CHAPTER 3

The Action Potential, Synaptic Transmission, and Maintenance of Nerve Function

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CHAPTER OUTLINE

- PASSIVE MEMBRANE PROPERTIES, THE ACTION POTENTIAL, AND ELECTRICAL SIGNALING BY NEURONS
- SYNAPTIC TRANSMISSION
- NEUROCHEMICAL TRANSMISSION
- THE MAINTENANCE OF NERVE CELL FUNCTION

KEY CONCEPTS

1. Nongated ion channels establish the resting membrane potential of neurons; voltage-gated ion channels are responsible for the action potential and the release of neurotransmitter.
2. Ligand-gated ion channels cause membrane depolarization or hyperpolarization in response to neurotransmitter.
3. Nongated ion channels are distributed throughout the neuronal membrane; voltage-gated channels are largely restricted to the axon and its terminals, while ligand-gated channels predominate on the cell body (soma) and dendritic membrane.
4. Membrane conductance and capacitance affect ion flow in neurons.
5. An action potential is a transient change in membrane potential characterized by a rapid depolarization followed by a repolarization; the depolarization phase is due to a rapid activation of voltage-gated sodium channels and the repolarization phase to an inactivation of the sodium channels and the delayed activation of voltage-gated potassium channels.
6. Initiation of an action potential occurs when an axon hillock is depolarized to a threshold for rapid activation of a large number of voltage-gated sodium channels.
7. Propagation of an action potential depends on local current flow derived from the inward sodium current depolarizing adjacent regions of an axon to threshold.
8. Conduction velocity depends on the size of an axon and the thickness of its myelin sheath, if present.
9. Following an action potential in one region of an axon, that region is temporarily refractory to the generation of another action potential because of the inactivation of the voltage-gated sodium channels.
10. When an action potential invades the nerve terminal, voltage-gated calcium channels open, allowing calcium to enter the terminal and start a cascade of events leading to the release of neurotransmitter.
11. Synaptic transmission involves a relatively small number of neurotransmitters that activate specific receptors on their postsynaptic target cells.
12. Most neurotransmitters are stored in synaptic vesicles and released upon nerve stimulation by a process of calcium-mediated exocytosis; once released, the neurotransmitter binds to and stimulates its receptors briefly before being rapidly removed from the synapse.
13. Metabolic maintenance of neurons requires specialized functions to match their specialized morphology and complex interconnections.

The nervous system coordinates the activities of many other organ systems. It activates muscles for movement, controls the secretion of hormones from glands, regulates the rate and depth of breathing, and is involved in modulating and regulating a multitude of other physiological processes. To perform these functions, the nervous system relies on neurons, which are designed for the rapid transmission of information from one cell to another by conducting electrical impulses and secreting chemical neurotransmitters. The electrical impulses propagate along the length of nerve fiber processes to their terminals, where they initiate a series of events that cause the release of

chemical neurotransmitters. The release of neurotransmitters occurs at sites of synaptic contact between two nerve cells. Released neurotransmitters bind with their receptors on the postsynaptic cell membrane. The activation of these receptors either excites or inhibits the postsynaptic neuron.

The propagation of action potentials, the release of neurotransmitters, and the activation of receptors constitute the means whereby nerve cells communicate and transmit information to one another and to nonneuronal tissues. In this chapter, we examine the specialized membrane properties of nerve cells that endow them with the ability to produce action potentials, explore the basic mechanisms of synaptic transmission, and discuss aspects of neuronal structure necessary for the maintenance of nerve cell function.

PASSIVE MEMBRANE PROPERTIES, THE ACTION POTENTIAL, AND ELECTRICAL SIGNALING BY NEURONS

Neurons communicate by a combination of electrical and chemical signaling. Generally, information is integrated and transmitted along the processes of a single neuron electrically and then transmitted to a target cell chemically. The chemical signal then initiates an electrical change in the target cell. Electrical signals that depend on the passive properties of the neuronal cell membrane spread electrotonically over short distances. These potentials are initiated by local current flow and decay with distance from their site of initiation. Alternatively, an **action potential** is an electrical signal that propagates over a long distance without a change in amplitude. Action potentials depend on a regenerative wave of channel openings and closings in the membrane.

Special Anatomic Features of Neurons Adapt Them for Communicating Information

The shape of a nerve cell is highly specialized for the reception and transmission of information. One region of the neuron is designed to receive and process incoming information; another is designed to conduct and transmit information to other cells. The type of information that is processed and transmitted by a neuron depends on its location in the nervous system. For example, nerve cells associated with visual pathways convey information about the external environment, such as light and dark, to the brain; neurons associated with motor pathways convey information to control the contraction and relaxation of muscles for walking. Regardless of the type of information transmitted by neurons, they transduce and transmit this information via similar mechanisms. The mechanisms depend mostly on the specialized structures of the neuron and the electrical properties of their membranes.

Emerging from the **soma** (cell body) of a neuron are processes called **dendrites** and **axons** (Fig. 3.1). Many neurons in the central nervous system (CNS) also have knob-like structures called **dendritic spines** that extend from the dendrites. The dendritic spines, dendrites, and soma receive information from other nerve cells. The axon conducts and transmits information and may also receive information. Some axons are coated with **myelin**, a lipid structure formed by **glial cells** (oligodendrocytes in the CNS or Schwann cells in the peripheral nervous system, the PNS). Regular intermittent gaps in the myelin sheath are called **nodes of Ranvier**. The speed with which an axon conducts information is directly proportional to the size of the axon and the thickness of the myelin sheath. The end of the axon, the **axon terminal,** contains small **vesicles** packed with **neurotransmitter** molecules. The site of contact between a neuron and its target cell is called a **synapse.** Synapses are classified according to their site of contact as axospinous, axodendritic, axosomatic, or axoaxonic (Fig. 3.2). When a neuron is activated, an action potential is generated in the **axon hillock** (or initial segment) and conducted along the axon. The action potential causes the release of a neurotransmitter from the terminal. These neurotransmitter molecules bind to **receptors** located on target cells.

