. Rather, they surround the cell bodies, axons, and dendrites of neurons. As far as is known, glia are not directly involved in information processing, but they are thought to have at least seven other vital roles:

- Glial cells support neurons, providing the brain with structure. They also separate and sometimes insulate neuronal groups and synaptic connections from each other.
- Two types of glial cells (oligodendrocytes and Schwann cells) produce the myelin used to insulate nerve cell axons, the cell outgrowths that conduct electrical signals.
- Some glial cells are scavengers, removing debris after injury or neuronal death.
- Glial cells perform important housekeeping chores that promote efficient signaling between neurons (Chapter 14). For example, some glia also take up chemical transmitters released by neurons during synaptic transmission.
- During the brain's development certain classes of glial cells (“radial glia”) guide migrating neurons and direct the outgrowth of axons.
- In some cases, as at the nerve-muscle synapse of vertebrates, glial cells actively regulate the properties of the presynaptic terminal.
- Some glial cells (astrocytes) help form an impermeable lining in the brain's capillaries and venules— the blood-brain barrier—that prevents toxic substances in the blood from entering the brain (Appendix B).
- Other glial cells apparently release growth factors and otherwise help nourish nerve cells, although this role has been difficult to demonstrate conclusively.

Glial cells in the vertebrate nervous system are divided into two major classes: *microglia* and *macroglia.*

Microglia are phagocytes that are mobilized after injury, infection, or disease. They arise from macrophages outside the nervous system and are physiologically and embryologically unrelated to the other cell types of the nervous system. Not much is known about what microglia do in the resting state, but they become activated and recruited during infection, injury, and seizure. The activated cell has a process that is stouter and more branched than that of inactivated cells, and it expresses a range of antigens, which suggests that it may serve as the major antigen presenting cell in the central nervous system. Microglia are thought to become activated in a number of diseases including multiple sclerosis and AIDS-related dementia, as well as various chronic neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.

Three types of macroglial cells predominate in the vertebrate nervous system: oligodendrocytes, Schwann cells, and astrocytes.

Oligodendrocytes and *Schwann* cells are small cells with relatively few processes. Both types carry out the important job of insulatingaxons, forming a myelin sheath by tightly winding their membranous processes around the axon in a spiral. Oligodendrocytes, which are found in the central nervous system, envelop an average of 15 axonal internodes each (Figure 2-1A). By contrast, Schwann cells, which occur in the peripheral nervous system, each envelop just one internode of only one axon (Figure 2-1B). The types of myelin produced by oligodendrocytes and Schwann cells differ to some degree in chemical makeup.

Astrocytes, the most numerous of glial cells, owe their name to their irregular, roughly star-shaped cell bodies (Figure 2-1C). They tend to have rather long processes, some of which terminate in end-feet. Some astrocytes form end-feet on the surfaces of nerve cells in the brain and spinal cord and may play a role in bringing nutrients to these cells. Other astrocytes place end-feet on the brain's blood vessels and cause the vessel's endothelial (lining) cells to form tight junctions, thus creating the protective blood-brain barrier (Figure 2-1C).

Astrocytes also help to maintain the right potassium ion concentration in the extracellular space between neurons. As we shall learn below and in Chapter 7, when a nerve cell fires, potassium ions flow out of the cell. Repetitive firing may create an excess of extracellular potassium that could interfere with signaling between cells in the vicinity. Because astrocytes are highly

permeable to potassium, they can take up the excess potassium and so protect those neighboring neurons. In addition, astrocytes take up neurotransmitters from synaptic zones after release and thereby help regulate synaptic activities by removing transmitters. But the role of astrocytes is largely a supporting one.

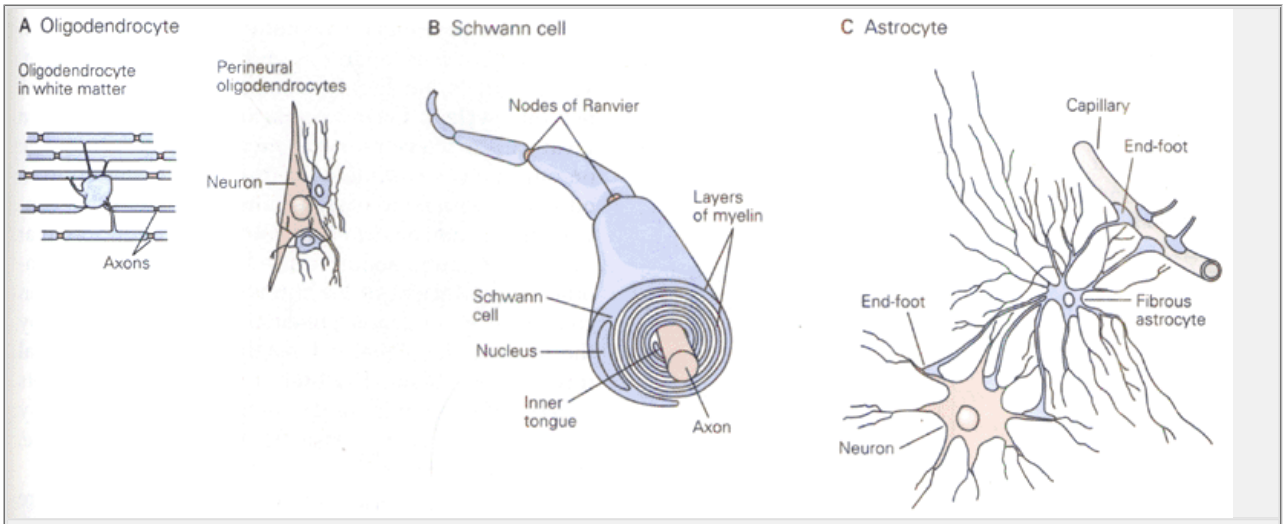

Figure 2-1 The principal types of glial cells in the central nervous system are astrocytes and oligodendrocytes and in the peripheral nervous system, Schwann cells.

A. Oligodendrocytes are small cells with relatively few processes. In white matter (left) they provide the myelin, and in gray matter (right) perineural oligodendrocytes surround and support the cell bodies of neurons. A single oligodendrocyte can wrap its membranous processes around many axons, insulating them with a myelin sheath.

B. Schwann cells furnish the myelin sheaths that insulate axons in the peripheral nervous system. Each of several Schwann cells, positioned along the length of a single axon, forms a segment of myelin sheath about 1 mm long. The sheath assumes its form as the inner tongue of the Schwann cell turns around the axon several times, wrapping it in concentric layers of membrane. The intervals between segments of myelin are known as the nodes of Ranvier. In living cells the layers of myelin are more compact than what is shown here. (Adapted from Alberts et al. 1994.)

C. Astrocytes, the most numerous of glial cells in the central nervous system, are characterized by their star-like shape and the broad end-feet on their processes. Because these endfeet put the astrocyte into contact with both capillaries and neurons, astrocytes are thought to have a nutritive function. Astrocytes also play an important role in forming the bloodbrain barrier.

There is no evidence that glia are directly involved in electrical signaling. Signaling is the function of nerve cells.

Nerve Cells Are the Main Signaling Units of the Nervous System

A typical neuron has four morphologically defined regions: the cell body, dendrites, the axon, and presynaptic terminals (Figure 2-2). As we shall see later, each of these regions has a distinct role in the generation of signals and the communication of signals between nerve cells.

The cell body (*soma*) is the metabolic center of the cell. It contains the nucleus, which stores the genes of the cell, as well as the endoplasmic reticulum, an extension of the nucleus where the cell's proteins are synthesized. The cell body usually gives rise to two kinds of processes: several short *dendrites* and one, long, tubular *axon*. Dendrites branch out in tree-like fashion and are the main apparatus for receiving incoming signals from other nerve cells. In contrast, the axon extends away from the cell body and is the main conducting unit for carrying signals to other neurons. An axon can convey electrical signals along distances ranging from 0.1 mm to 3 m. These electrical signals, called *action potentials*, are rapid, transient, all-or-none nerve impulses, with an amplitude of 100 mV and a duration of about 1 ms (Figure 2-3). Action potentials are initiated at a specialized trigger region at the origin of the axon called the *axon hillock* (or *initial segment* of the axon); from there they are conducted down the axon without failure or distortion at rates of 1–100 m per second. The amplitude of an action potential traveling down the axon remains constant because the action potential is an all-or-none impulse that is regenerated at regular intervals along the axon.

Action potentials constitute the signals by which the brain receives, analyzes, and conveys information. These signals are highly stereotyped throughout the

nervous system, even though they are initiated by a great variety of events in the environment that impinge on our bodies—from light to mechanical contact, from odorants to pressure waves. Thus, the signals that convey information about vision are identical to those that carry information about odors. Here we encounter another key principle of brain function. The information conveyed by an action potential is determined not by the form of the signal but by the pathway the signal travels in the brain. The brain analyzes and interprets *patterns* of incoming electrical signals and in this way creates our everyday sensations of sight, touch, taste, smell, and sound.

To increase the speed by which action potentials are conducted, large axons are wrapped in a fatty, insulating sheath of myelin. The sheath is interrupted at regular intervals by the nodes of Ranvier. It is at these uninsulated spots on the axon that the action potential becomes regenerated. We shall learn more about myelination in Chapter 4 and about action potentials in Chapter 9.

