Membrane Potential

The plasma membranes of all living cells have a membrane potential, or are polarized electrically. The term membrane potential refers to a separation of charges across the membrane or to a difference in the relative number of cations and anions in the ICF (intracellular fluid) and ECF (extracellular fluid). All cells have membrane potential. The cells of **excitable tissues** – namely nerve cells and muscle cells- have the ability to produce rapid, transient changes in their membrane potential when excited. These brief fluctuations in potential serve as electrical signals.

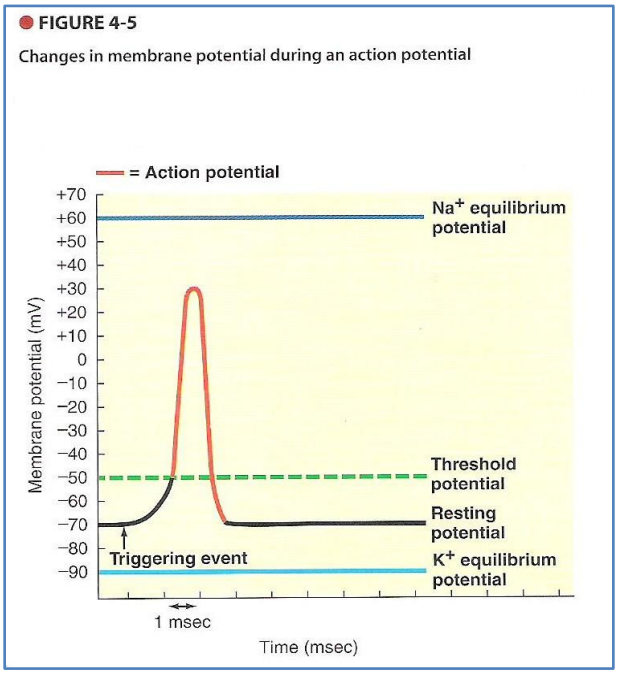
The unequal distribution of a few key ions between the ICF and ECF and their selective movement through the plasma membrane are responsible for the electrical properties of membrane. Sodium ions (Na^+) is in greater concentration in the extracellular fluid and potassium ions (K^+) is in much higher concentration in the intracellular fluid. These concentration differences are maintained by the Na^+-K^+ pump. The concentration gradient for K^+ will always be outward and the concentration gradient for Na^+ will always be inward.

GRADED POTENTIALS

Graded potentials are local changes in membrane potential that occur in varying grades or degrees of magnitude or strength. Graded potentials are usually produced by a specific triggering event that causes gated ion channels to open in a specialized region of the excitable cell membrane. The stronger the triggering event, the more gated channels that open, the greater the positive charge entering the cell, and the larger the depolarizing graded potential at the point of origin.

ACTION POTENTIALS

Action potentials are brief, rapid, large (100 mV) changes in membrane potential. Action potentials are conducted, or propagated, throughout the entire membrane in *nondecremental* fashion; that is, they do not diminish in strength as they travel from their site of initiation throughout the remainder of the cell membrane. To initiate an action potential, a triggering event causes the membrane to depolarize from the resting potential of ~70 mV (Figure 4-5). Depolarization proceeds slowly at first, until it reaches a critical level known as threshold potential, typically between -50 and -55 mV. At threshold potential, an explosive depolarization takes place. A recording of the potential at this time shows a sharp upward deflection to +30 mV as the



potential rapidly reverses itself so that the inside of the cell becomes positive compared to the outside. Just as rapidly, the membrane repolarizes, dropping back to resting potential. The entire rapid change in potential from threshold to peak and then back to resting is called the *action potential.* The duration of an action potential is always the same in a given excitable cell. In a nerve cell, an action potential lasts for only 1 msec. Membrane at rest is considerably more permeable to K^+ than to Na^+. During an action potential, marked changes in membrane permeability to Na^+ and K^+ take place, permitting rapid fluxes of these ions down their electrochemical gradients. These ion movements carry the current responsible for the potential changes that occur during an action potential. Action potentials take place as a result of the triggered opening and subsequent closing of two specific types of channels: voltage-gated Na^+ channels and voltage-gated K^+ channels.

ION MOVEMENT DURING AN ACTION POTENTIAL

At resting potential (-70 mV), all the voltage-gated Na^+ and K^+ channels are closed. Therefore, passage of Na^+ and K^+ does not occur through these voltage-gated channels at resting potential. However, because of the presence of many K^+ leak channels and very few Na^+ leak channels, the resting membrane is 50 to 75 times more permeable to K^+ than to Na^+. When a membrane starts to depolarize toward threshold as a result of a triggering event, the activation gates of some of its voltage-gated Na^+ channels open, Na^+ starts to move in. The inward movement of positively charged Na^+ depolarizes the membrane further, thereby opening even more voltage-gated Na^+ channels and allowing more Na^+ to enter, and so on, in a positive-feedback cycle (Figure 4-7).

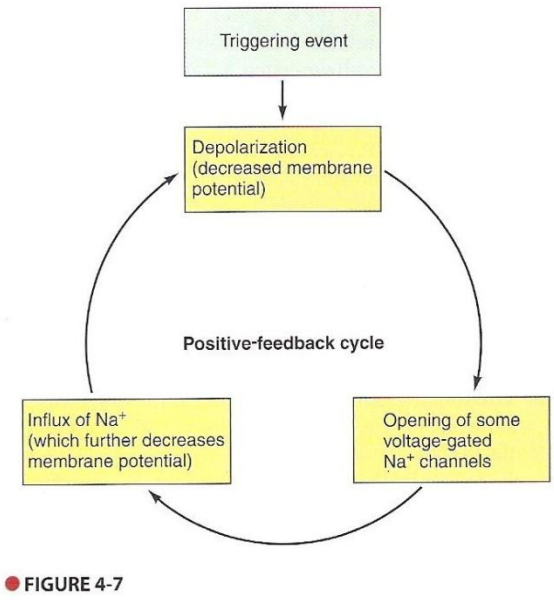


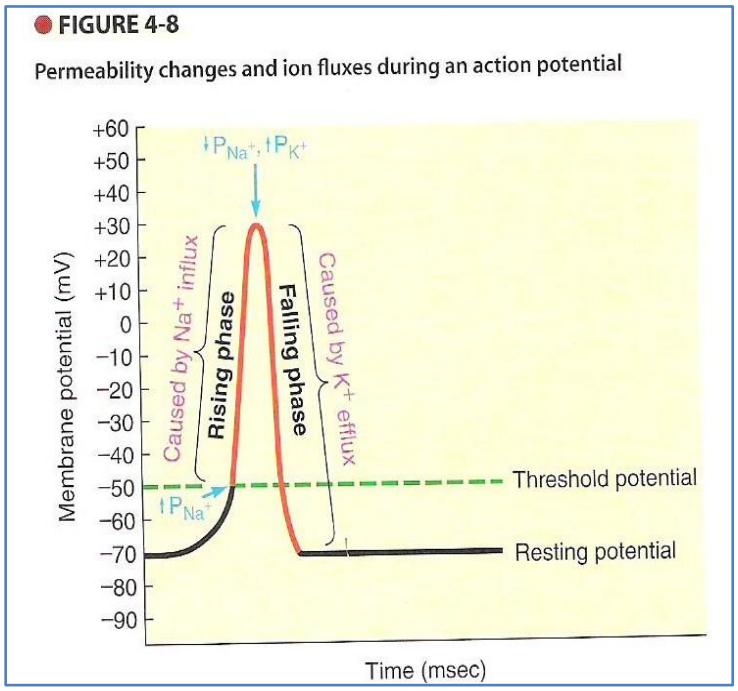
FIGURE 4-7
Positive-feedback cycle responsible for opening Na^+ channels at threshold

At threshold potential, there is an explosive increase in Na^+ permeability, as the membrane swiftly becomes 600 times more permeable to Na^+ than to K^+. Now Na^+ permeability dominates the membrane, in contrast to the K^+ domination at resting potential. Thus at threshold Na^+ rushes into the cell, rapidly eliminating the internal negativity and even making the inside of the cell more positive than the outside. The potential reaches +30 mV. Surprisingly, this channel opening initiates the process of channel closing. This closure process takes time, so the inactivation gate *closes slowly* compared to the rapidity of channel opening. Simultaneous with inactivation of Na^+ channels, the voltage-gated K^+ channels start to slowly open, with maximum opening occurring at the peak of the action potential. Opening of the K^+ channel gate is a delayed voltage-gated response triggered by the initial depolarization to threshold. Thus three action-potential-related events occur at threshold: (1) the rapid opening of the Na^+ activation gates, which permits Na^+ to enter, moving the potential from threshold to its positive peak; (2) the slow closing of the Na^+

inactivation gates, which halts further Na^+ entry after a brief time delay, thus keeping the potential from rising any further; and (3) the slow opening of the K^+ gates, which is responsible for the potential falling from its peak back to resting.