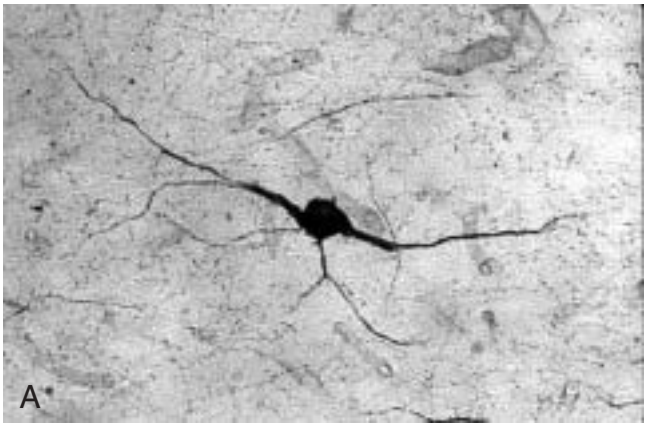
The binding of a neurotransmitter to its receptor typically causes a flow of ions across the membrane of the postsynaptic cell. This temporary redistribution of ionic charge can lead to the generation of an action potential, which itself is mediated by the flow of specific ions across the membrane. These electrical charges, critical for the transmission of information, are the result of ions moving through ion channels in the plasma membrane (see Chapter 2).

Channels Allow Ions to Flow Through the Nerve Cell Membrane

Ions can flow across the nerve cell membrane through three types of ion channels: nongated (leakage), ligand-gated, and voltage-gated (Fig. 3.3). **Nongated ion channels** are always open. They are responsible for the influx of Na^+ and efflux of K^+ when the neuron is in its resting state. **Ligand-gated ion channels** are directly or indirectly activated by chemical neurotransmitters binding to membrane receptors. In this type of channel, the receptor itself forms part of the ion channel or may be coupled to the channel via a G protein and a second messenger. When chemical transmitters bind to their receptors, the associated ion channels can either open or close to permit or block the movement of specific ions across the cell membrane. **Voltage-gated ion channels** are sensitive to the voltage difference across the membrane. In their initial resting state, these channels are typically closed; they open when a critical voltage level is reached.

Each type of ion channel has a unique distribution on the nerve cell membrane. Nongated ion channels, important for the establishment of the resting membrane potential, are found throughout the neuron. Ligand-gated channels, located at sites of synaptic contact, are found predominantly on dendritic spines, dendrites, and somata. Voltage-gated channels, required for the initiation and propagation of action potentials or for neurotransmitter release, are found predominantly on axons and axon terminals.

In the unstimulated state, nerve cells exhibit a **resting membrane potential** that is approximately -60 mV relative to the extracellular fluid. The resting membrane potential reflects a steady state that can be described by the Goldman equation (see Chapter 2). One should remember that the extracellular concentration of Na^+ is much greater than the



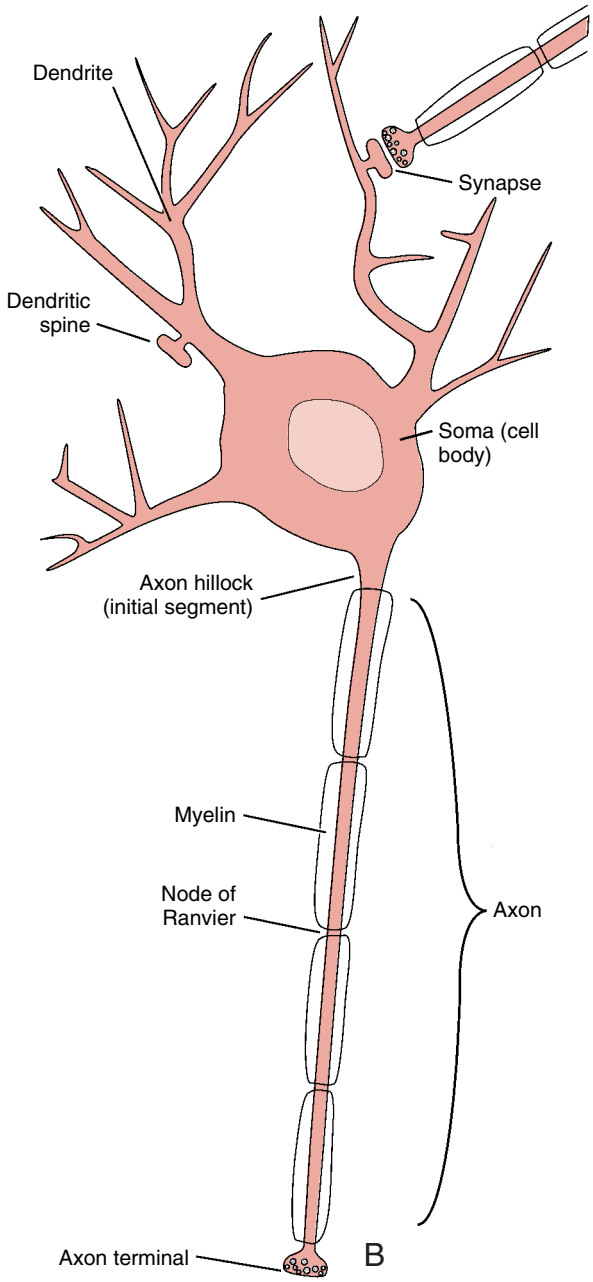


FIGURE 3.1 **The structure of a neuron.** **A,** A light micrograph. **B,** The structural components and a synapse.

intracellular concentration of Na^+, while the opposite is true for K^+. Moreover, the permeability of the membrane to potassium (P_K) is much greater than the permeability to sodium (P_{Na}) because there are many more leakage (nongated) channels in the membrane for K^+ than in the membrane for Na^+; therefore, the resting membrane potential is much closer to the equilibrium potential for potassium (E_K) than it is for sodium (see Chapter 2). Typical values for equilibrium potentials in neurons are +70 mV for sodium and −100 mV for potassium. Because sodium is far from its equilibrium potential, there is a large driving force on sodium, so sodium ions move readily whenever a voltage-gated or ligand-gated sodium channel opens in the membrane.