Near its end, the tubular axon divides into fine branches that form communication sites with other neurons. The point at which two neurons communicate is known as a *synapse*. The nerve cell transmitting a signal is called the *presynaptic cell.* The cell receiving the signal is

the *postsynaptic cell.* The presynaptic cell transmits signals from the swollen ends of its axon's branches, called *presynaptic terminals.* However, a presynaptic cell does not actually touch or communicate anatomically with the postsynaptic cell since the two cells are separated by a space, the *synaptic cleft.* Most presynaptic terminals end on the postsynaptic neuron's dendrites, but the terminals may also end on the cell body or, less often, at the beginning or end of theaxon of the receiving cell (Figure 2-2).

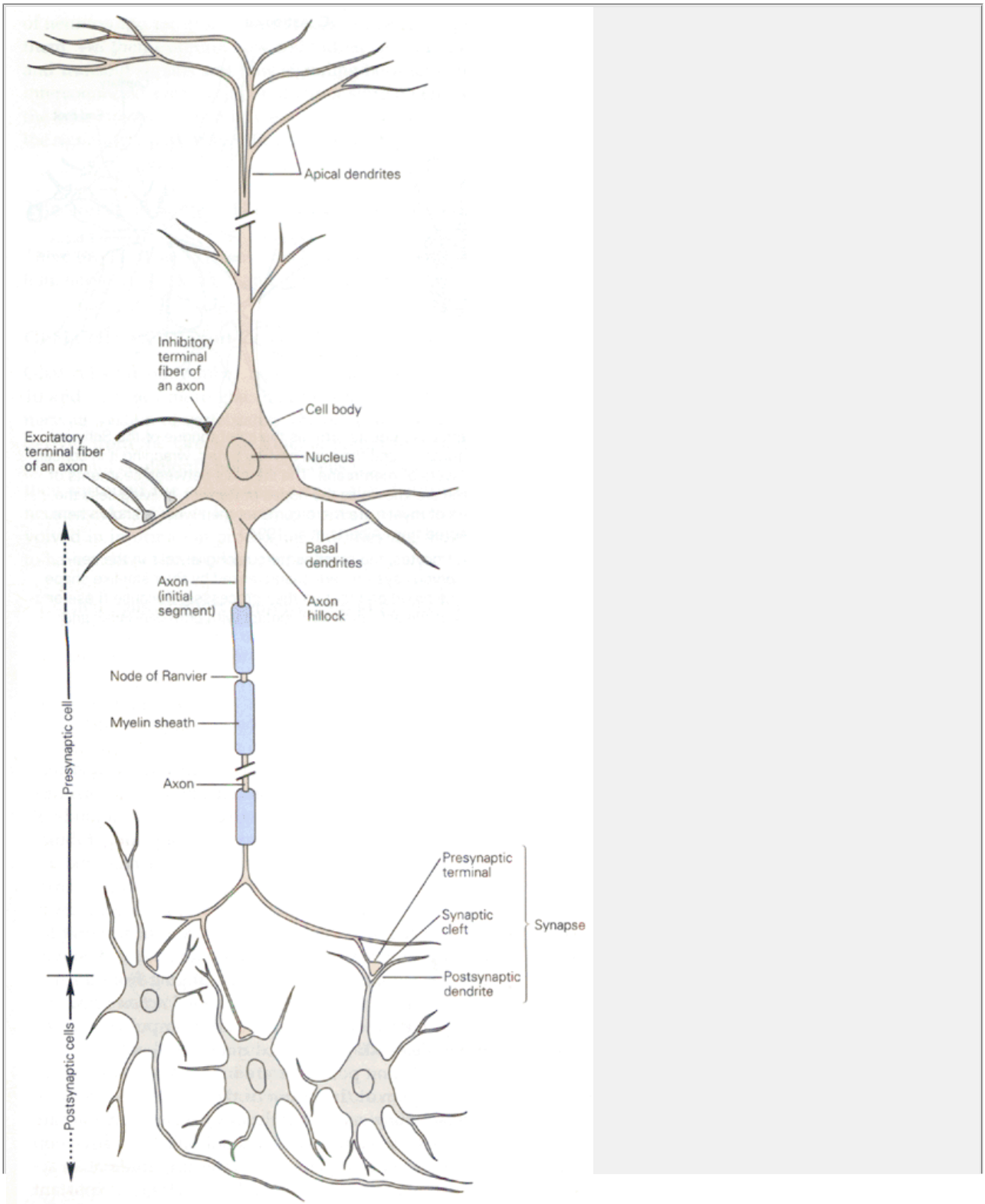

Figure 2-2 Structure of a neuron. Most neurons in the vertebrate nervous system have several main features in common. The cell body contains the nucleus, the storehouse of genetic information, and gives rise to two types of cell processes, axons and dendrites. Axons, the transmitting element of neurons, can vary greatly in length; some can extend more than 3 m within the body. Most axons in the central nervous system are very thin (between 0.2 and 20 μm in diameter) compared with the diameter of the cell body (50 μm or more). Many axons are insulated by a fatty sheath of myelin that is interrupted at regular intervals by the nodes of Ranvier. The action potential, the cell's conducting signal, is initiated either at the axon hillock, the initial segment of the axon, or in some cases slightly farther down the axon at the first node of Ranvier. Branches of the axon of one neuron (the presynaptic neuron) transmit signals to another neuron (the postsynaptic cell) at a site called the synapse. The branches of a single axon may form synapses with as many as 1000 other neurons. Whereas the axon is the output element of the neuron, the dendrites (apical and basal) are input elements of the neuron. Together with the cell body, they receive synaptic contacts from other neurons.

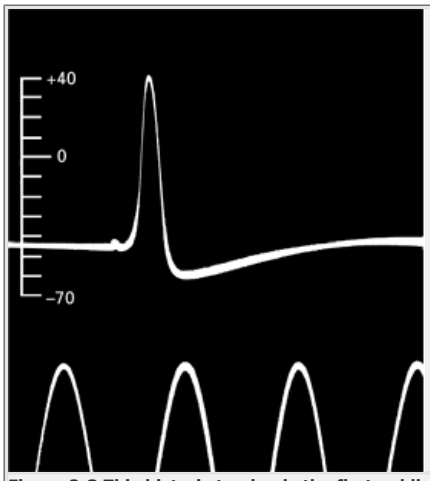

Figure 2-3 This historic tracing is the first published intracellular recording of an action potential. It was obtained in 1939 by Hodgkin and Huxley from the squid giant axon, using glass capillary electrodes filled with sea water. Time marker is 500 Hz. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as zero potential. (From Hodgkin and Huxley 1939.)

As we saw in Chapter 1, Ramón y Cajal provided much of the early evidence for the now basic understanding that neurons are the signaling units of the nervous system and that each neuron is a discrete cell with distinctive processes arising from its cell body (the neuron doctrine). In retrospect, it is hard to appreciate how difficult it was to persuade scientists of this elementary idea. Unlike other tissues, whose cells have simple shapes and fit into a single field of the light microscope, nerve cells have complex shapes; the elaborate patterns of dendrites and the seemingly endless course of some axons made it extremely difficult initially to establish a relationship between these elements. Even after the anatomists Jacob Schleiden and Theodor Schwann put forward the cell theory in the early 1830s—when the idea that cells are the structural units of all living matter became a central dogma of biology—most anatomists would not accept that the cell theory applied to the brain, which they thought of as a continuous web-like reticulum.

The coherent structure of the neuron did not become clear until late in the nineteenth century, when Ramón y Cajal began to use the silver staining method introduced by Golgi. This method, which continues to be used today, has two advantages. First, in a random manner that is still not understood, the silver solution stains only about 1% of the cells in any particular brain region, making it possible to study a single nerve cell in isolation from its neighbors. Second, the neurons that do take up the stain are delineated in their entirety, including the cell body, axon, and full dendritic tree. The stain shows that (with rare exceptions we shall consider later) there is no cytoplasmic continuity between neurons, even at the synapse between two cells. Thus, neurons do not form a syncytium; each neuron is clearly segregated from every other neuron.

Ramón y Cajal applied Golgi's method to the embryonic nervous systems of many animals, including the human brain. By examining the structure of neurons in almost every region of the nervous system and tracing the contacts they made with one another, Ramón y Cajal was able to describe the differences between classes of nerve cells and to map the precise connections between a good many of them. In this way Ramón y Cajal grasped, in addition to the neuron doctrine, two other principles of neural organization that would prove particularly valuable in studying communication in the nervous system.

The first of these has become known as the *principle of dynamic polarization.* It states that electrical signals within a nerve cell flow only in one direction: from the receiving sites of the neuron (usually the dendrites and cell body) to the trigger region at the axon. From there, the action potential is propagated unidirectionally along the entire length of the axon to the cell's presynaptic terminals. Although neurons vary in shape and function, the operation of most follows this rule of information flow. Later in this chapter we shall describe the physiological basis of this principle.

The second principle, the *principle of connectional specificity*, states that nerve cells do not connect indiscriminately with one another to form random networks; rather each cell makes specific connections—at particular contact points—with certain postsynaptic target cells but not with others. Taken together, the principles of dynamic polarization and connectional specificity form the cellular basis of the modern connectionist approach to the brain discussed in Chapter 1.