To review (Figure 4-8), the *rising* phase of the *action potential* (from threshold to +30 mV) is due to *Na^+ influx* (Na^+ entering the cell) induced by an explosive increase in Na^+ permeability at threshold. The *falling* phase (from +30 mV to resting potential) is brought about largely by K^+ *efflux* (K^+ leaving the cell) caused by the marked increase in K^+ permeability occurring simultaneously with the inactivation of the Na^+ channels at the peak of the action potentia1.

The Na^+ - K^+ pump



At the completion of an action potential, the membrane potential has been restored to its resting condition, but the ion distribution has been altered slightly. Sodium has entered the cell during the rising phase, and a comparable amount of K^+ has left during the falling phase. The Na^+ – K^+ pump restores these ions to their original locations in the long run, but not after each action potential.

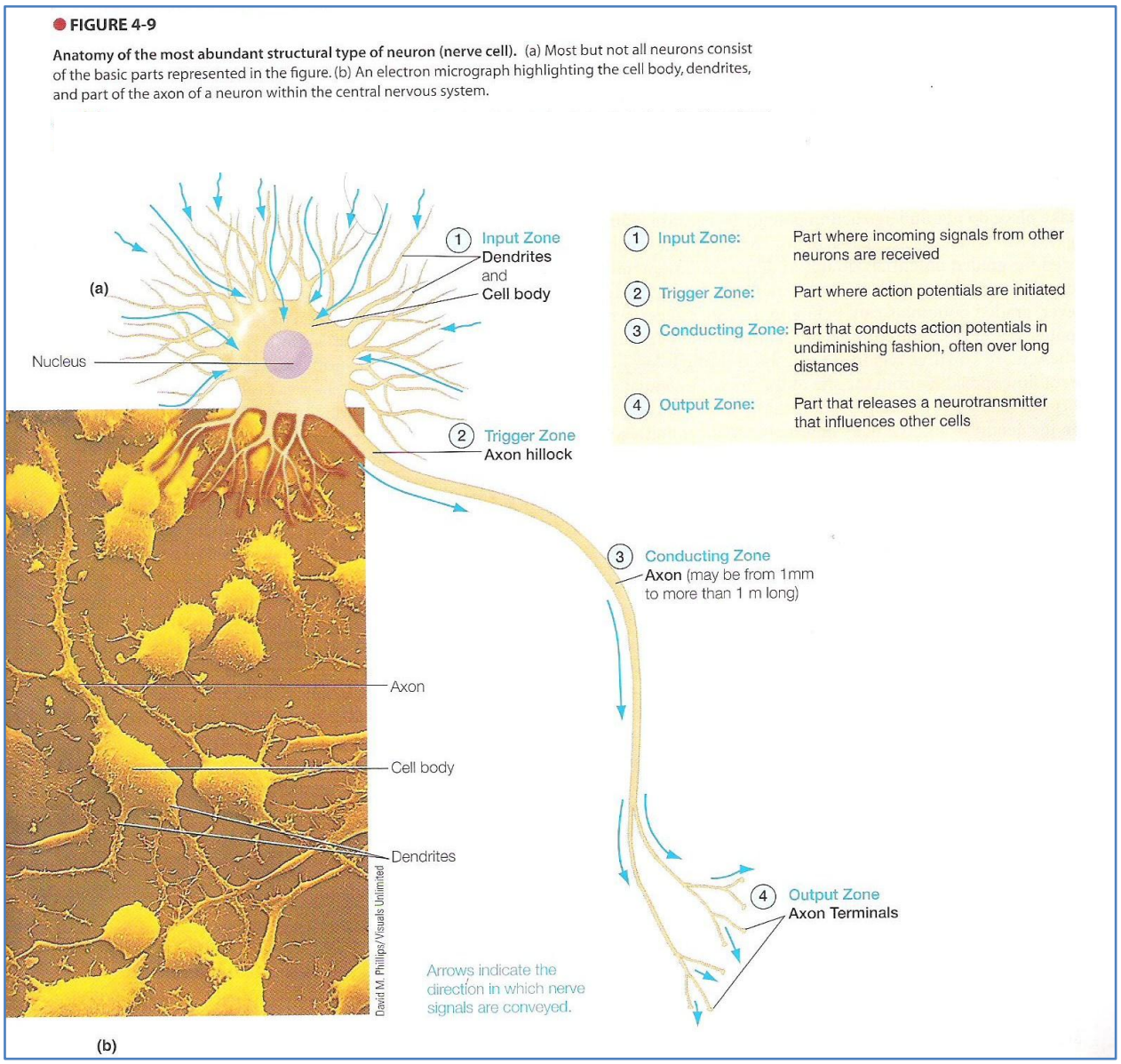
The active pumping process takes much longer to restore Na^+ and K^+ to their original locations than it takes for the passive fluxes of these ions during an action potential. However, the membrane does not need to wait until the Na^+ - K^+ pump slowly restores the concentration gradients before it can undergo another action potential. The Na^+ - K^+ pump is critical to maintaining the concentration gradients in the long run. However, it does not have to perform its role between action potentials, nor is it directly involved in the ion fluxes or potential changes that occur during an action potential.

Action potentials are propagated from the axon hillock to the axon terminals

A single action potential involves only a small patch of the total surface membrane of an excitable cell. But if action potentials are to serve as long-distance signals, they must spread the action potential throughout the entire cell membrane. Furthermore, the signal must be transmitted from one cell to the next cell (for example, along specific nerve pathways).

A single nerve cell, or neuron, typically consists of three basic parts: the *cell body,* the dendrites, and the *axon,* although there are variations in structure, depending on the location and function of the neuron. The nucleus and organelles are housed in the cell body, from which numerous extensions known as *dendrites* typically project like antennae to increase the surface area

available for receiving signals from other nerve cells (Figure 4-9). Some neurons have up to 400,000 of these elongated surface extensions. Dendrites carry signals *toward* the cell body. In most neurons the plasma membrane of the dendrites and cell body contains protein receptors for binding chemical messengers from other neurons. Therefore, the dendrites and cell body are the neuron's *input zone*, because these components receive and integrate incoming signals.



The *axon*, or *nerve fiber*, is a single, elongated, tubular extension that conducts action potentials *away from* the cell body and eventually terminates at other cells. The axon frequently gives off side branches along its course. The first portion of the axon plus the region of the cell body from which the axon leaves is known as the axon hi1lock. The axon hillock is the neuron's trigger *zone*, because it is the site where action potentials are triggered, or initiated. The action potentials are then conducted along the axon from the

axon hillock to the typically highly branched ending at the axon terminals. These terminals release chemical messengers that simultaneously influence numerous other cells with which they come into close association.