Electrical Properties of the Neuronal Membrane Affect Ion Flow

The electrical properties of the neuronal membrane play important roles in the flow of ions through the membrane, the initiation and conduction of action potentials along the axon, and the integration of incoming information at the dendrites and the soma. These properties include membrane conductance and capacitance.

The movement of ions across the nerve membrane is driven by ionic concentration and electrical gradients (see Chapter 2). The ease with which ions flow across the membrane through their channels is a measure of the membrane's **conductance;** the greater the conductance, the greater the flow of ions. Conductance is the inverse of **resistance**, which is measured in ohms. The conductance (g) of a membrane or single channel is measured in siemens. For an individual ion channel and a given ionic solution, the conductance is a constant value, determined in part by such factors as the relative size of the ion with respect to that of the channel and the charge distribution within the channel. Ohm's law describes the relationship between a single channel conductance, ionic current, and the membrane potential:

$$I_{ion} = g_{ion}(E_m - E_{ion})$$

or

$$g_{ion} = I_{ion}/(E_m - E_{ion}) \quad (1)$$

where I_{ion} is the ion current flow, E_m is the membrane potential, E_{ion} is the equilibrium (Nernst) potential for a specified ion, and g_{ion} is the channel conductance for an ion. Notice that if $E_m = E_{ion}$, there is no net movement of the ion and $I_{ion} = 0$. The conductance for a nerve membrane is the summation of all of its single channel conductances.

Another electrical property of the nerve membrane that influences the movement of ions is **capacitance**, the membrane's ability to store an electrical charge. A capacitor consists of two conductors separated by an insulator. Positive charge accumulates on one of the conductive plates while negative charge accumulates on the other plate. The biological capacitor is the lipid bilayer of the plasma membrane, which separates two conductive regions, the extracellular and intracellular fluids. Positive charge accumulates on the extracellular side while negative charge accumulates

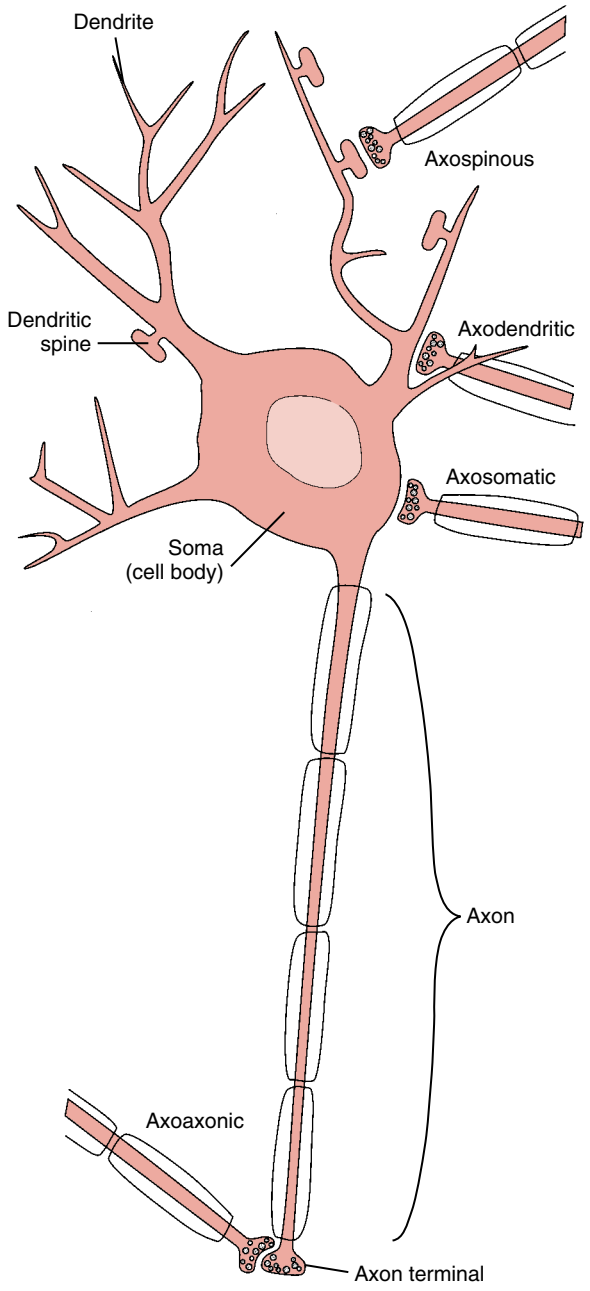


FIGURE 3.2 **Types of synapses.** The dendritic and somatic areas of the neuron, where most synapses occur, integrate incoming information. Synapses can also occur on the axon, which conducts information in the form of electrical impulses.

on the intracellular side. Membrane capacitance is measured in units of farads (F).