Ramón y Cajal was also among the first to realize that the feature that most distinguishes one neuron from another is *shape*—specifically, the number and form of the processes arising from the cell body. On the basis of shape, neurons are classified into three large groups: unipolar, bipolar, and multipolar.

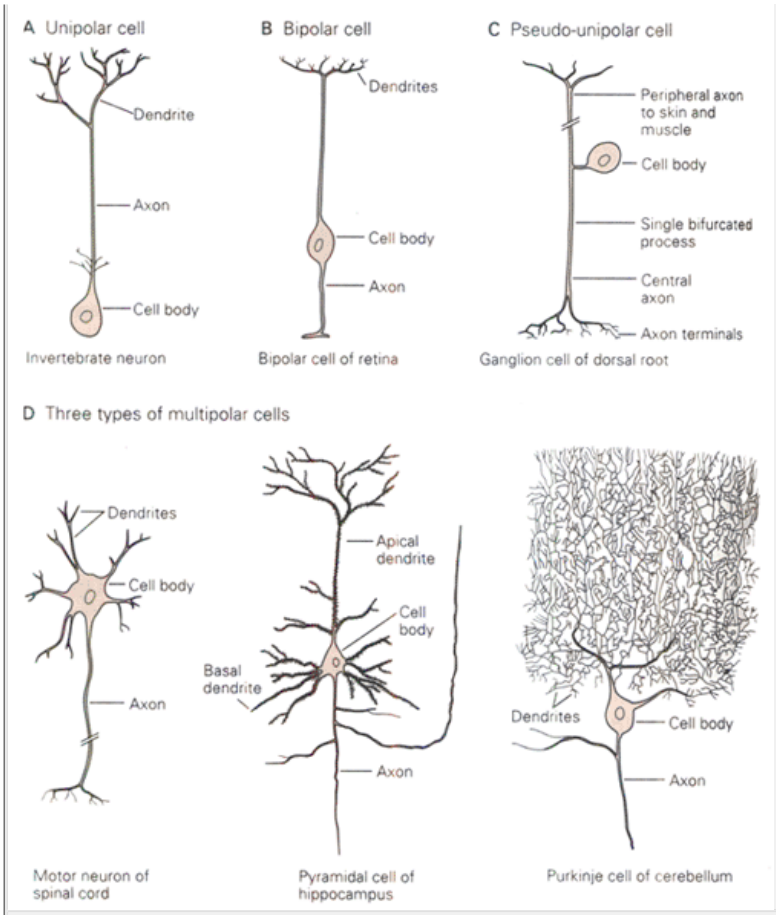

Figure 2-4 Neurons can be classified as unipolar, bipolar, or multipolar according to the number of processes that originate from the cell body.

A. Unipolar cells have a single process, with different segments serving as receptive surfaces or releasing terminals. Unipolar cells are characteristic of the invertebrate nervous system.

B. Bipolar cells have two processes that are functionally specialized: the dendrite carries information to the cell, and the axon transmits information to other cells.

C. Certain neurons that carry sensory information, such as information about touch or stretch, to the spinal cord belong to a subclass of bipolar cells designated as 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 outgrowth then splits into two processes, both of which function as axons, one going to peripheral skin or muscle, the other going to the central spinal cord.

D. Multipolar cells have an axon and many dendrites. They are the most common type of neuron in the mammalian nervous system. Three examples illustrate the large diversity of these cells. Spinal motor neurons (left) innervate skeletal muscle fibers. Pyramidal cells (middle) have a roughly triangular cell body; dendrites emerge from both the apex (the apical dendrite) and the base (the basal dendrites). Pyramidal cells are found in the hippocampus and throughout the cerebral cortex. Purkinje cells of the cerebellum (right) are characterized by the rich and extensive dendritic tree in one plane. Such a structure permits enormous synaptic input. (Adapted from Ramón y Cajal 1933.)

P.24

Unipolar neurons are the simplest nerve cells because they have a single primary process, which usually gives rise to many branches. One branch serves as the axon; other branches function as dendritic receiving structures (Figure 2-4A). These cells predominate in the nervous systems of invertebrates; in vertebrates they occur in the autonomic nervous system.

Bipolar neurons have an oval-shaped soma that gives rise to two processes: a dendrite that conveys information from the periphery of the body, and an axon that carries information toward the central nervous system (Figure 2-4B). Many sensory cells are bipolar cells, including those in the retina of the eye and in the olfactory epithelium of the nose. The mechanoreceptors that convey touch, pressure, and pain to the spinal cord are variants of bipolar cells called *pseudo-unipolar* cells. These cells develop initially as bipolar cells; later the two cell processes fuse to form one axon that emerges from the cell body. The axon then splits into two; one branch runs to the periphery (to sensory receptors in the skin, joints, and muscle), the other to the spinal cord (Figure 2-4C).

Multipolar neurons predominate in the nervous system of vertebrates. They have a single axon and, typically, many dendrites emerging from various points around the cell body (Figure 2-4D). Multipolar cells vary greatly in shape, especially in the length of their

P.25

axons and in the number, length, and intricacy of dendrite branching. Usually the number and extent of their dendrites correlate with the number of synaptic contacts that other neurons make onto them. A spinal motor cell with a relatively modest number of dendrites receives about 10,000 contacts—2000 on its cell body and 8000 on its dendrites. The dendritic tree of a Purkinje cell in the cerebellum is much larger and bushier, as well it might be—it receives approximately 150,000 contacts!

Neurons are also commonly classified into three major functional groups: sensory, motor, and interneuronal. Sensory neurons carry information from the body's periphery into the nervous system for the purpose of both perception and motor coordination.[1] Motor neurons carry commands from the brain or spinal cord to muscles and glands. Interneurons constitute by far the largest class, consisting of all nerve cells that are not specifically sensory or motor. Interneurons are subdivided into two classes. Relay or projection interneurons have long axons and convey signals over considerable distances, from one brain region to another. Local interneurons have short axons and process information within local circuits.

Nerve Cells Form Specific Signaling Networks That Mediate Specific Behaviors

All the behavioral functions of the brain—the processing of sensory information, the programming of motor and emotional responses, the vital business of storing information (memory)—are carried out by specific sets of interconnected neurons. Here we shall examine in general terms how a behavior is produced by considering a simple stretch reflex, the knee jerk. We shall see how a transient imbalance of the body, which puts a stretch on the extensor muscles of the leg, produces sensory information that is conveyed to motor cells, which in turn convey commands to the extensor muscles to contract so that balance will be restored.

The anatomical components of the knee jerk are shown in Figure 2-5. The tendon of the quadriceps femoris, an extensor muscle that moves the lower leg, is attached to the tibia through the tendon of the kneecap, the patellar tendon. Tapping this tendon just below the patella will pull (stretch) the quadriceps femoris. This initiates a reflex contraction of the quadriceps muscle to produce the familiar knee jerk, an extension of the leg smoothly coordinated with a relaxation of the hamstrings, the opposing flexor muscles. By increasing the tension of a selected group of muscles, the stretch reflex changes the position of the leg, suddenly extending it outward. (The regulation of movement by the nervous system is discussed in Section VI.)