Axons vary in length from less than a millimeter in neurons that communicate only with neighboring cells to longer than a meter in neurons that communicate with distant parts of the nervous system or with peripheral organs. Once an action potential is initiated at the axon hil1ock, no further triggering event is necessary to activate the remainder of the nerve fiber. The impulse is automatically conducted throughout the neuron without further stimulation by one of two methods of propagation: *contiguous conduction* or *saltatory conduction.*

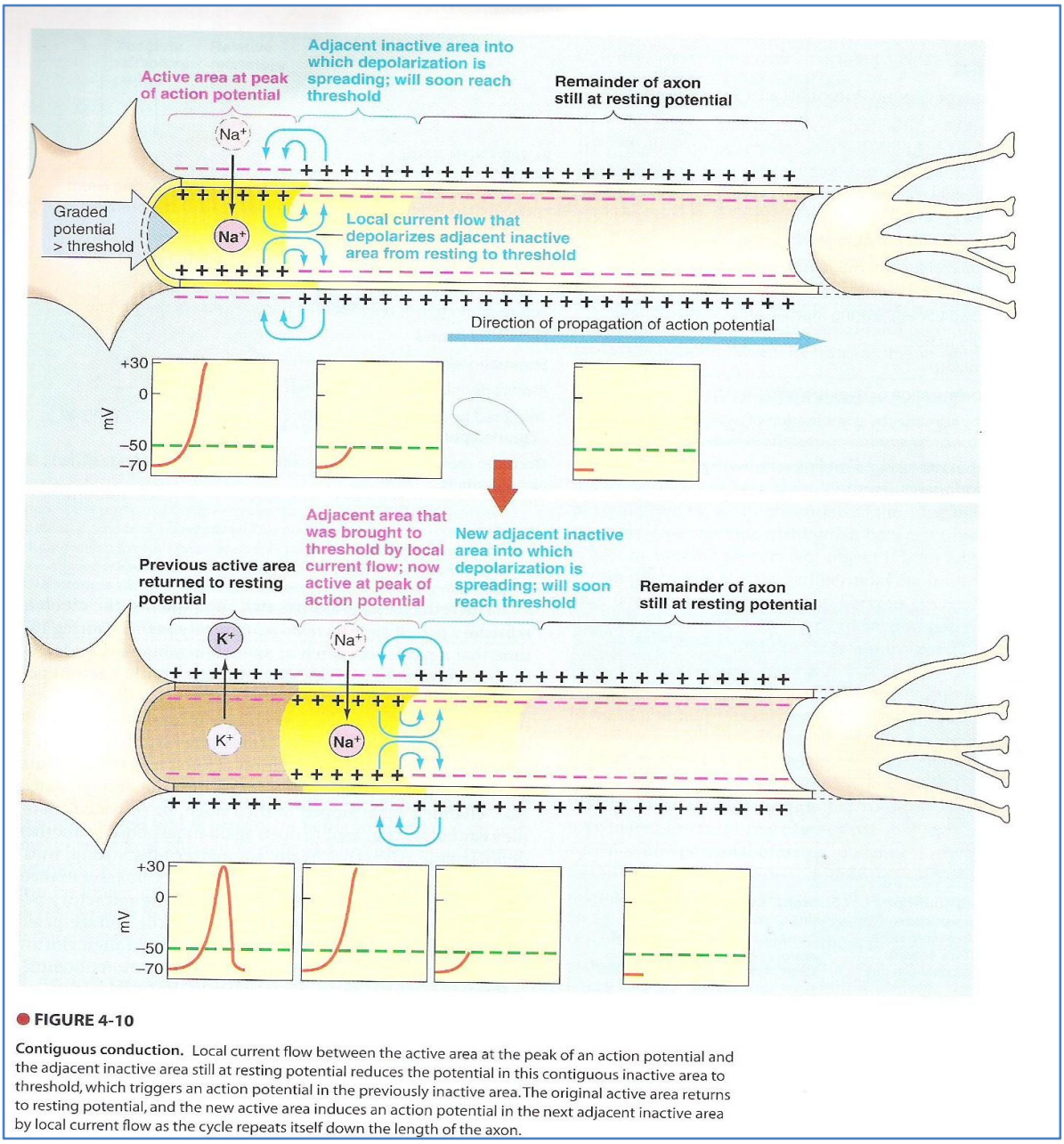


FIGURE 4-10

Contiguous conduction. Local current flow between the active area at the peak of an action potential and the adjacent inactive area still at resting potential reduces the potential in this contiguous inactive area to threshold, which triggers an action potential in the previously inactive area. The original active area returns to resting potential, and the new active area induces an action potential in the next adjacent inactive area by local current flow as the cycle repeats itself down the length of the axon.

Contiguous conduction involves the spread of the action potential along every patch of membrane down the length of the axon *(contiguous* means "touching" or "next to in sequence.") This process is illustrated in Figure 4-10. For the action potential to spread from the active to the inactive areas, the inactive areas must somehow be depolarized to threshold before they can undergo an action potential. This depolarization is accomplished by local current flow between the area already undergoing an action potential and the adjacent inactive area. Because opposite charges attract, current can flow locally between the active area and the neighboring inactive area on both the inside and the outside of the membrane. This depolarizing effect quickly brings the involved inactive area to threshold, at which time the voltage-gated Na^+ channels in this region of the membrane are all open, leading to an action potential in this previously inactive area. Meanwhile, the original active area returns to resting potential as a result of K^+ efflux. *Once an action potential is initiated in one part of a nerve cell membrane, a self-perpetuating cycle is initiated so that the action potential is propagated along the rest of the fiber automatically.* Note that the original action potential does not travel along the membrane. Instead, it triggers an identical new action potential in the adjacent area of the membrane, with this process being repeated along the axon's length, the last action potential at the end of the axon is identical to the original one, no matter how long the axon. Thus an action potential is spread along the axon in undiminished fashion. In this way, action potentials can serve as longdistance signals.

Action potential occur in all-or-none fashion

A triggering event stronger than one necessary to bring the membrane to threshold does not produce a larger action potential. However, a triggering event that fails to depolarize the membrane to threshold does not trigger an action potential at all. Thus an excitable membrane either responds to a triggering event with a maximal action potential that spread nondecrementally throughout the membrane, or it does not respond with an action potential at all. This property is called the **all-or-none** law.

The strength of a stimulus is coded by the frequency of action potentials

A stronger stimulus does not produce a larger action potential, but it does trigger a greater number of action potentials per second. In addition, a stronger stimulus is a region causes more neurons to reach threshold, increasing the total information sent to the central nervous system.

Myelination increases the speed of conduction of action potential

A faster method of propagation, *saltatory conduction*, takes place in myelinated fiber. Myelinated fibers are covered with myelin at regular intervals along the length of the axon (Figure 4-13a). Myelin is composed primarily of lipids and acts as an insulator. Between the myelinated regions, at the *nodes of Ranvier*, the axonal membrane is bare and exposed to the ECF. Only at these bare spaces can current flow across the membrane to produce action potentials. Voltage-gated Na^+ channels are concentrated at the nodes, whereas the

myelin-covered regions are almost devoid of these special passageways. By contrast, an unmyelinated fiber has a high density of voltage-gated Na^+ channels throughout its entire length. As you now know, action potentials can be generated only at portions of the membrane with an abundance of these channels. In a myelinated fiber, the impulse "jumps" from node to node, skipping over the myelinated sections of the axon; this process is called *saltatory conduction* (*saltere* means "to jump or leap"). Saltatory conduction propagates action potentials more rapidly than does contiguous conduction, because the action potential does not have to be regenerated at myelinated sections but must be regenerated within every section of an unmyelinated axonal membrane from beginning to end. Myelinated fibers conduct impulses about 50 times faster than unmyelinated fibers of comparable size. Thus the most urgent types of information are transmitted via myelinated fibers, whereas nervous pathways carrying less urgent information are unmyelinated.