One factor that contributes to the amount of charge a membrane can store is its surface area; the greater the surface area, the greater the storage capacity. Large-diameter dendrites can store more charge than small-diameter dendrites of the same length. The speed with which the charge accumulates when a current is applied depends on the resistance of the circuit. Charge is delivered more rapidly when resistance is low. The time required for the mem-

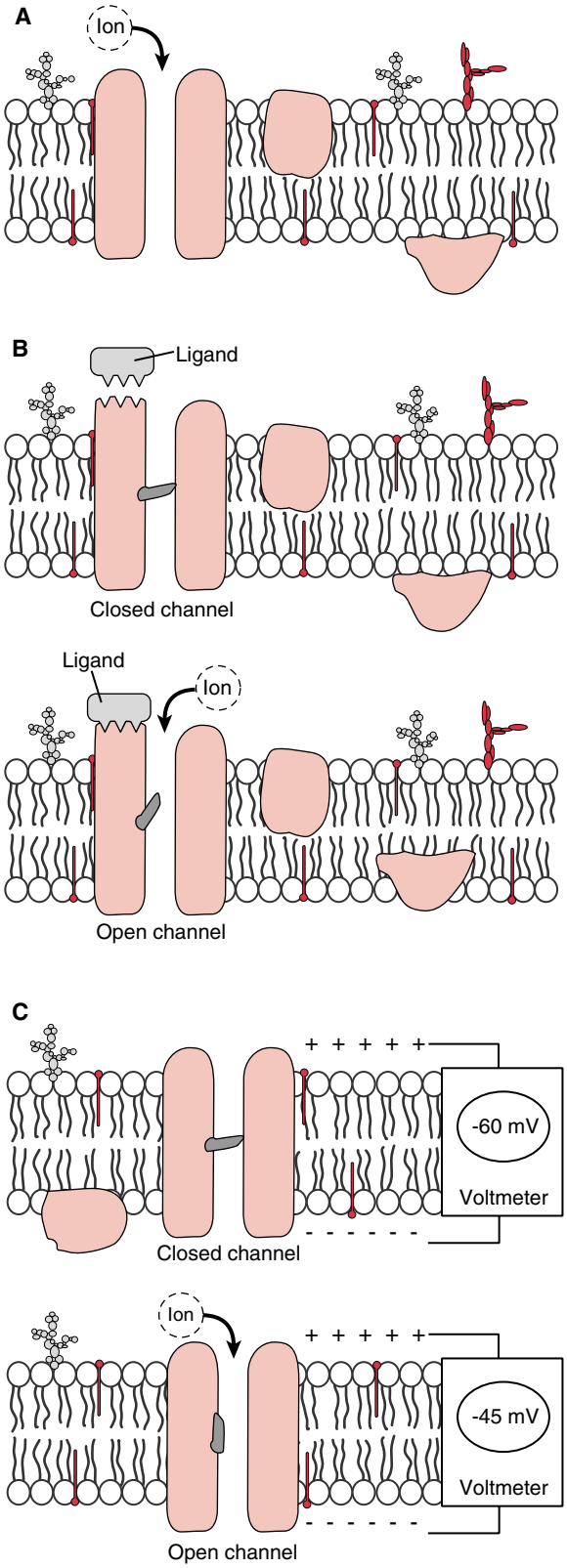


FIGURE 3.3 **The three types of ion channels.** **A**, The nongated channel remains open, permitting the free movement of ions across the membrane. **B**, The ligand-gated channel remains closed (or open) until the binding of a neurotransmitter. **C**, The voltage-gated channel remains closed until there is a change in membrane potential.

brane potential to change after a stimulus is applied is called the **time constant** or τ, and its relationship to capacitance (C) and resistance (R) is defined by the following equation:

$$\tau = RC \quad (2)$$

In the absence of an action potential, a stimulus applied to the neuronal membrane results in a local potential change that decreases with distance away from the point of stimulation. The voltage change at any point is a function of current and resistance as defined by Ohm's law. If a ligand-gated channel opens briefly and allows positive ions to enter the neuron, the electrical potential derived from that current will be greatest near the channels that opened, and the voltage change will steadily decline with increasing distance away from that point. The reason for the decline in voltage change with distance is that some of the ions backleak out of the membrane because it is not a perfect insulator, and less charge reaches more distant sites. Since membrane resistance is a stable property of the membrane, the diminished current with distance away from the source results in a diminished voltage change. The distance at which the initial transmembrane voltage change has fallen to 37% of its peak value is defined as the **space constant** or λ. The value of the space constant depends on the internal axoplasmic resistance (R_a) and on the transmembrane resistance (R_m) as defined by the following equation:

$$\lambda = \sqrt{R_m / R_a} \quad (3)$$

R_m is usually measured in ohm-cm and R_a in ohm/cm. R_a decreases with increasing diameter of the axon or dendrite; thus, more current will flow farther along inside the cell, and the space constant is larger. Similarly, if R_m increases, less current leaks out and the space constant is larger. The larger the space constant, the farther along the membrane a voltage change is observed after a local stimulus is applied.

Membrane capacitance and resistance, and the resultant time and space constants, play an important role in both the propagation of the action potential and the integration of incoming information.

An Action Potential Is Generated at the Axon Hillock and Conducted Along the Axon

An action potential depends on the presence of voltage-gated sodium and potassium channels that open when the neuronal membrane is depolarized. These voltage-gated channels are restricted to the axon of most neurons. Thus, neuronal dendrites and cell bodies do not conduct action potentials. In most neurons, the axon hillock of the axon has a very high density of these voltage-gated channels. This region is also known as the **trigger zone** for the action potential. In sensory neurons that convey information to the CNS from distant peripheral targets, the trigger zone is in the region of the axon close to the peripheral target.

When the axon is depolarized slightly, some voltage-gated sodium channels open; as Na^+ ions enter and cause more depolarization, more of these channels open. At a critical membrane potential called the **threshold**, incoming Na^+ exceeds outgoing K^+ (through leakage channels), and the resulting explosive opening of the remaining voltage-gated sodium channels initiates an action potential. The action potential then propagates to the axon terminal, where the associated depolarization causes the release of neurotransmitter. The initial depolarization to start this process derives from synaptic inputs causing ligand-gated channels to open on the dendrites and somata of most neurons. For peripheral sensory neurons, the initial depolarization results from a generator potential initiated by a variety of sensory receptor mechanisms (see Chapter 4).

Characteristics of the Action Potential. Depolarization of the axon hillock to threshold results in the generation and propagation of an action potential. The action potential is a transient change in the membrane potential characterized by a gradual depolarization to threshold, a rapid rising phase, an overshoot, and a repolarization phase. The repolarization phase is followed by a brief **afterhyperpolarization (undershoot)** before the membrane potential again reaches resting level (Fig. 3.4A).