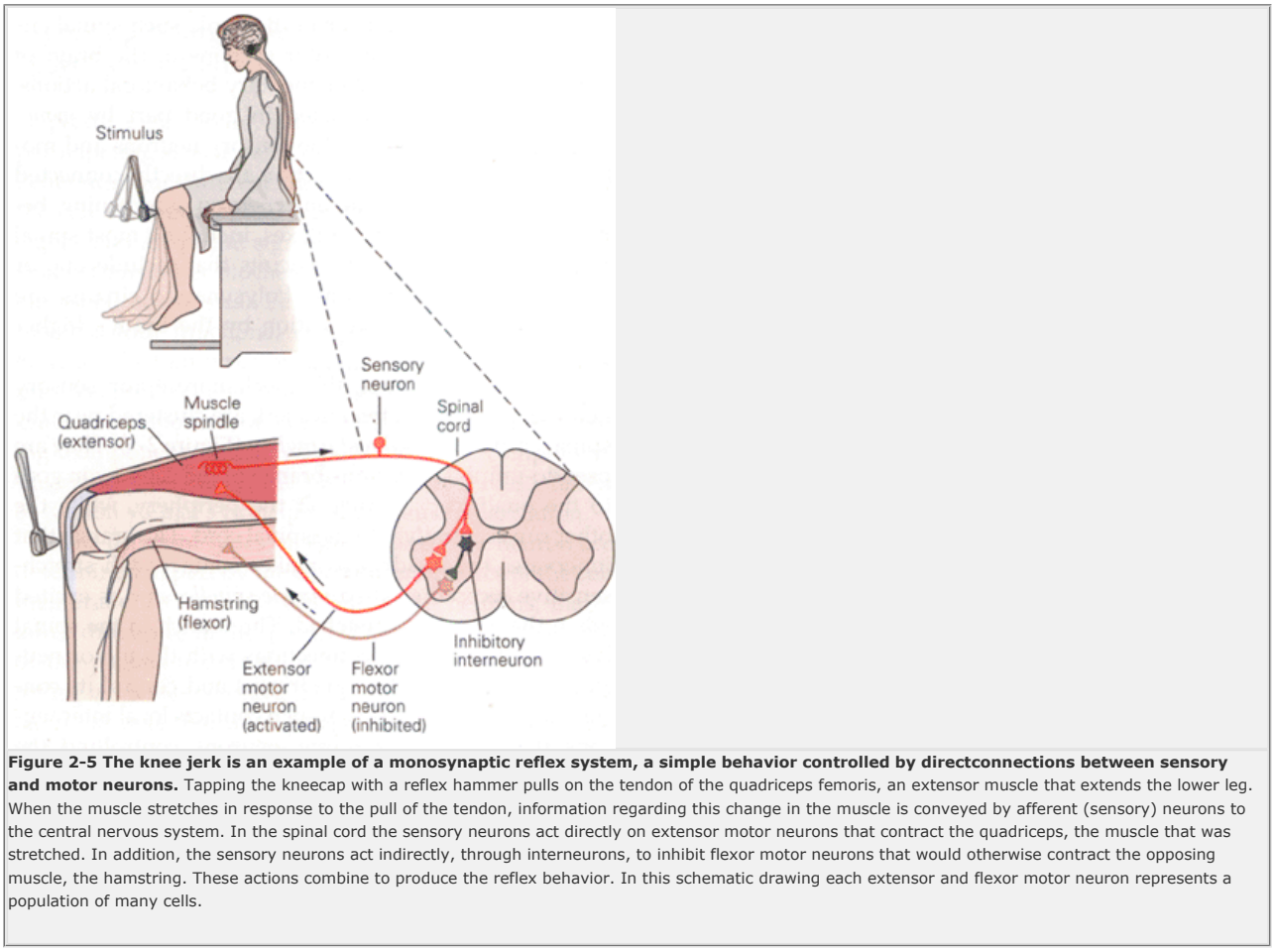

Figure 2-5 The knee jerk is an example of a monosynaptic reflex system, a simple behavior controlled by directconnections between sensory and motor neurons. Tapping the kneecap with a reflex hammer pulls on the tendon of the quadriceps femoris, an extensor muscle that extends the lower leg. When the 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 extensor motor neurons that contract the quadriceps, the muscle that was stretched. In addition, the sensory neurons act indirectly, through interneurons, to inhibit flexor motor neurons that would otherwise contract the opposing muscle, the hamstring. These actions combine to produce the reflex behavior. In this schematic drawing each extensor and flexor motor neuron represents a population of many cells.

Stretch reflexes like the knee jerk are a special type of reflex called *spinal reflexes*, behaviors mediated by neural circuits that are entirely confined to the spinal

cord. As we shall see later in the book, such spinal circuits relieve the major motor systems of the brain of having to micromanage elementary behavioral actions. Stretch reflexes are mediated in good part by *monosynaptic circuits*, in which the sensory neurons and motor neurons executing the action are directly connected to one another, with no interneuron intervening between them. Most other reflexes, including most spinal reflexes, use polysynaptic circuits that include one or more sets of interneurons. Polysynaptic circuits are more amenable to modification by the brain's higher processing centers.

The cell bodies of the mechanoreceptor sensory neurons involved in the knee jerk are clustered near the spinal cord in a *dorsal root ganglion* (Figure 2-5). They are pseudo-unipolar cells; one branch of the cell's axongoes to the quadriceps muscle at the periphery, while the other runs centrally into the spinal cord. The branch that innervates the quadriceps makes contact with stretchsensitive receptors called *muscle spindles* and is excited when the muscle is stretched. The branch in the spinal cord forms excitatory connections with the motor neurons that innervate the quadriceps and control its contraction. In addition, this branch contacts local interneurons that inhibit the motor neurons controlling the *opposing* flexor muscles. These local interneurons are not involved in the stretch reflex itself, but by coordinating motor action they increase the stability of the reflex response. Thus, the electrical signals that produce the stretch reflex convey four kinds of information:

- Sensory information is conveyed to the central nervous system (the spinal cord) from the body's surface.
- Motor commands from the central nervous system are issued to the muscles that carry out the knee jerk.
- Complementary, inhibitory commands are issued to motor neurons that innervate opposing muscles, providing coordination of muscle action.
- Information about local neuron activity related to the knee jerk is conveyed to higher centers of the central nervous system, thus permitting the brain to coordinate behavioral commands.

The stretching of just one muscle, the quadriceps, activates several hundred sensory neurons, each of which makes direct contact with 100–150 motor neurons (Figure 2-6A). This pattern of connection, in which one neuron activates many target cells, is called *neuronal divergence;* it is especially common in the input stages of the nervous system. By distributing its signals to many target cells, a single neuron can exert wide and diverse influence. For example, sensory neurons involved in a stretch reflex also contact projection interneurons that transmit information about the local neural activity to higher brain regions concerned with coordinating movements. In contrast, because there are usually five to 10 times more sensory neurons than motor neurons, a single motor cell typically receives input from many sensory cells (Figure 2-6B). This pattern of connection, called *convergence*, is common at the output stages of the nervous system. By receiving signals from numerous neurons, the target motor cell is able to integrate diverse information from many sources.

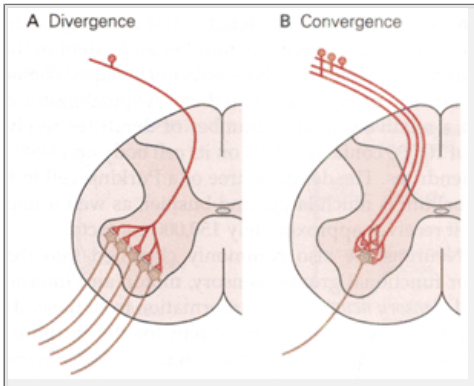

Figure 2-6 Diverging and convergingneuronal connections are a key organizational feature of the brain.

A. In the sensory systems receptor neurons at the input stage usually branch out and make multiple, divergent connections with neurons that represent the second stage of processing. Subsequent connections diverge even more.

B. By contrast, motor neurons are the targets of progressively converging connections. With convergence, the target cell receives the sum of information from many presynaptic cells.

A stretch reflex such as the knee jerk is a simple behavior produced by two classes of neurons connecting at excitatory synapses. But not all important signals in the brain are excitatory. In fact, half of all neurons produce inhibitory signals. Inhibitory neurons release a transmitter that reduces the likelihood of firing. As we have seen, even in the knee-jerk reflex, the sensory neurons make both excitatory connections and connections through inhibitory interneurons. Excitatory connections with the leg's extensor muscles cause these muscles to contract, while connections with certain inhibitory interneurons prevent the antagonist flexor muscles from being called to action. This feature of the circuit is an example of *feed-forward inhibition* (Figure 2-7A). Feedforward inhibition in the knee-jerk reflex is *reciprocal*, ensuring that the flexor and extensor pathways always

inhibit each other, so only muscles appropriate for the movement, and not those that oppose it, are recruited.

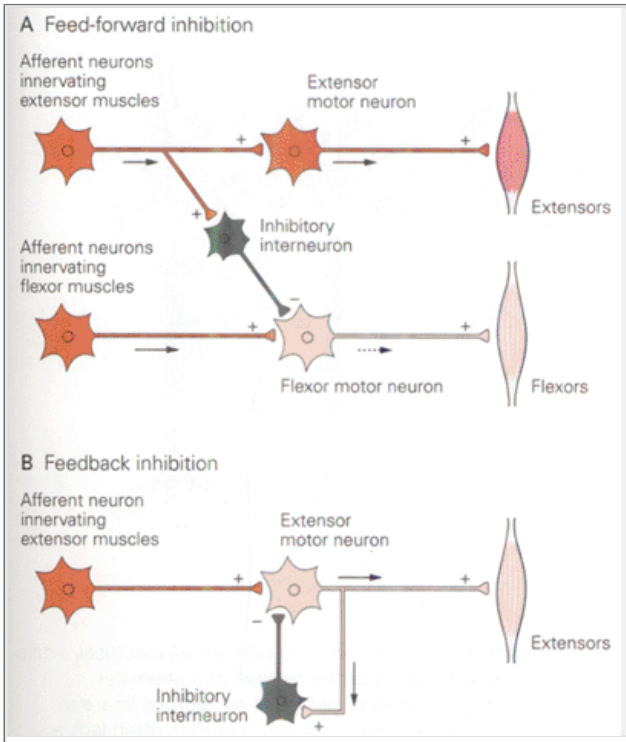

Figure 2-7 Inhibitory interneurons can produce either feed forward or feedback inhibition.

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

B. Negative feedback inhibition is a self-regulating mechanism. The effect is to dampen activity within the stimulated pathway and prevent it from exceeding a certain critical maximum. Here the extensor motor neurons act on inhibitory interneurons, which feed back to the extensor motor neurons themselves and thus reduce the probability of firing by these cells.

Neurons can also have connections that provide *feedback inhibition.* For example, an active neuron may have excitatory connections withboth a target cell and an inhibitory interneuron that has its own feedbackconnection with the active neuron. In this way signals from the active neuron simultaneously excite the target neuron and the inhibitory interneuron, which thus is able to limit the ability of the active neuron to excite its target (Figure 2-7B). We will encounter many examples of feed-forward and feedback inhibition when we examine more complex behaviors in later chapters.