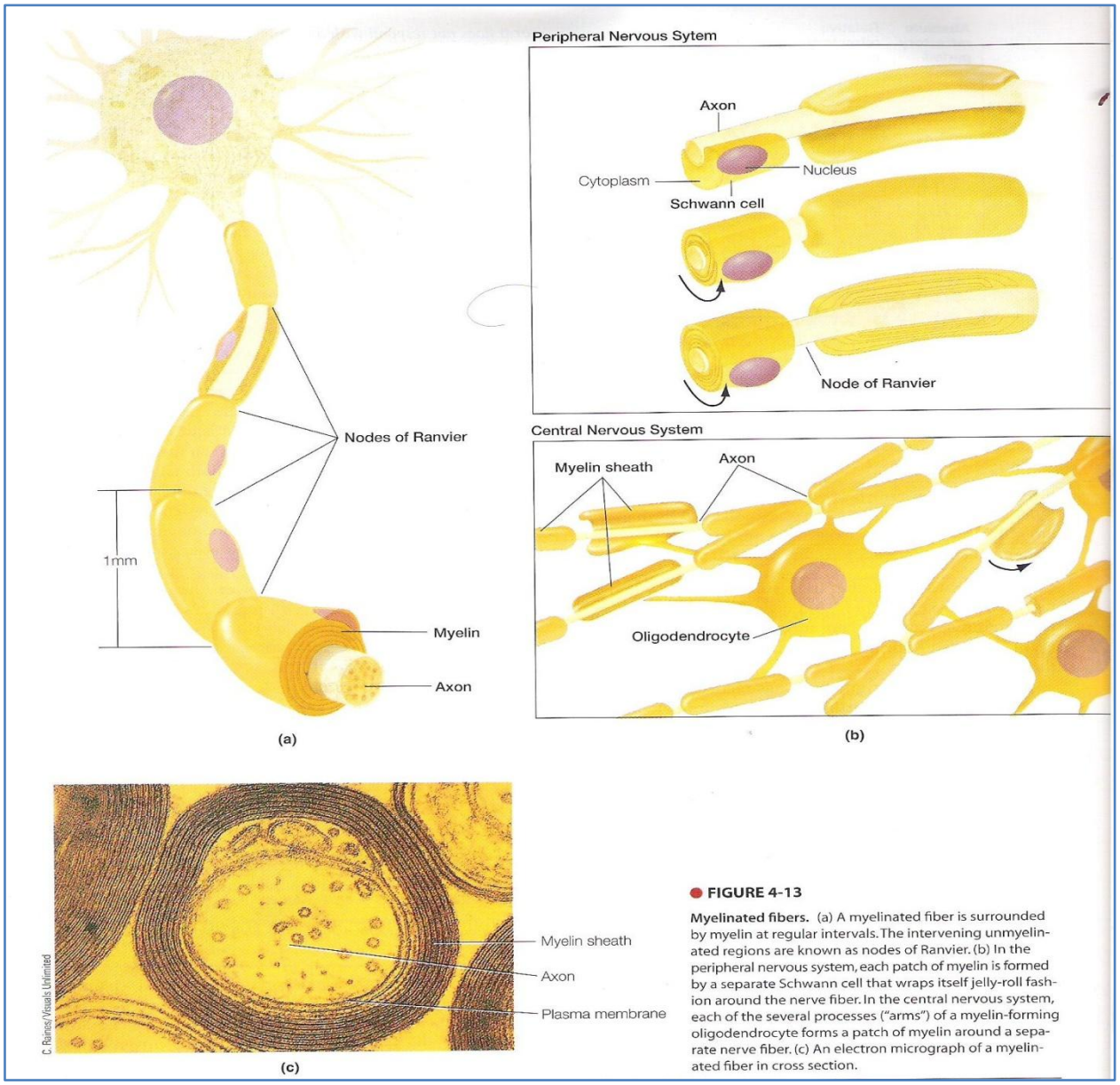


FIGURE 4-13

Myelinated fibers. (a) A myelinated fiber is surrounded by myelin at regular intervals. The intervening unmyelinated regions are known as nodes of Ranvier. (b) In the peripheral nervous system, each patch of myelin is formed by a separate Schwann cell that wraps itself jelly-roll fashion around the nerve fiber. In the central nervous system, each of the several processes ("arms") of a myelin-forming oligodendrocyte forms a patch of myelin around a separate nerve fiber. (c) An electron micrograph of a myelinated fiber in cross section.

Multiple sclerosis (MS) is a pathophysiological condition in which nerve fibers in various locations throughout the nervous system become demyelinated (lose their myelin). MS is an autoimmune disease, in which the body's defense system erroneously (**بالخطأ**) attacks the myelin sheath surrounding myelinated nerve fibers *(auto* means "self"; *immune* means "defense against"). Loss of myelin slows transmission of impulses in the affected neurons. A hardened scar, known as a *sclerosis* (meaning "hardness"), forms at the multiple sites of myelin damage. These scars further interfere with and can eventually block action potential propagation in the underlying axons. The symptoms of MS vary considerably, depending on the extent and location of the myelin damage. You have now seen how an action potential is propagated along the axon. But what happens when an action potential reaches the end of the axon?

SYNAPSES AND NEURONAL INTEGRATION

When the action potential reaches the axon terminals, they release a chemical messenger that alters the activity of the cells on which the neuron terminates. A neuron may terminate on one of three structures: a *muscle*, a *gland*, or another *neuron*. Therefore, depending on where a neuron terminates, it can cause a muscle cell to contract, a gland cell to secrete, another neuron to convey an electrical message along a nerve pathway, or some other function. When a neuron terminates on a muscle or a gland, the neuron is said to **innervate**, or supply, the structure.

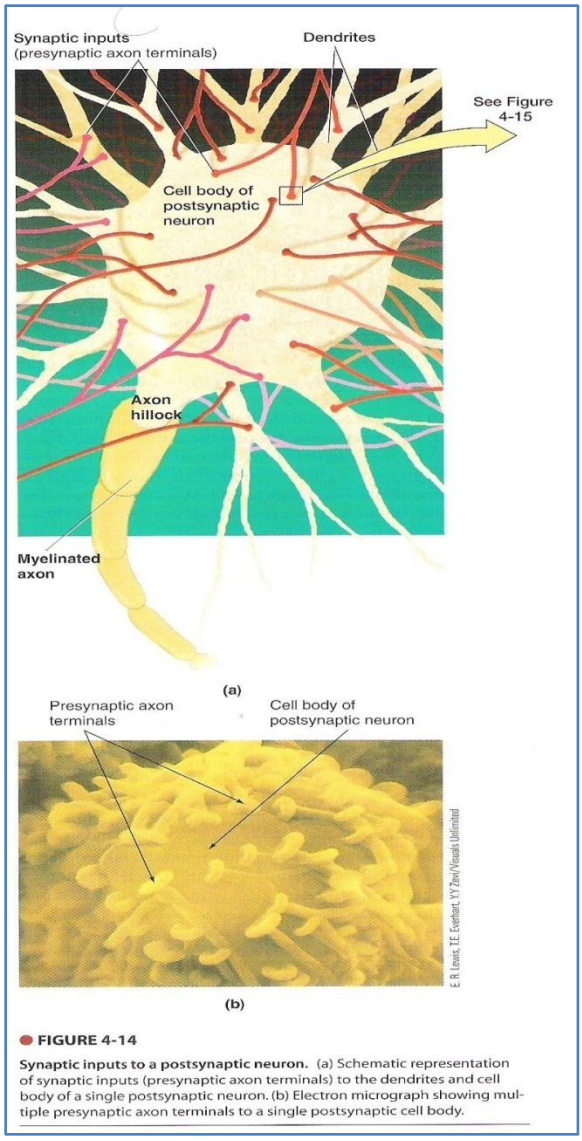


FIGURE 4-14

Synaptic inputs to a postsynaptic neuron. (a) Schematic representation of synaptic inputs (presynaptic axon terminals) to the dendrites and cell body of a single postsynaptic neuron. (b) Electron micrograph showing multiple presynaptic axon terminals to a single postsynaptic cell body.

Synapses are junctions between presynaptic and postsynaptic neurons

Typically, a synapse involves a junction between an axon terminal of one neuron, known as *the presynaptic neuron*, and the dendrites or cell body of a second neuron, known as the *postsynaptic neuron* (*pre* means "before" and *post* means "after"; the presynaptic neuron lies before the synapse and the postsynaptic neuron lies after the synapse). The dendrites and to a lesser extent the cell body of most neurons receive thousands of synaptic inputs, which are axon terminals from many other neurons. It has been estimated that some neurons within the central nervous system receive as many as 100,000 synaptic inputs **(**Figure 4-14).

The anatomy of one of these thousands of synapses is shown in Figure 4-15a. The axon terminal of the presynaptic neuron, which conducts its action potentials to*ward* the synapse, ends in a slight swelling, the **synaptic knob**. The synaptic knob contains **synaptic vesicles**, which store a specific chemical messenger, a **neurotransmitter** that has been synthesized and packaged by the presynaptic neuron. The synaptic knob comes into close proximity to, but does not actually directly touch, the **postsynaptic neuron**, the neuron whose action potentials are propagated *away* from the synapse. The space between the presynaptic and postsynaptic neurons, the **synaptic cleft**, is too wide for the direct spread of current from one cell to the other and therefore prevents action potentials from electrically passing between the neurons. The portion of the postsynaptic membrane immediately underlying the synaptic knob is referred to as the **subsynaptic membrane** *(sub* means "under"). Synapses operate in one direction only; that is, the presynaptic neuron brings about changes in membrane potential of the postsynaptic neuron, but the postsynaptic neuron does not directly influence the potential of the presynaptic neuron.