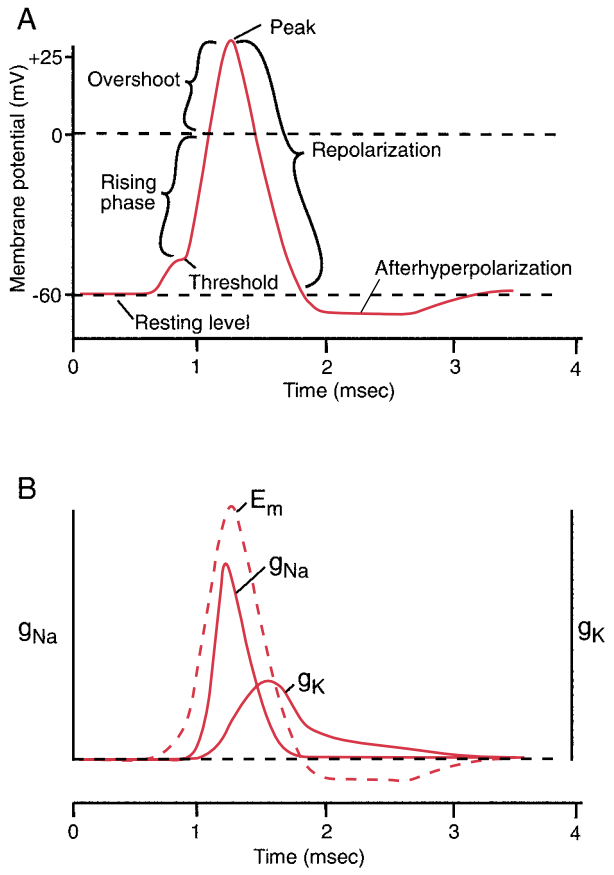


FIGURE 3.4 **The phases of an action potential.** A, Depolarization to threshold, the rising phase, overshoot, peak, repolarization, afterhyperpolarization, and return to the resting membrane potential. B, Changes in sodium (g_{Na}) and potassium (g_K) conductances associated with an action potential. The rising phase of the action potential is the result of an increase in sodium conductance, while the repolarization phase is a result of a decrease in sodium conductance and a delayed increase in potassium conductance.

The action potential may be recorded by placing a microelectrode inside a nerve cell or its axon. The voltage measured is compared to that detected by a reference electrode placed outside the cell. The difference between the two measurements is a measure of the membrane potential. This technique is used to monitor the membrane potential at rest, as well as during an action potential.

Action Potential Gating Mechanisms. The depolarizing and repolarizing phases of the action potential can be explained by relative changes in membrane conductance (permeability) to sodium and potassium. During the rising phase, the nerve cell membrane becomes more permeable to sodium; as a consequence, the membrane potential begins to shift more toward the equilibrium potential for sodium. However, before the membrane potential reaches E_{Na}, sodium permeability begins to decrease and potassium permeability increases. This change in membrane conductance again drives the membrane potential toward E_K, accounting for repolarization of the membrane (Fig. 3.4B).

The action potential can also be viewed in terms of the flow of charged ions through selective ion channels. These voltage-gated channels are closed when the neuron is at rest (Fig. 3.5A). When the membrane is depolarized, these channels begin to open. The Na^+ channel quickly opens its **activation gate** and allows Na^+ ions to flow into the cell (Fig. 3.5B). The influx of positively charged Na^+ ions causes the membrane to depolarize. In fact, the membrane potential actually reverses, with the inside becoming positive; this is called the **overshoot.** In the initial stage of the action potential, more Na^+ than K^+ channels are opened because the K^+ channels open more slowly in response to depolarization. This increase in Na^+ permeability compared to that of K^+ causes the membrane potential to move toward the equilibrium potential for Na^+.

At the peak of the action potential, the sodium conductance begins to fall as an **inactivation gate** closes. Also, more K^+ channels open, allowing more positively charged K^+ ions to leave the neuron. The net effect of inactivating Na^+ channels and opening additional K^+ channels is the repolarization of the membrane (Fig. 3.5C).

As the membrane continues to repolarize, the membrane potential becomes more negative than its resting level. This **afterhyperpolarization** is a result of K^+ channels remaining open, allowing the continued efflux of K^+ ions. Another way to think about afterhyperpolarization is that the membrane's permeability to K^+ is higher than when the neuron is at rest. Consequently, the membrane potential is driven even more toward the K^+ equilibrium potential (Fig. 3.5D).

The changes in membrane potential during an action potential result from selective alterations in membrane conductance (see Fig. 3.4B). These membrane conductance changes reflect the summated activity of individual voltage-gated sodium and potassium ion channels. From the temporal relationship of the action potential and the membrane conductance changes, the depolarization and rising phase of the action potential can be attributed to the increase in sodium ion conductance, the repolarization phases to both the decrease in sodium conductance and the increase in potassium conductance, and afterhyperpolarization to the sustained increase of potassium conductance. Alterations in voltage-gated sodium and potassium channels, as well as in voltage-gated calcium and chloride channels, are now known to be the basis of several diseases of nerve and muscle. These diseases are collectively known as **channelopathies** (see Clinical Focus Box 3.1).

Initiation of the Action Potential. In most neurons, the axon hillock (initial segment) is the trigger zone that generates the action potential. The membrane of the initial segment contains a high density of voltage-gated sodium and potassium ion channels. When the membrane of the initial segment is depolarized, voltage-gated sodium channels are opened, permitting an influx of sodium ions. The influx of these positively charged ions further depolarizes the membrane, leading to the opening of other voltage-gated sodium channels. This cycle of membrane depolarization, sodium channel activation, sodium ion influx, and membrane depolarization is an example of positive feedback, a regenerative process (Fig. 1.3) that results in the explosive activation of many sodium ion channels when the threshold membrane potential is reached. If the depolarization of the initial segment does not reach threshold, then not enough sodium channels are activated to initiate the regenerative process. The initiation of an action potential is, therefore, an "all-or-none" event; it is generated completely or not at all.