Signaling Is Organized in the Same Way in All Nerve Cells

To produce a behavior, a stretch reflex for example, each participating sensory and motor nerve cell sequentially generates four different signals at different sites within the cell: an input signal, a trigger signal, a conducting signal, and an output signal. Regardless of cell size and shape, transmitter biochemistry, or behavioral function, almost all neurons can be described by a model neuron that has four functional components, or regions, that generate the four types of signals (Figure 2-8): a local input (receptive) component, a trigger (summing or integrative) component, a long-range conducting (signaling) component, and an output (secretory) component. This model neuron is the physiological representation of Ramón y Cajal's principle of dynamic polarization.

The different types of signals used by a neuron are determined in part by the electrical properties of the cell membrane. At rest, all cells, including neurons, maintain a difference in the electrical potential on either side of the plasma (external) membrane. This is called the resting membrane potential. In a typical resting neuron the electrical potential difference is about 65 mV. Because the net charge outside of the membrane is arbitrarily defined as zero, we say the resting membrane potential is -65 mV. (In different nerve cells it may range from about -40 to -80 mV; in muscle cells it is greater still, about -90 mV.) As we shall see in Chapter 7, the difference in electrical potential when the cell is at rest results from two factors: (1) the unequal distribution of electrically charged ions, in particular, the positively charged Na^+ and K^+ ions and the negatively charged amino acids and proteins on either side of the cell membrane, and (2) the selective permeability of the membrane to just one of these ions, K^+.

The unequal distribution of positively charged ions on either side of the cell membrane is maintained by a membrane protein that pumps Na^+ out of the cell and K^+ back into it. This *Na^+-K^+ pump*, which we shall learn more about in Chapter 7, keeps the Na^+ ion concentration in the cell low (about 10 times lower than that outside the cell) and the K^+ ion concentration high (about 20 times higher than that outside).

At the same time, the cell membrane is selectively permeable to K^+ because the otherwise impermeable membrane contains *ion channels*, pore-like structures that span the membrane and are highly permeable to K^+ but considerably less permeable to Na^+. When the cell is at rest, these channels are open and K^+ ions tend to leak out. As K^+ ions leak from the cell, they leave behind a cloud of unneutralized negativecharge on the inner surface of the membrane, so that the net charge inside

the membrane is more negative than on the outside (Figure 2-9).

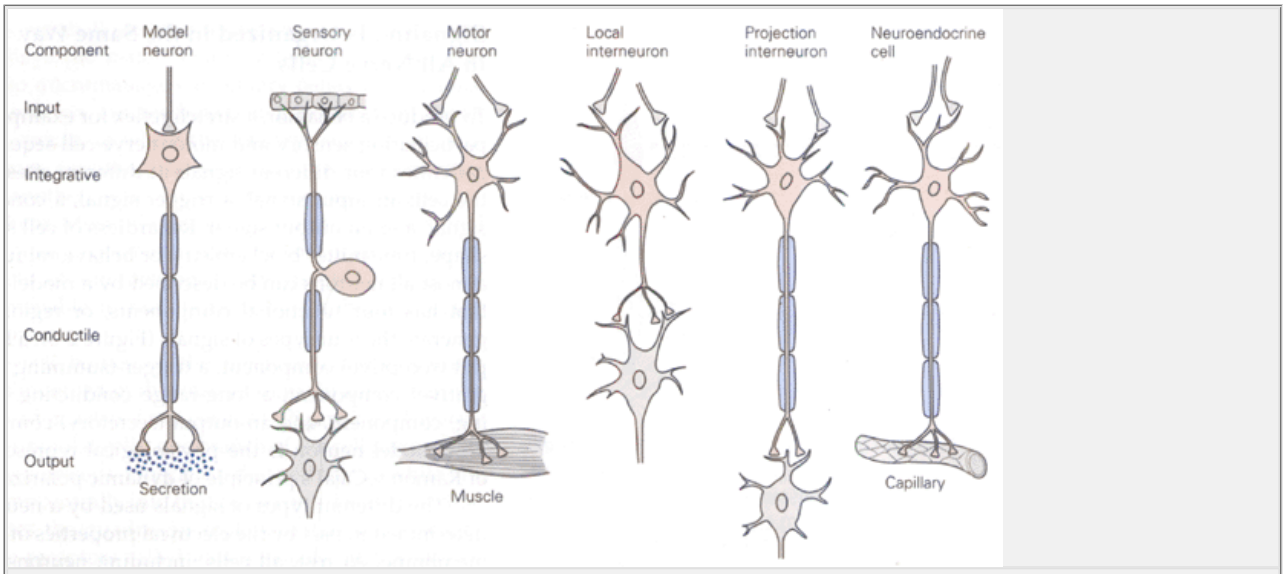

Figure 2-8 Most neurons, regardlessof type, have four functional regions in common: an input component, a trigger or integrative component, a conductile component, and an output component. Thus, the functional organization of most neurons can be schematically represented by a model neuron. Each component produces a characteristic signal: the input, integrative, and conductile signals are all electrical, while the output signal consists of the release of a chemical transmitter into the synaptic cleft. Not all neurons share all these features; for example, local interneurons often lack a conductile component.

Excitable cells, such as nerve and muscle cells, differ from other cells in that their membrane potential can be significantly and quickly altered; this change can serve as a signaling mechanism. Reducing the membrane potential by say 10 mV (from -65 mV to -55 mV) makes the membrane much more permeable to Na^+ than to K^+. This influx of positively charged Na^+ ions tends to neutralize the negative charge inside the cell and results in an even greater reduction in membrane potential— the action potential. The action potential is conducted down the cell's axon to the axon's terminals which end on other cells (neurons or muscle), where the action potential initiates communication with the other cells. As noted earlier, the action potential is an all-or-none impulse that is actively propagated along the axon, so that its amplitude is not diminished by the time it reaches the axon terminal. Typically, an action potential lasts about one millisecond, after which the membrane returns to its resting state, with its normal separation of charges and higher permeability to K^+ than to Na^+. We shall learn more about the mechanisms underlying the resting potential and action potential in Chapters 6,7,8,9.

In addition to the long-range signal of the action potential, nerve cells also produce local signals, such as receptor potentials and synaptic potentials, that are not actively propagated and therefore typically decay within just a few millimeters. Both long-range and local signals result from changes in the membrane potential, either a decrease or increase from the resting potential. The resting membrane potential therefore provides the baseline against which all signals are expressed. A reduction in membrane potential (eg, from -65 mV to -55 mV) is called *depolarization.* Because depolarization enhances a cell's ability to generate an action potential, it is *excitatory.* In contrast, an increase in membrane potential (eg, from about -65 mV to -75 mV) is called *hyperpolarization.* Hyperpolarization makes a cell less likely to generate an action potential and is therefore *inhibitory*.

The Input Component Produces Graded Local Signals

In most neurons at rest no current flows from one part of the neuron to another, so the resting potential is the same throughout the cell. In sensory neurons current flow is typically initiated by a sensory stimulus, which activates specialized receptor proteins at the neuron's receptive surface. In our example of the knee jerk,

stretch of the quadriceps muscle activates specific proteins that are sensitive to stretch of the sensory neuron. The specialized receptor protein forms ion channels in the membrane, through which Na^+ and K^+ flow. These channels open when the cell is stretched, as we shall learn in Chapters 7 and 9, permitting a rapid influx of ions into the sensory cell. This ionic current disturbs the resting potential of the cell membrane, driving the membrane potential to a new level called the *receptor potential.* The amplitude and duration of the receptor potential depends on the intensity of the muscle stretch. The larger or longer-lasting the stretch, the larger and longer-lasting the resulting receptor potential (Figure 2-10A). Most receptor potentials are depolarizing (excitatory). However, hyperpolarizing (inhibitory) receptor potentials are found in the retina of the eye, as we shall learn in Chapter 26.