A neurotransmitter carries the signal across a synapse

Here are the events that occur at a synapse (Figure 4-15):

1. When an action potential in a presynaptic neuron has been propagated to the axon terminal (step 1 in Figure 4-15), this local change in potential triggers the opening of a voltage-gated Ca^{2+} channels in the synaptic knob.
2. Because Ca^{2+} is much more highly concentrated in the ECF and its electrical gradient is inward, this ion flows into the synaptic knob through the opened channels (step 2).
3. Ca^{2+} induces the release of a neurotransmitter from some of the synaptic vesicles into the synaptic cleft (step 3). The release is accomplished by exocytosis.
4. The released neurotransmitter diffuses across the cleft and binds with specific protein receptor sites on the subsynaptic membrane.
5. This binding triggers the opening of specific ion channels in the subsynaptic membrane, changing the ion permeability of the postsynaptic neuron (step 5). These are chemically gated channels, in contrast to the voltage-gated channels responsible for the action potential and for the Ca^{2+} influx into the synaptic knob.

Because the presynaptic terminal releases the neurotransmitter and the subsynaptic membrane of the postsynaptic neuron has receptor sites for the neurotransmitter, the synapse can operate only in the direction from presynaptic to postsynaptic neuron.

Drugs and diseases can modify synaptic transmission

The vast majority of drugs that influence the nervous system perform their function by altering synaptic mechanisms. Synaptic drugs may block an undesirable effect or enhance a desirable effect. Possible drug actions include (1) altering the synthesis, storage, or release of a neurotransmitter; (2) modifying neurotransmitter interaction with the postsynaptic receptor; (3) influencing neurotransmitter reuptake or destruction; and (4) replacing a deficient neurotransmitter with a substitute transmitter.

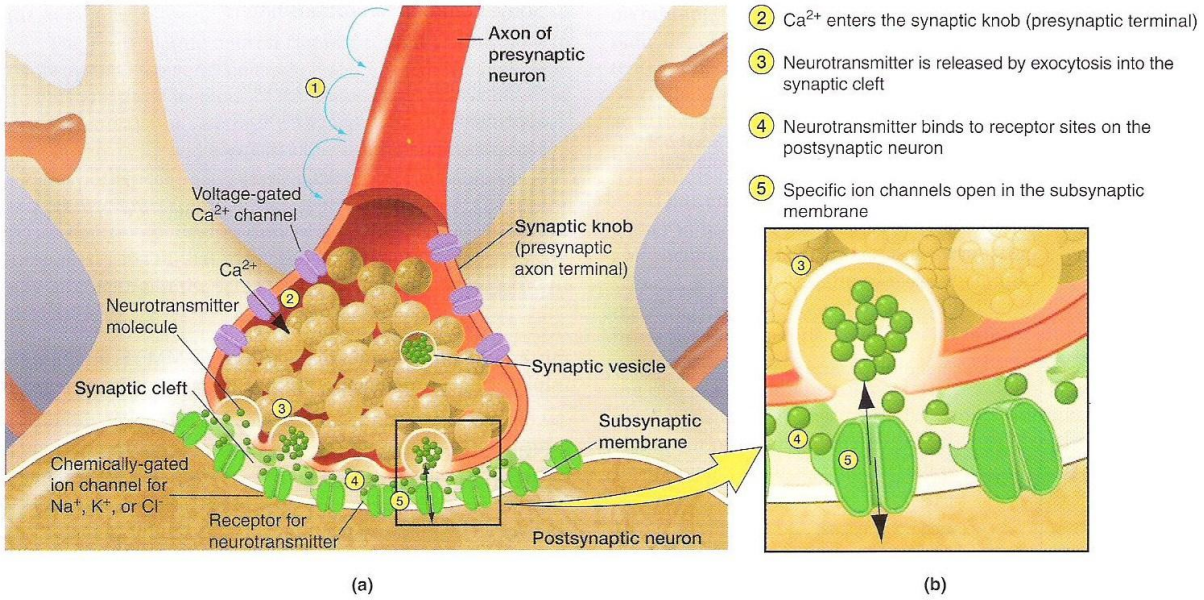


FIGURE 4-15

Synaptic structure and function. (a) Schematic representation of the structure of a single synapse. The circled numbers designate the sequence of events that take place at a synapse. (b) A blow-up depicting the release by exocytosis of neurotransmitter from the presynaptic axon terminal and its subsequent binding with receptor sites specific for it on the subsynaptic membrane of the postsynaptic neuron.

For example, the socially abused drug **cocaine** blocks the reuptake of the neurotransmitter *dopamine* at presynaptic terminals. It does so by binding competitively with the dopamine reuptake transporter, which is a protein molecule that picks up released dopamine from the synaptic cleft and shuttles it back to the axon terminal. With cocaine occupying the dopamine transporter, dopamine remains in the synaptic cleft longer than usual and continues to interact with its postsynaptic receptor sites. The result is prolonged activation of neural pathways that use this chemical as a neurotransmitter. Among these pathways are those that play a role in emotional responses, especially feelings of pleasure. In essence, when cocaine is present the neural switches in the pleasure pathway are locked in the "on" position.

Cocaine is addictive because it causes long-term molecular adaptations of the involved neurons such that they cannot transmit normally across synapses without increasingly higher doses of the drug. Because the postsynaptic cells are continually stimulated for an extended time, they become accustomed or adapt to "expecting" this high level of stimulation; that is, they are "hooked" on the drug. The term tolerance refers to this *desensitization* to an addictive drug so that the user needs greater quantities of the drug to achieve the same effect. Specifically, with prolonged use of cocaine, the number of dopamine receptors in the brain is reduced in response to the surplus of the abused substance. As a result of this desensitization, the user must steadily increase the dosage of the drug to get the same "high," or sensation of pleasure. When the cocaine molecules diffuse away, the sense of pleasure evaporates, because the normal level of dopamine activity does not sufficiently "satisfy" the overly needy demands of the postsynaptic cells for stimulation. Cocaine users reaching this low become frantic and profoundly depressed. Only more cocaine makes them feel good again. But repeated use of cocaine modifies

responsiveness to the drug. Over the course of abuse, the user often no longer can derive pleasure from the drug but suffers unpleasant *withdrawal symptoms* once the effect of the drug has worn off. Furthermore, the amount of cocaine needed to overcome the devastating crashes progressively increases. The user typically becomes addicted to the drug, compulsively seeking out and taking the drug at all costs, first to experience the pleasurable sensations and later to avoid the negative withdrawal symptoms, even when the drug no longer provides pleasure.

Whereas cocaine abuse leads to excessive dopamine activity, **Parkinson's disease** is attributable to a deficiency of dopamine in the *basal nuclei*, a region of the brain involved in controlling complex movements. This movement disorder is characterized by muscle rigidity and involuntary tremors at rest. The standard treatment for Parkinson's disease is the administration *of levodopa* (L-dopa), a precursor of dopamine. Dopamine itself cannot be administered because it is unable to cross the blood-brain barrier, but L-dopa can enter the brain from the blood. Once inside the brain, L-dopa is converted into dopamine, thus substituting for the deficient neurotransmitter. This therapy greatly alleviates the symptoms associated with the deficit in most patients.

Synaptic transmission is also vulnerable to **neural toxins**, which may cause nervous system disorders by acting at either presynaptic or postsynaptic sites. For example, tetanus toxin prevents the release of the neurotransmitter GABA from inhibitory presynaptic inputs terminating at neurons that supply skeletal muscles. Unchecked excitatory inputs to these neurons result in uncontrolled muscle spasms. These spasms occur especially in the jaw muscles early in the disease, giving rise to the common name of *lockjaw* for this condition. Later they progress to the muscles responsible for breathing, at which point death occurs. Other drugs and diseases that influence synaptic transmission are too numerous to mention, but as these examples illustrate, any site along the synaptic pathway is vulnerable to interference.