Propagation and Speed of the Action Potential. After an action potential is generated, it propagates along the axon toward the axon terminal; it is conducted along the axon with no decrement in amplitude. The mode in which action potentials propagate and the speed with which they are conducted along an axon depend on whether the axon is myelinated. The diameter of the axon also influences the speed of action potential conduction: larger-diameter axons have faster action potential conduction velocities than smaller-diameter axons.

In unmyelinated axons, voltage-gated Na^+ and K^+ channels are distributed uniformly along the length of the axonal membrane. An action potential is generated when the axon hillock is depolarized by the passive spread of synaptic potentials along the somatic and dendritic membrane (see below). The hillock acts as a "sink" where Na^+ ions enter the cell. The "source" of these Na^+ ions is the extracellular space along the length of the axon. The entry of Na^+ ions into the axon hillock causes the adjacent region of the axon to depolarize as the ions that entered the cell, during the peak of the action potential, flow away from the sink. This local spread of the current depolarizes the adjacent region to threshold and causes an action potential in that region. By sequentially depolarizing adjacent segments of the axon, the action potential propagates or moves along the length of the axon from point to point, like a traveling wave (Fig. 3.6A).

Just as large-diameter tubes allow a greater flow of water than small-diameter tubes because of their decreased resistance, large-diameter axons have less cytoplasmic resistance, thereby permitting a greater flow of ions. This increase in ion flow in the cytoplasm causes greater lengths of the axon to be depolarized, decreasing the time needed for the action potential to travel along the axon. Recall

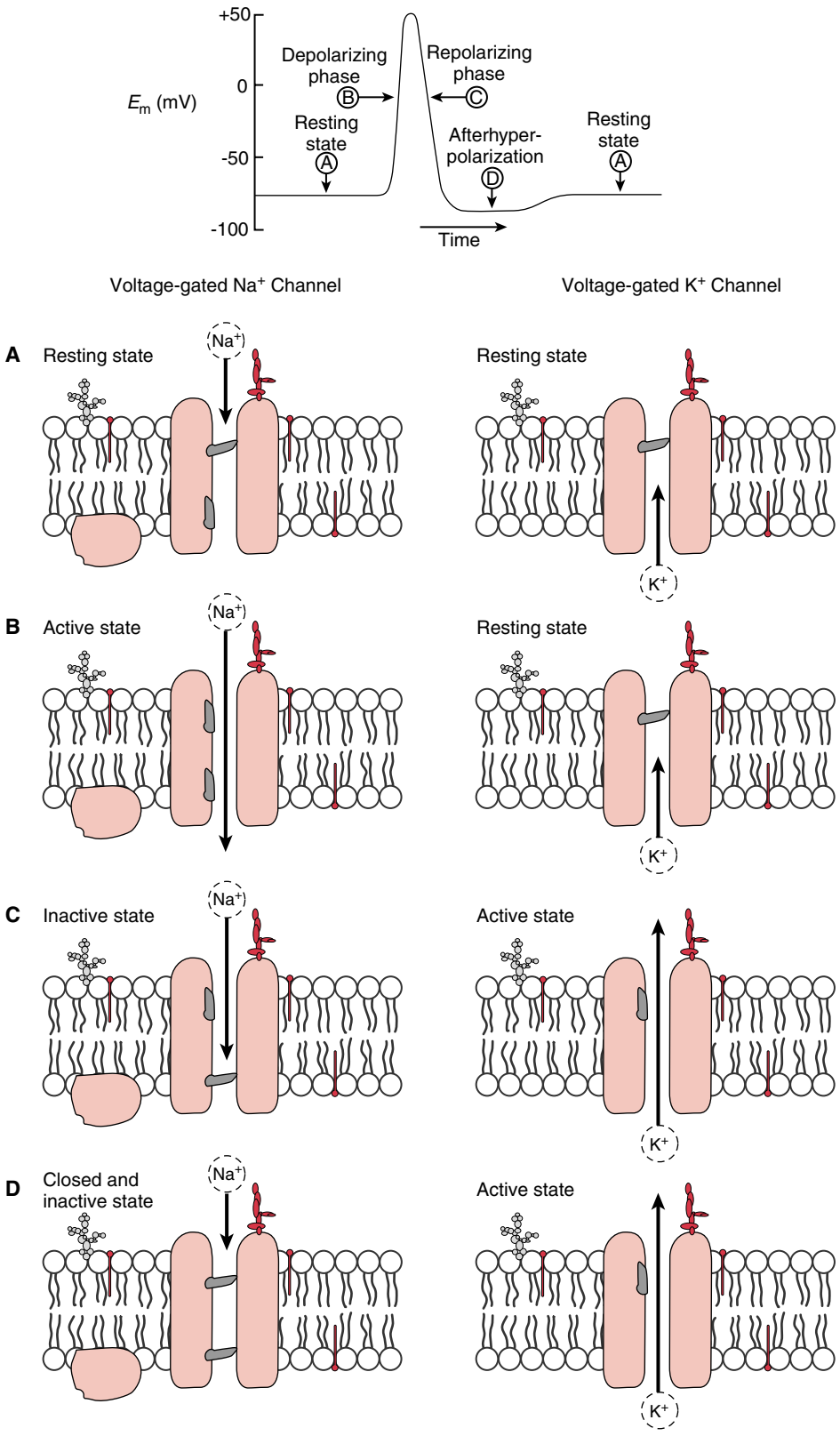


FIGURE 3.5 The states of voltage-gated sodium and potassium channels correlated with the course of the action potential. **A**, At the resting membrane potential, both channels are in a closed, resting state. **B**, During the depolarizing phase of the action potential the voltage-gated sodium channels are activated (open), but the potassium channels open more slowly and, therefore, have not yet responded to the depolarization. **C**, During the repolarizing phase, sodium channels become inactivated, while the potassium channels become activated (open). **D**, During the afterhyperpolarization, the sodium channels are both closed and inactivated, and the potassium channels remain in their active state. Eventually, the potassium channels close and the sodium channel inactivation is removed, so that both channels are in their resting state and the membrane potential returns to resting membrane potential. Note that the voltage-gated potassium channel does not have an inactivated state. (Modified from Matthews GG. Neurobiology: Molecules, Cells and Systems. Malden, MA: Blackwell Science, 1998.)