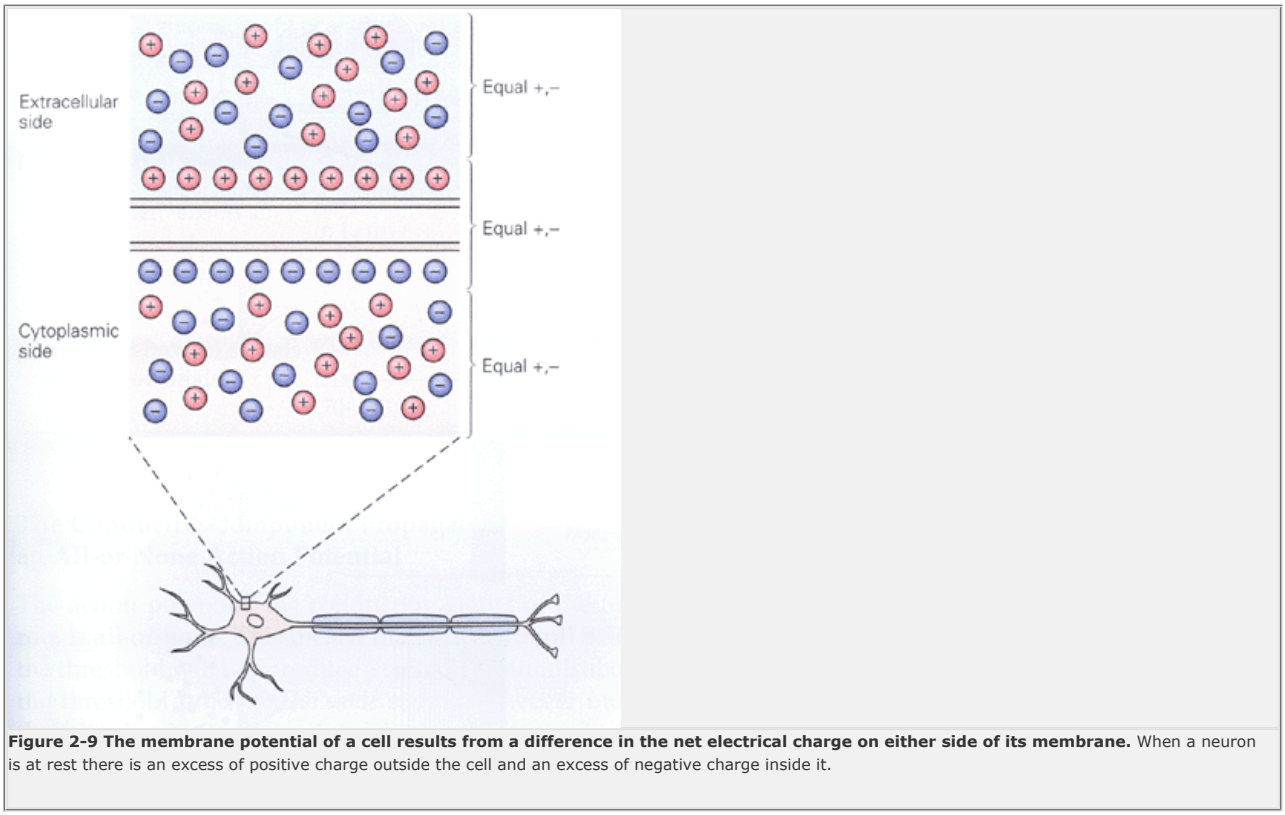

Figure 2-9 The membrane potential of a cell results from a difference in the net electrical charge on either side of its membrane. When a neuron is at rest there is an excess of positive charge outside the cell and an excess of negative charge inside it.

The receptor potential is the first representation of stretch to be coded in the nervous system. It is, however, a purely *local signal.* The receptor potential—the electrical activity in the sensory neuron initiated by a stimulus —spreads only passively along the axon. It therefore decreases in amplitude with distance and cannot be conveyed much farther than 1 or 2 mm. In fact, 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. To be carried successfully to the rest of the nervous system, the local signal must be amplified—it must generate an action potential. In the knee jerk the receptor potential in the sensory neuron propagates to the first node of Ranvier in the axon, where, if it is large enough, it generates an action potential, which then propagates without failure (by a regenerative mechanism discussed in Chapter 9) to the axon terminals in the spinal cord. Here, at the synapse, between the sensory neuron and a motor neuron activating the leg muscles, the action potential produces a chain of events that result in an input signal to the motor neuron.

In our example of the knee jerk, the action potential in the sensory neuron releases a chemical signal (a neurotransmitter) across the synaptic cleft. The transmitter binds to receptor proteins on the motor neuron, and the resulting reaction transduces the potential chemical energy of the transmitter into electrical energy. This in turn alters the membrane potential of the motor cell, a change called the *synaptic potential.*

Like the receptor potential, the synaptic potential is graded. The amplitude of the synaptic potential depends on how much chemical transmitter is released, and its duration on how long the transmitter is active. The synaptic potential can be either depolarizing or hyperpolarizing, depending on the type of receptor molecule that is activated. Synaptic potentials, like receptor potentials, are local changes in membrane potential that spread passively along the neuron. The signal does not reach beyond the axon's initial segment unless it gives rise to an action potential. The features ofreceptor and synaptic potentials are summarized in Table 2-1.

The Trigger Component Makes the Decision to Generate an Action Potential

Charles Sherrington first pointed out that the quintessential action of the nervous system is its ability to weigh the consequences of different types of information and then decide on appropriate responses. This *integrative action* of the nervous system is clearly seen in the actions of the trigger component of the neuron.

Action potentials are generated by a sudden influx of Na^+ ions through voltage-sensitive channels in the cell membrane. When an input signal (a receptor potential or synaptic potential) depolarizes the cell membrane, the change in membrane potential opens the Na^+ ion channels, allowing Na^+ to flow down its concentration gradient, from outside the cell where the Na^+ con-

centration is high to inside the cell where it is low. These voltage-sensitive Na^+ channels are concentrated at the initial segment of the axon, an uninsulated portion of the axon just beyond the neuron's input region. In sensory neurons the highest density of Na^+ channels occurs at the myelinated axon's first node of Ranvier; in interneurons and motor neurons the highest density occurs at the axon hillock, where the axon emerges from the cell body.

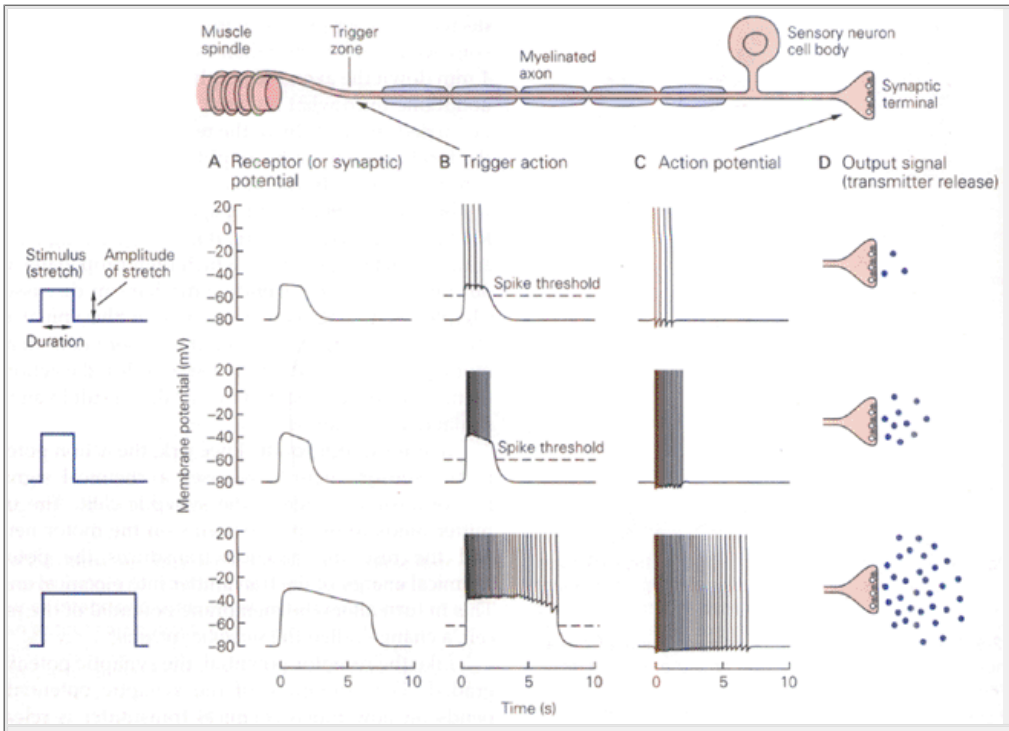

Figure 2-10 A sensory neuron transforms a physical stimulus (in our example, a stretch) into electrical activity in the cell. Each of the neuron's four signaling components produces a characteristic signal.

A. The input signal (a receptor or synaptic potential) is graded in amplitude and duration, proportional to the amplitude and duration of the stimulus.

B. The trigger zone integrates the input signal—the receptor potential in sensory neurons, or synaptic potential in motor neurons—into a trigger action that produces action potentials that will be propagated along the axon. An action potential is generated only if the input signal is greater than a certain *spike threshold.* Once the input signal surpasses this threshold, any further increase in amplitude of the input signal increases the *frequency* with which the action potentials are generated, not their amplitude. The *duration* of the input signal determines the number of action potentials. Thus, the graded nature of input signals is translated into a frequency code of action potentials at the trigger zone.

C. Action potentials are all-or-none. Every action potential has the same amplitude and duration, and thus the same wave form on an oscilloscope. Since action potentials are conducted without fail along the full length of the axon to the synaptic terminals, the information in the signal is represented only by the frequency and number of spikes, not by the amplitude.

D. When the action potential reaches the synaptic terminal, the cell releases a chemical neurotransmitter that serves as the output signal. The total number of action potentials in a given period of time determines exactly how much neurotransmitter will be released by the cell.

Because it has the highest density of voltagesensitive Na^+ channels, the initial segment of the axon has the lowest threshold for generating an action potential. Thus, an input signal spreading passively along the cell membrane is more likely to give rise to an action potential at the initial segment of the axon than at other sites in the cell. This part of the axon is therefore known as the impulse initiation zone, or *trigger zone.* It is here that the activity of all receptor (or synaptic) potentials is summed and where, if the size of the input signal reaches threshold, the neuron fires an action potential.