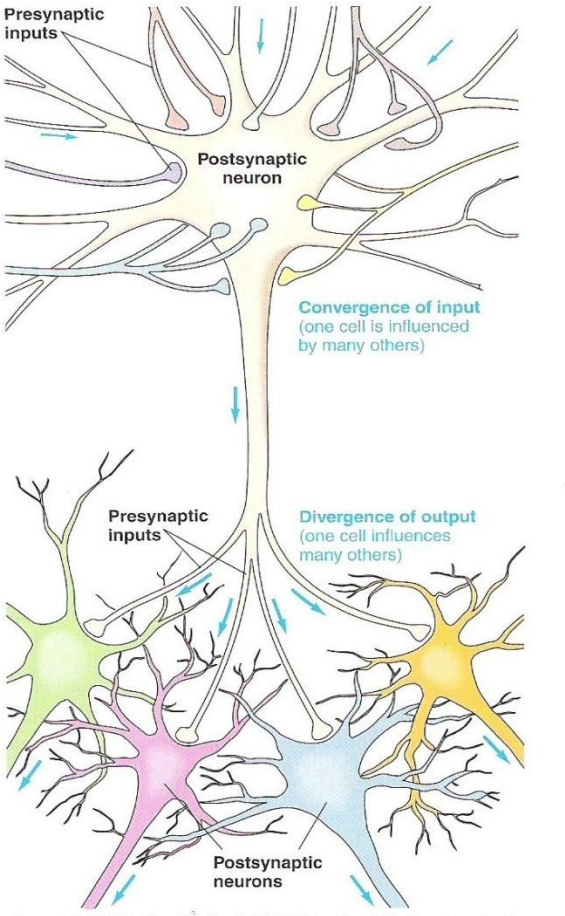


FIGURE 4-18
Convergence and divergence

Neurons are linked through complex converging and diverging pathways

Two important relationships exist between neurons: convergence and divergence. A given neuron may have many other neurons synapsing on it. Such a relationship is known as convergence **(**Figure 4-18). Through this converging input, a single cell is

influenced by thousands of other cells. This single cell, in turn, influences the level of activity in many other cells by divergence of output. The term divergence refers to the branching of axon terminals so that a single cell synapses with and influences many other cells.

Note that a particular neuron is postsynaptic to the neurons converging on it but presynaptic to the other cells at which it terminates. Thus the terms *presynaptic* and *postsynaptic* refer only to a single synapse. Most neurons are presynaptic to one group of neurons and postsynaptic to another group.

There are an estimated 100 billion neurons and 10^{14} synapses in the brain alone! When you consider the vast and intricate interconnections possible between these neurons through converging and diverging pathways, you can begin to imagine how complex the wiring mechanism of our nervous system really is. The "language" of the nervous system that is, all communication between neurons, is in the form of graded potentials, action potentials, neurotransmitter signaling across synapses. All activities for which the nervous system is responsible include every sensation you feel, every command to move a muscle, every thought, every emotion, every memory, every spark of creativity all depend on the patterns of electrical and chemical signaling between neurons along these complexly wired neural pathways.

ORGANIZATION OF THE NERVOUS SYSTEM

The nervous system is organized into the **central nervous system** (CNS), consisting of the **brain** and **spinal** cord, and the **peripheral nervous system** CPNS), consisting of nerve fibers that carry information between the CNS and other parts of the body (the periphery) (Figure 5-1). The PNS is further subdivided into **afferent** and **efferent** divisions. The afferent division carries information *to* the CNS, apprising it of the external environment and providing status reports on internal activities being regulated by the nervous system *(a* is from *ad*, meaning "toward," as in *advance; ferent* means "carrying"; thus *afferent* means "carrying toward"). Instructions *from* the CNS are transmitted via the efferent division to effector organs -the muscles or glands that carry out the orders to bring about the desired effect (*e* is from *ex*, meaning "from," as in *exit;* thus *efferent* means "carrying from"). The efferent nervous system is divided into the **somatic nervous system**, which consists of the fibers of the **motor neurons** that supply the skeletal muscles, and the **autonomic nervous system** fibers, which innervate smooth muscle, cardiac muscle, and glands. The latter system is further subdivided into the **sympathetic** nervous system and the **parasympathetic** nervous system, both of which innervate most of the organs supplied by the autonomic system.

It is important to recognize that all these "nervous systems" are really subdivisions of a single, integrated nervous system. They are arbitrary divisions based on differences in the structure, location, and functions of the various diverse parts of the whole nervous system.

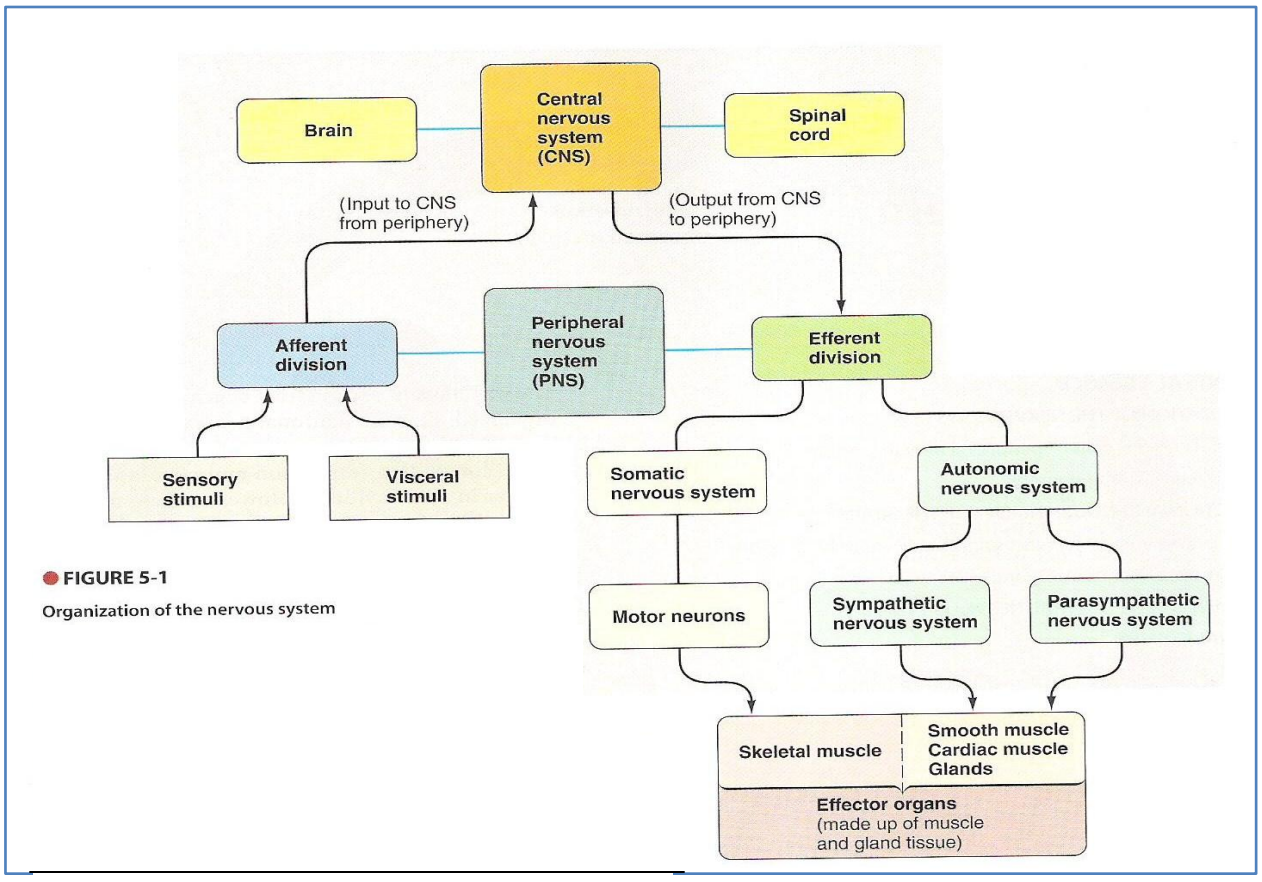
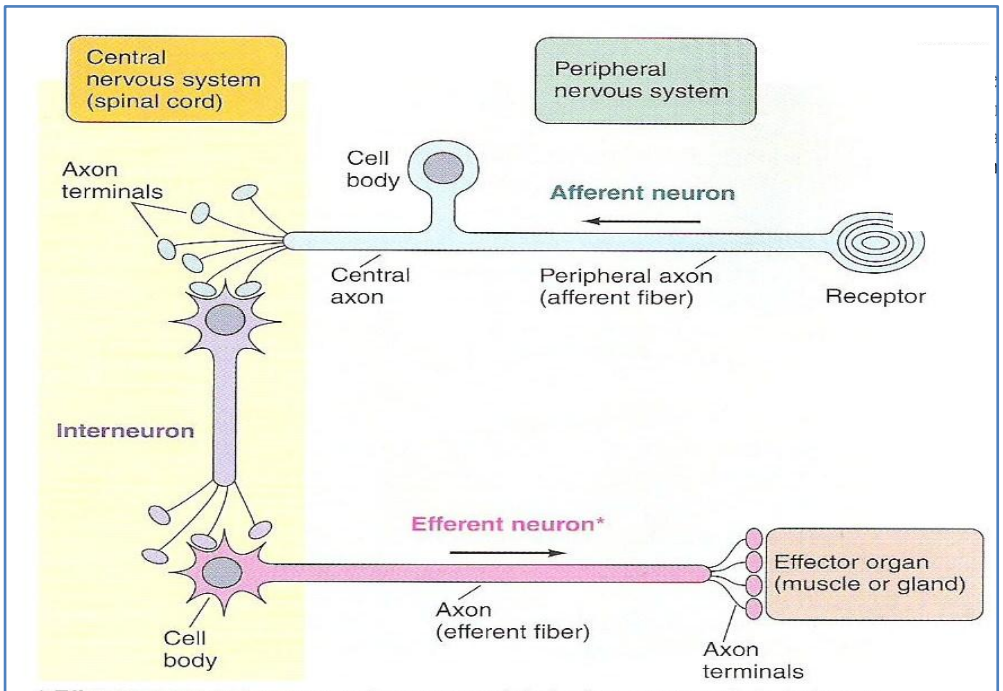