that the space constant, λ, determines the length along the axon that a voltage change is observed after a local stimulus is applied. In this case, the local stimulus is the inward sodium current that accompanies the action potential. The larger the space constant, the farther along the membrane a voltage change is observed after a local stimulus is applied. The space constant increases with axon diameter because the internal axoplasmic resistance, R_a, decreases, allowing the current to spread farther down the inside of the axon before leaking back across the membrane. Therefore,

CLINICAL FOCUS BOX 3.1

Channelopathies

Voltage-gated channels for sodium, potassium, calcium, and chloride are intimately associated with excitability in neurons and muscle cells and in synaptic transmission. Until the early 1990s, most of our knowledge about channel properties derived from biophysical studies of isolated cells or their membranes. The advent of molecular approaches resulted in the cloning of the genes for a variety of channels and the subsequent expression of these genes in a large cell, such as the *Xenopus* oocyte, for further characterization.

This approach also allowed experimental manipulation of the channels by expressing genes that were altered in known ways. In this way, researchers could determine which parts of channel molecules were responsible for particular properties, including voltage sensitivity, ion specificity, activation, inactivation, kinetics, and interaction with other cellular components. This genetic understanding of the control of channel properties led to the realization that many unexplained diseases may be caused by alterations in the genes for ion channels. Diseases based on altered ion channel function are now collectively called **channelopathies**. These diseases affect neurons, skeletal muscle, cardiac muscle, and even nonexcitable cells, such as kidney tubular cells.

One of the best-known sets of channelopathies is a group of channel mutations that lead to the Long Q-T (LQT) syndrome in the heart. The QT interval on the electrocardiogram is the time between the beginning of ventricular depolarization and the end of ventricular repolarization. In patients with LQT, the QT interval is abnormally long because of defective membrane repolarization, which can lead to ventricular arrhythmia and sudden death. Affected individuals generally have no cardiovascular disease other than that associated with electrical abnormality. The defect in membrane repolarization could be a result of a prolonged inward sodium current or a reduced outward potassium current. In fact, mutations in potassium channels account for two different LQT syndromes, and a third derives from a sodium channel mutation.

Myotonia is a condition characterized by a delayed relaxation of muscle following contraction. There are several types of myotonias, all related to abnormalities in muscle membrane. Some myotonias are associated with a skeletal muscle sodium channel, and others are associated with a skeletal muscle chloride channel.

Channelopathies affecting neurons include episodic and spinocerebellar ataxias, some forms of epilepsy, and familial hemiplegic migraine. Ataxias are a disruption in gait mediated by abnormalities in the cerebellum and spinal motor neurons. One specific ataxia associated with an abnormal potassium channel is episodic ataxia with myokymia. In this disease, which is autosomal-dominant, cerebellar neurons have abnormal excitability and motor neurons are chronically hyperexcitable. This hyperexcitability causes indiscriminant firing of motor neurons, observed as the twitching of small groups of muscle fibers, akin to worms crawling under the skin (myokymia). It is likely that many other neuronal (and muscle) disorders of currently unknown pathology will be identified as channelopathies.

when an action potential is generated in one region of the axon, more of the adjacent region that is depolarized by the inward current accompanying the action potential reaches the threshold for action potential generation. The result is that the speed at which action potentials are conducted, or **conduction velocity**, increases as a function of increasing axon diameter and concomitant increase in the space constant.

Several factors act to increase significantly the conduction velocity of action potentials in myelinated axons. Schwann cells in the PNS and oligodendrocytes in the CNS wrap themselves around axons to form myelin, layers of lipid membrane that insulate the axon and prevent the passage of ions through the axonal membrane (Fig. 3.6B). Between the myelinated segments of the axon are the nodes of Ranvier, where action potentials are generated.

The signal that causes these glial cells to myelinate the axons apparently derives from the axon, and its potency is a function of axon size. In general, axons larger than approximately 1 μm in diameter are myelinated, and the thickness of the myelin increases as a function of axon diameter. Since the smallest myelinated axon is bigger than the largest unmyelinated axon, conduction velocity is faster for myelinated axons based on size alone. In addition, the myelin acts to increase the effective resistance of the axonal membrane, R_m, since ions that flow across the axonal membrane must also flow through the tightly wrapped layers of myelin before they reach the extracellular fluid. This increase in R_m increases the space constant. The layers of myelin also decrease the effective capacitance of the axonal membrane because the distance between the extracellular and intracellular conducting fluid compartments is increased. Because the capacitance is decreased, the time constant is decreased, increasing the conduction velocity.

While the effect of myelin on R_m and capacitance are important for increasing conduction velocity, there is an even greater factor at play—an alteration in the mode of conduction. In myelinated axons, voltage-gated Na^+ channels are highly concentrated in the nodes of Ranvier, where the myelin sheath is absent, and are in low density beneath the segments of myelin. When an action potential is initiated at the axon hillock, the influx of Na^+ ions causes the adjacent node of Ranvier to depolarize, resulting in an action potential at the node. This, in turn, causes depolarization of the next node of Ranvier and the eventual initiation of an action potential. Action potentials are successively generated at neighboring nodes of Ranvier; therefore, the action potential in a myelinated axon appears to jump from one node to the next, a process called **saltatory conduction** (Fig. 3.6C). This process results in a faster conduction velocity for myelinated than unmyelinated axons. The conduction velocity in mammals ranges from 3 to 120 m/sec for myelinated axons and 0.5 to 2.0 m/sec for unmyelinated axons.