Table 2-1 Comparison of Local (Passive) and Propagated Signals

Signal type	Amplitude (mV)	Duration	Summation	Effect of signal	Type of propagation
Local (passive) signals					
Receptor potentials	Small (0.1–10)	Brief (5–100 ms)	Graded	Hyperpolarizing or depolarizing	Passive
Synaptic potentials	Small (0.1–10)	Brief to long (5 ms to 20 min)	Graded	Hyperpolarizing or depolarizing	Passive
Propagated (active) signals					
Action potentials	Large (70–110)	Brief (1–10 ms)	All-or-none	Depolarizing	Active

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

The action potential, the conducting signal of the neuron, is all-or-none. This means that while stimuli below the threshold will not produce a signal, all stimuli

above the threshold produce the *same* signal. However much the stimuli vary in intensity or duration, the amplitude and duration of each action potential are pretty much the same. In addition, unlike receptor and synaptic potentials, which spread passively and decrease in amplitude, the action potential does not decay as it travels along the axon to its target—a distance that can measure 3 m in length—because it is periodically regenerated. This conducting signal can travel at rates as fast as 100 meters per second.

The remarkable feature of action potentials is that they are highly stereotyped, varying only subtly (although in some cases importantly) from one nerve cell to another. This feature was demonstrated in the 1920s by Edgar Adrian, who was one of the first to study the nervous system at the cellular level. Adrian found that all action potentials have a similar shape or wave form on the oscilloscope (see Figure 2-3). Indeed, the voltage signals of action potentials carried into the nervous system by a sensory axon often are indistinguishable from those carried out of the nervous system to the muscles by a motor axon.

Only two features of the conducting signal convey information: the number of action potentials and the time intervals between them (Figure 2-10C). 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." Thus, what determines the intensity of sensation or speed of movement is not the magnitude or duration of individual action potentials, but their *frequency.* Likewise, the duration of a sensation or movement is determined by the period over which action potentials are generated.

If signals are stereotyped and do not reflect the properties of the stimulus, how do neural signals carry specific behavioral information? How is a message that carries visual information distinguished from one that carries pain information about a bee sting, and how do both of these signals differ from messages that send commands for voluntary movement? As we have seen, and will learn to appreciate even more in later chapters, the message of an action potential is determined by the neural pathway that carries it. The visual pathways activated by receptor cells in the retina that respond to light are completely distinct from the somatic sensory pathways activated by sensory cells in the skin that respond to touch or to pain. The function of the signal—be it visual, tactile, or motor—is determined not by the signal itself but by the pathway along which it travels.

The Output Component Releases Neurotransmitter

When an action potential reaches a neuron's terminal it stimulates the release of a chemical transmitter from the cell. Transmitters can be small molecules, such as L-glutamate and acetylcholine, or they can be peptides like enkephalin (Chapter 15). Transmitter molecules are held in subcellular organelles called synaptic vesicles, which are loaded into specialized release sites in the presynaptic terminals called active zones. To unload their transmitter, the vesicles move up to and fuse with the neuron's plasma membrane, a process known as exocytosis. (We shall consider neurotransmitter release in Chapter 14.)

The release of chemical transmitter serves as a neuron's output signal. Like the input signal, the output signal is graded. The amount of transmitter released is

determined by the number and frequency of the action potentials in the presynaptic terminals (see Figure 2-10). After the transmitter is released from the presynaptic neuron, it diffuses across the synaptic cleft to receptors in the membrane of the postsynaptic neuron. The binding of transmitter to receptors causes the postsynaptic cell to generate a synaptic potential. Whether the synaptic potential has an excitatory or inhibitory effect will depend on the type of *receptors* in the postsynaptic cell, not on the particular neurotransmitter. The same transmitter can have different effects on different types of receptors.

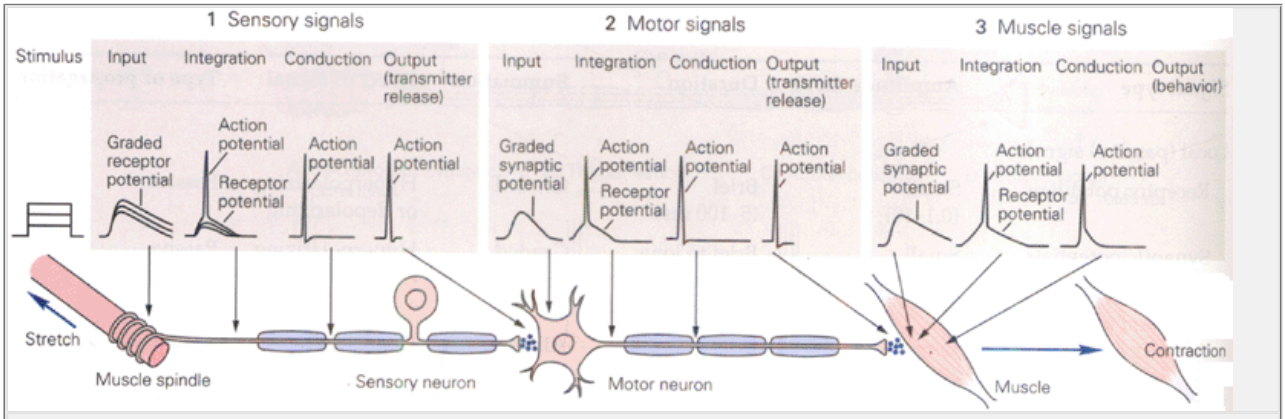

Figure 2-11 The sequence of signals that produces a reflex action.

1. The stretching of a muscle produces a receptor potential in the terminal fibers of the sensory neuron (the dorsal root ganglion cell). The amplitude of the receptor potential is proportional to the intensity of the stretch. This potential then spreads passively to the integrative segment, or trigger zone, at the first node of Ranvier. There, if the receptor potential is sufficiently large, it triggers an action potential, which then propagates actively and without change along the axon to the terminal region. At the terminal the action potential leads to an output signal: the release of a chemical neurotransmitter. The transmitter diffuses across the synaptic cleft and interacts with receptor molecules on the external membranes of the motor neurons that innervate the stretched muscle. **2.** This interaction initiates a synaptic potential in the motor cell. The synaptic potential then spreads passively to the trigger zone of the motor neuron axon, where it initiates an action potential that propagates actively to the terminal of the motor neuron. The action potential releases transmitter at the nerve-muscle synapse. **3.** The binding of the neurotransmitter with receptors in the muscle triggers a synaptic potential in the muscle. This signal produces an action potential in the muscle, causing con-traction of the muscle fiber.

The Transformation of the Neural Signal From Sensory to Motor Is Illustrated by the Stretch Reflex Pathway

We have seen that a signal is transformed as it is conveyed from one component of the neuron to the next and from one neuron to the next. This transformation— from input to output—can be seen in perspective by tracing the relay of signals for the stretch reflex.

When a muscle is stretched, the features of the stimulus —its amplitude and duration—are reflected in the amplitude and duration of the receptor potential in the sensory neuron. If the receptor potential exceeds the threshold for action potentials in that cell, the graded signal is transformed at the trigger component into an action potential, an all-or-none signal. The more the receptor potential exceeds threshold, the greater the depolarization and consequently the greater the frequency of action potentials in the axon; likewise, the duration of the input signal determines the number of action potentials. (Several action potentials together are called a *train* of action potentials.) This information—the frequency and number of action potentials—is then faithfully conveyed along the entire axon's length to its terminals, where the frequency of action potentials determines how much transmitter is released.

These stages of transformation have their counterparts in the motor neuron. The transmitter released by a sensory neuron interacts with receptors on the motor neuron to initiate a graded synaptic potential, which spreads to the initial segment of the motor axon. If the membrane potential of the motor neuron reaches a

critical threshold, an action potential will be generated and propagate without fail to the motor cell's presynaptic terminals. There the action potential causes transmitter release, which triggers a synaptic potential in the muscle. That in turn produces an action potential in the leg muscle, which leads to the final transformation —muscle contraction and an overt behavior. The sequence of transformations of a signal from sen-

P.33

sory neuron to motor neuron to muscle is illustrated in Figure 2-11.

Nerve Cells Differ Most at the Molecular Level

The model of neuronal signaling we have outlined is a simplification that applies to most neurons, but there are some important variations. For example, some neurons do not generate action potentials. These are typically local interneurons without a conductile component—they have no axon, or such a short one that a conducted signal is not required. In these neurons the input signals are summed and spread passively to the nearby terminal region, where transmitter is released. There are also neurons that lack a steady resting potential and are spontaneously active.

Even cells with similar organization can differ in important molecular details, expressing different combinations of ion channels, for example. As we shall learn in Chapters 6 and 9, different ion channels provide neurons with various thresholds, excitability properties, and firing patterns. Thus, neurons with different ion channels can encode the same class of synaptic potential into different firing patterns and thereby convey different signals.