FIGURE 5-1
Organization of the nervous system

Afferent neurons, **Efferent neurons**, and **Interneurons**

Three functional classes of neurons make up the nervous system: *afferent* neurons, *efferent* neurons, and *interneurons.* The afferent division of the peripheral nervous system consists of afferent neurons, which are shaped differently from efferent neurons and interneurons (Figure 5-2). At its peripheral ending, a typical afferent neuron has a sensory receptor that generates action potentials in response to a particular type of stimulus. The afferent neuron cell body, which is devoid of dendrites and presynaptic inputs, is located adjacent to the spinal cord. A long *peripheral* axon extends from the receptor to the cell body and a short central axon passes from the cell body into the spinal cord. Action potentials are initiated at the receptor end of the peripheral axon in response to a stimulus and are propagated along the peripheral axon and central axon toward the spinal cord. The terminals of the central axon diverge and synapse with other neurons within the spinal cord, thus disseminating information about the stimulus. Afferent neurons lie primarily within the peripheral nervous system. Only a small portion of their central axon endings project into the spinal cord to relay peripheral signals.



Efferent neurons also lie primarily in the peripheral nervous system (Figure 5-2). Efferent neuron cell bodies originate in the CNS, where many centrally located presynaptic inputs converge on them to influence their outputs to the effector organs. Efferent axons *(efferent fibers)* leave the CNS to course their way to the muscles or glands they innervate, conveying their integrated output for the effector organs to put into effect. (An autonomic nerve pathway consists of a two-neuron chain between the CNS and the effector organ.)

Interneurons lie entirely within the CNS. About 99% of all neurons belong to this category. The human CNS is estimated to have over 100 billion interneurons! These neurons serve two main roles. First, as their name implies, they lie between the afferent and efferent neurons and are important in integrating peripheral responses to peripheral information (inter means "between"). For example, on receiving information through afferent neurons that you are touching a hot object, appropriate interneurons signal efferent neurons that transmit to your hand and arm muscles the message, "Pull the hand away from the hot object!" The more complex the required action, the greater the number of interneurons interposed between the afferent message and efferent response. Second, interconnections between interneurons themselves are responsible for the abstract phenomena associated with the "mind," such as thoughts, emotions, memory, creativity, intellect, and motivation. These activities are the least understood functions of the nervous system.

SOMATIC NERVOUS SYSTEM

Skeletal muscle is innervated by **motor neurons**, the axons of which constitute the somatic nervous system. The cell bodies of almost all motor neurons are within the spinal cord. Unlike the two-neuron chain of autonomic nerve fibers, the axon of a motor neuron is continuous from its origin in the CNS to its ending on skeletal muscle. Motor neuron axon terminals release **acetylcholine**, which brings about excitation and contraction of the innervated muscle cells. Motor neurons can only stimulate **skeletal muscles**, in contrast to autonomic fibers, which can either stimulate or inhibit their effector organs. Inhibition of skeletal muscle activity can be accomplished only within the CNS through inhibitory synaptic input to the dendrites and cell bodies of the motor neurons supplying that particular muscle.

Motor neurons are the final common pathway

Motor neuron dendrites and cell bodies are influenced by many converging presynaptic inputs, both excitatory and inhibitory. Some of these inputs are part of spinal reflex pathways originating with peripheral sensory receptors. Others are part of descending pathways originating within the brain. Areas of the brain that exert control over skeletal muscle movements include the motor regions of the cortex, the basal nuclei, the cerebellum, and the brain stem. Motor neurons are considered the final common pathway, because the only way any other parts of the nervous system can influence skeletal muscle activity is by acting on these motor neurons. The somatic system is under voluntary control, but much of the skeletal muscle activity involving posture, balance, and stereotypical movements is subconsciously controlled. You may decide you want to start walking, but you do not have to consciously bring about the alternate contraction and relaxation of the involved muscles because these movements are involuntarily coordinated by lower brain centers.

The cell bodies of the crucial motor neurons may be selectively destroyed by **poliovirus**. The result is paralysis of the muscles innervated by the affected neurons.

Motor neurons and skeletal muscle fibers

An action potential in a motor neuron is rapidly propagated from the cell body within the CNS to the skeletal muscle along the large myelinated axon (efferent fiber) of the neuron. As the axon approaches a muscle, it divides into many terminal branches and loses its myelin sheath. Each of these axon terminals forms a special junction, **a neuromuscular junction**, with one of the many muscle cells that compose the whole musc1e. A single muscle cell, called a muscle fiber, is long and cylindrical. The axon terminal is enlarged into a knoblike structure, the terminal button, which fits into a shallow depression, or groove, in the underlying muscle fiber (Figure 7-6).