Neurons also differ in the chemical transmitters they use to transmit information to other neurons, and in the receptors they have to receive information from other neurons. Indeed, many drugs that act on the brain do so by modifying the actions of specific chemical transmitters or a particular subtype of receptor for a given transmitter. These differences not only have physiological importance for day-to-day functioning of the brain, but account for the fact that a disease may affect one class of neurons but not others. Certain diseases, such as amyotrophic lateral sclerosis and poliomyelitis, strike only motor neurons, while others, such as tabes dorsalis, a late stage of syphilis, affect primarily sensory neurons. Parkinson's disease, a disorder of voluntary movement, damages a small population of interneurons that use dopamine as a chemical transmitter. Some diseases are selective even within the neuron, affecting only the receptive elements, the cell body, or the axon. In Chapter 16 we shall see how research into myasthenia gravis, caused by a faulty transmitter receptor in the muscle membrane, has provided important insights into synaptic transmission. Indeed, because the nervous system has so many cell types and variations at the molecular level, it is susceptible to more diseases (psychiatric as well as neurological) than any other organ of the body.

Despite the differences among nerve cells, the basic mechanisms of electrical signaling are surprisingly similar. This simplicity is fortunate for those who study the brain. By understanding the molecular mechanisms that produce signaling in one kind of nerve cell, we are well on the way to understanding these mechanisms in many other nerve cells.

Nerve Cells Are Able to Convey Unique Information Because They Form Specific Networks

The stretch reflex illustrates how just a few types of nerve cells can interact to produce a simple behavior. But even the stretch reflex involves populations of neurons— perhaps a few hundred sensory neurons and a hundred motor neurons. Can the individual neurons implicated in a complex behavior be identified with the same precision? In invertebrate animals, and in some lower vertebrates, a single cell (the so-called *command cell*) can initiate a complex behavioral sequence. But, as far as we know, no complex human behavior is initiated by a single neuron. Rather, each behavior is generated by the actions of many cells. Broadly speaking, as we have seen, there are three neural components of behavior: sensory input, intermediate (interneuronal) processing, and motor output. Each of these components is mediated by a single group or several distinct groups of neurons.

As discussed in Chapter 1, one of the key strategies of the nervous system is localization of function: specific types of information are processed in particular brain regions. Thus, information for each of our senses is processed in a distinct brain region where the afferent connections typically form a precise map of the pertinent receptor sheet on the body surface—the skin (touch), the retina (sight), the basilar membrane of the cochlea (hearing), or the olfactory epithelium (smell). These maps are the first stage in creating a representation in the brain of the outside world in which we live. Similarly, areas of the brain concerned with movement contain an orderly arrangement of neural connections representing the musculature and specific movements. The brain, therefore, contains at least two types of neural maps: one for sensory perceptions and another for motor commands. The two maps are interconnected in ways we do not yet fully understand.

The neurons that make up these maps—motor, sensory, and interneuronal—do not differ greatly in their electrical properties. They have different functions because of the connections they make. These connections, established as the brain develops, determine the behavioral function of individual cells. Although our understanding of how sensory and motor information is processed and represented in the brain is based on the

P.34

detailed studies of only a few regions, in those regions in which our understanding is particularly well advanced it is clear that the logical operations of a mental representation can be understood only by defining the flow of information through the connections that make up the various maps.

A single component of behavior sometimes recruits a number of groups of neurons that simultaneously provide the same or similar information. The deployment of several neuron groups or several pathways to convey similar information is called *parallel processing.* Parallel processing also occurs in a single pathway when different neurons in the pathway perform similar computations simultaneously. Parallel processing makes enormous sense as an evolutionary strategy for building a more powerful brain: it increases both the speed and reliability of function within the central nervous system.

The importance of abundant, highly specific parallel connections is now also being recognized by scientists attempting to construct computer models of the brain. Scientists working in this field, a branch of computer science known as *artificial intelligence*, first used serial processing to simulate the brain's higher-level cognitive processes—processes such as pattern recognition, learning, memory, and motor performance. They soon realized that although these serial models solved many problems rather well, including the challenge of playing chess, they performed poorly with other computations that the brain does almost instantaneously, such as recognizing faces or comprehending speech.

As a result, most computational neurobiologists have turned to systems with both serial and parallel (distributed) components, which they call *connectionist models.* In these models elements distributed throughout the system process related information simultaneously. Preliminary insights from this work are often consistent with physiological studies. Connectionist models show that individual elements of a system do not transmit large amounts of information. Thus, what makes the brain a remarkable information processing machine is not the complexity of its neurons, but rather its many elements and, in particular, the complexity of connections between them. Individual stereotyped neurons are able to convey unique information because they are wired together and organized in different ways.

The Modifiability of Specific Connections Contributes to the Adaptability of Behavior

That neurons make specific connections with one another simple reflexes can undergo modification that lasts minutes, and much learning results in behavioral change that can endure for years. How can neural activity produce such long-term changes in the function of a set of prewired connections? A number of solutions for these dilemmas have been proposed. The proposal that has proven most farsighted is the *plasticity hypothesis*, first put forward at the turn of the century by Ramón y Cajal. A modern form of this hypothesis was advanced by the Polish psychologist Jerzy Konorski in 1948:

The application of a stimulus leads to changes of a twofold kind in the nervous system. … [T]he first property, by virtue of which the nerve cells *react* to the incoming impulse … we call *excitability*, and … changes arising … because of this property we shall call *changes due to excitability.* The second property, by virtue of which certain permanent functional transformations arise in particular systems of neurons as a result of appropriate stimuli or their combination, we shall call *plasticity* and the corresponding changes *plastic changes.*

There is now considerable evidence for plasticity at chemical synapses. Chemical synapses often have a remarkable capacity for short-term physiological changes (lasting hours) that increase or decrease the effectiveness of the synapse. Long-term changes (lasting days) can give rise to further physiological changes that lead to anatomical changes, including pruning of preexisting connections, and even growth of new connections. As we shall see in later chapters, chemical synapses can be modified functionally and anatomically during development and regeneration, and, most importantly, through experience and learning. Functional alterations are typically short term and involve changes in the effectiveness of existing synaptic connections. Anatomical alterations are typically long-term and consist of the growth of new synaptic connections between neurons. It is this potential for plasticity of the relatively stereotyped units of the nervous system that endows each of us with our individuality.

Selected Readings

Adrian ED. 1928. *The Basis of Sensation: The Action of the Sense Organs.* London: Christophers.

Gazzaniga MS (ed). 1995. *The Cognitive Neurosciences.* Cambridge, MA: MIT Press.

Jones EG. 1988. The nervous tissue. In: LWeiss (ed), *Cell and Tissue Biology: A Textbook of Histology*, 6th ed., pp. 277–351. Baltimore: Urban and Schwarzenberg.

Newan EA. 1993. Inward-rectifying potassium channels in retinal glial (Muller) cells. J Neurosci 13:3333–3345.

Perry VH. 1996. Microglia in the developing and mature central nervous system. In: KR Jessen, WD Richardson (eds).*Glial Cell Development: Basic Principles & Clinical Relevance*, pp. 123–140. Oxford: Bios.

Ramón y Cajal S. 1937. 1852–1937. *Recollections of My Life.* EH Craigie (transl). Philadelphia: American Philosophical Society; 1989. Reprint. Cambridge, MA: MIT Press.

References

Adrian ED. 1932. *The Mechanism of Nervous Action: Electrical Studies of the Neurone.* Philadelphia: Univ. Pennsylvania Press.

Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. 1994. *Molecular Biology of the Cell*, 3rd ed. New York: Garland.

Erlanger J, Gasser HS. 1937. *Electrical Signs of Nervous Activity.* Philadelphia: Univ. Pennsylvania Press.

Hodgkin AL, Huxley AF. 1939. Action potentials recorded from inside a nerve fiber. Nature 144:710–711.

Kandel ER. 1976. The study of behavior: the interface between psychology and biology. In: *Cellular Basis of Behavior: An Introduction to Behavioral Neurobiology*, pp. 3–27. San Francisco: WH Freeman.

Konorski J. 1948. *Conditioned Reflexes and Neuron Organization.* Cambridge: Cambridge Univ. Press.

Martinez Martinez PFA. 1982. *Neuroanatomy: Development and Structure of the Central Nervous System.* Philadelphia: Saunders.

Newman EA. 1986. High potassium conductance in astrocyte endfeet. Science 233:453–454.

Nicholls JG, Martin AR, Wallace BG. 1992. *From Neuron to Brain: A Cellular and Molecular Approach to the Function of the Nervous System*, 3rd ed. Sunderland, MA: Sinauer.

Penfield W (ed). 1932. *Cytology & Cellular Pathology of the Nervous System*, Vol. 2. New York: Hoeber.

Ramón y Cajal S. 1933. Histology, 10th ed. Baltimore: Wood.

Sears ES, Franklin GM. 1980. Diseases of the cranial nerves. In: RN Rosenberg (ed). *The Science and Practice of Clinical Medicine.* Vol. 5, *Neurology*, pp. 471–494. New York: Grune & Stratton.

Sherrington C. 1947. *The Integrative Action of the Nervous System*, 2nd ed. Cambridge: Cambridge Univ. Press

1. Some primary sensory neurons are also commonly called afferent neurons, and we use these two terms interchangeably in the book. 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 sensation. The term sensory should, strictly speaking, be applied only to afferent input that leads to a perception.