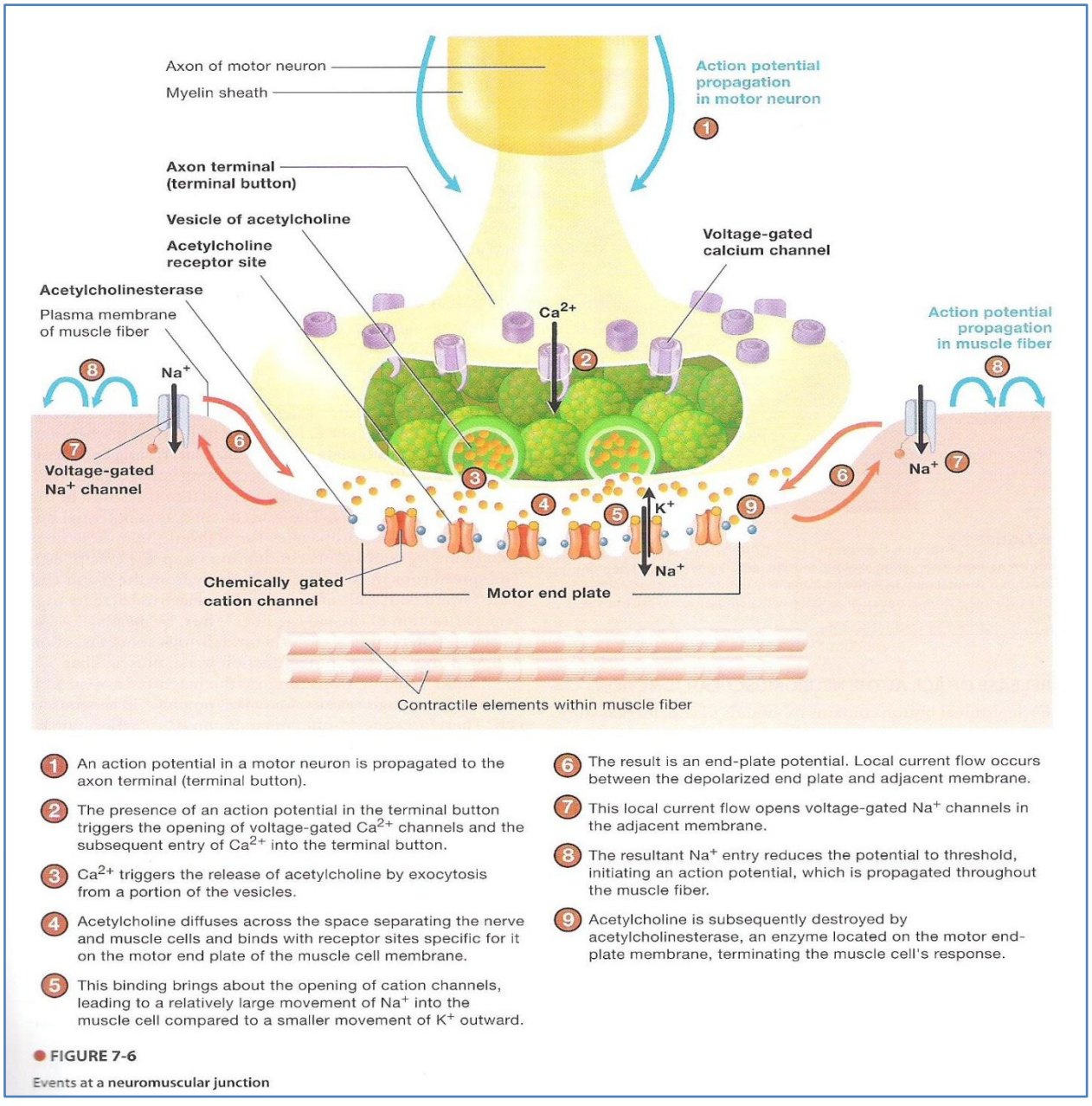


FIGURE 7-6
Events at a neuromuscular junction

Acetylcholine is the neuromuscular junction neurotransmitter

Nerve and muscle cells do not actually come into direct contact at a neuromuscular junction. The space, or **cleft**, between these two structures is too large to permit electrical transmission of an impulse between them (that is, the action potential cannot "jump" that far). Therefore, just as a neuronal synapse, a chemical messenger carries the signal between the neuron terminal and the muscle fiber. This neurotransmitter is acetylcholine (ACh.)

RELEASE OF ACh ATTHE NEUROMUSCULAR JUNCTION

Each terminal button contains thousands of vesicles that store ACh. Propagation of an action potential to the axon terminal (step 1, Figure 7-6) triggers the opening of voltage-gated Ca^{2+} channels in the terminal button. Opening of Ca^{2+} channels permits Ca^{2+} to diffuse into the terminal button from its higher extracellular concentration (step 2), which in turn causes the release of ACh by exocytosis from several hundred of the vesicles into the cleft (step 3). The released ACh diffuses across the cleft and binds with specific receptor sites, which are specialized membrane proteins unique to the motor end-plate portion of the muscle fiber membrane (step 4). Binding of ACh with these receptor sites induces the opening of chemically gated channels in the motor end plate. These channels permit a small amount of cation traffic through them (both Na^+ and K^+) but no anions (step 5). Because the permeability of the end-plate membrane to Na^+ and K^+ on opening of these channels is essentially equal, the relative movement of these ions through the channels depends on their electrochemical driving forces. ACh triggers the opening of these channels, considerably more Na^+ moves inward than K^+ outward, depolarizing the motor end plate.

INITIATION OF AN ACTION POTENTIAL

The motor end-plate region itself does not have a threshold potential, so an action potential cannot be initiated at this site. The neuromuscular junction is usually in the middle of the long, cylindrical muscle fiber. Local current flow occurs between the depolarized end plate and the adjacent, resting cell membrane in both directions (step 6), opening voltage-gated Na^+ channels and thus reducing the potential to threshold in the adjacent areas (step 7). The subsequent action potential initiated at these sites propagates throughout the muscle fiber membrane by contiguous conduction (step 8). The spread runs in both directions, away from the motor end plate toward both ends of the fiber. This electrical activity triggers contraction of the muscle fiber. Thus, by means of ACh, an action potential in a motor neuron brings about an action potential and subsequent contraction in the muscle fiber.

Acetylcholinesterase ends acetylcholine activity at the neuromuscular junction

To ensure purposeful movement, electrical activity and the resultant contraction of the muscle cell turned on by motor neuron action potentials must be switched off promptly when there is no longer a signal from the motor neuron. The muscle cell's electrical response is turned off by an enzyme present in the motor end-plate membrane, **acetylcholinesterase** (AChE), which inactivates ACh. As a result of diffusion, many of the released ACh molecules come into contact with and bind to the receptor sites, which are on the surface of the motor end-plate

membrane. However, some of the ACh molecules bind with AChE, which is also at the end-plate surface. Being quickly inactivated, this ACh never contributes to the end-plate potential. The acetylcholine that does bind with receptor sites does so very briefly for about 1 millionth of a second), then detaches. Some of the detached ACh molecules quickly rebind with receptor sites, keeping the end-plate channels open, but some randomly contact AChE instead and are inactivated (step 9). As this process repeats, more and more ACh is inactivated until it has been virtually removed from the cleft within a few milliseconds after its release. Removing ACh causes the remainder of the muscle cell membrane returns to resting potential. Now the muscle cell can relax. Or, if sustained contraction is essential for the desired movement, another motor neuron action potential leads to the release of more ACh, which keeps the contractile process going. By removing contraction-inducing ACh from the motor end plate, AChE permits the choice of allowing relaxation to take place (no more ACh released) or keeping the contraction going (more ACh released), depending on the body's momentary needs.

The neuromuscular junction is vulnerable to several chemical agents and diseases

Several chemical agents and diseases are known to alter the neuromuscular junction by acting at different sites in the transmission process. Two well-known toxins -**black widow spider venom** and **botulinum toxin**- alter the release of ACh, but in opposite directions.

BLACK WIDOW SPIDER VENOM CAUSES EXPLOSIVE RELEASE OF ACh

The venom of black widow spiders exerts its deadly effect by triggering explosive release of ACh from the storage vesicles, not only at neuromuscular junctions but at all cholinergic sites. All cholinergic sites undergo prolonged depolarization, the most harmful result of which is respiratory failure. Breathing is accomplished by alternate contraction and relaxation of skeletal muscles, particularly the diaphragm. Respiratory paralysis occurs as a result of prolonged depolarization of the diaphragm. During this so-called *depolarization block*, the voltage-gated Na^+ channels are trapped in their inactivated state, prohibiting the initiation of new action potentials and resultant contraction of the diaphragm. Thus the victim cannot breathe.

BOTULINUM TOXIN BLOCKS RELEASE OF ACh

Botulinum toxin, in contrast, exerts its lethal blow by blocking the release of ACh from the terminal button in response to a motor neuron action potential. *Clostridium Botulinum* toxin causes **botulism**, a form of food poisoning. It most frequently results from improperly canned foods contaminated with *clostridial bacteria* that survive and multiply, producing their toxin in the process. When this toxin is consumed, it prevents muscles from responding to nerve impulses. Death is due to respiratory failure caused by inability to contract the diaphragm. Botulinum toxin is one of the most lethal poisons known; ingesting less than 0.0001 mg can kill an adult human.