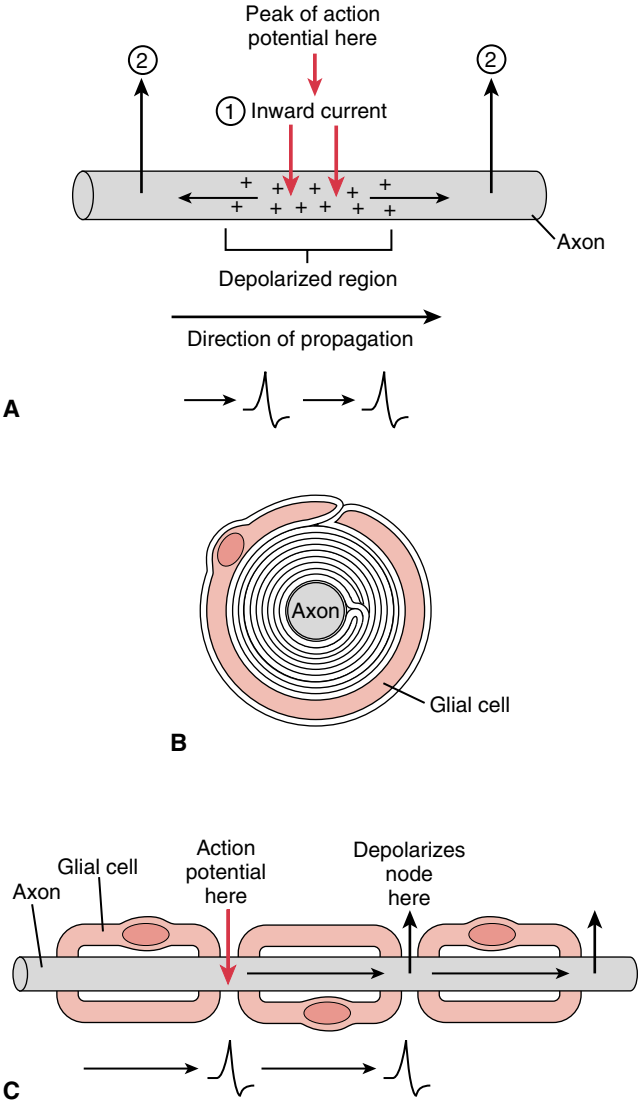


FIGURE 3.6 **Myelinated axons and saltatory conduction.** **A,** Propagation of an action potential in an unmyelinated axon. The initiation of an action potential in one segment of the axon depolarizes the immediately adjacent section, bringing it to threshold and generating an action potential. **B,** A sheath of myelin surrounding an axon. **C,** The propagation of an action potential in a myelinated axon. The initiation of an action potential in one node of Ranvier depolarizes the next node. Jumping from one node to the next is called saltatory conduction. (Modified from Matthews GG. Neurobiology: Molecules, Cells and Systems. Malden, MA: Blackwell Science, 1998.)

Refractory Periods. After the start of an action potential, there are periods when the initiation of additional action potentials requires a greater degree of depolarization and when action potentials cannot be initiated at all. These are called the **relative** and **absolute refractory periods,** respectively (Fig. 3.7).

The inability of a neuronal membrane to generate an action potential during the absolute refractory period is primarily due to the state of the voltage-gated Na^+ channel. After the inactivation gate closes during the repolarization phase of an action potential, it remains closed for some time; therefore, another action potential cannot be generated no matter how much the membrane is depolarized. The importance of the absolute refractory period is that it limits the rate of firing of action potentials. The absolute refractory period also prevents action potentials from traveling in the wrong direction along the axon.

In the relative refractory period, the inactivation gate of a portion of the voltage-gated Na^+ channels is open. Since these channels have returned to their initial resting state, they can now respond to depolarizations of the membrane. Consequently, when the membrane is depolarized, many of the channels open their activation gates and permit the influx of Na^+ ions. However, because only a portion of the Na^+ channels have returned to the resting state, depolarization of the membrane to the original threshold level activates an insufficient number of channels to initiate an action potential. With greater levels of depolarization, more channels are activated, until eventually an action potential is generated. The K^+ channels are maintained in the open state during the relative refractory period, leading to membrane hyperpolarization. By these two mechanisms, the action potential threshold is increased during the relative refractory period.

SYNAPTIC TRANSMISSION

Neurons communicate at synapses. Two types of synapses have been identified: electrical and chemical. At **electrical synapses**, passageways known as **gap junctions** connect the cytoplasm of adjacent neurons (see Fig. 1.6) and permit the bidirectional passage of ions from one cell to another. Electrical synapses are uncommon in the adult mammalian nervous system. Typically, they are found at dendrodendritic sites of contact; they are thought to synchronize the activity of neuronal populations. Gap junctions are more common in the embryonic nervous system, where they may act to aid the development of appropriate synaptic connections based on synchronous firing of neuronal populations.

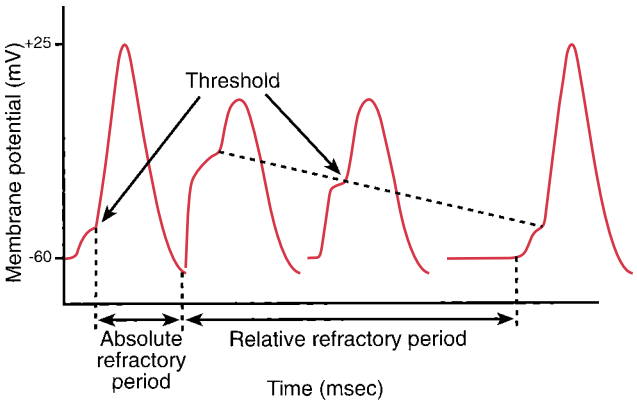
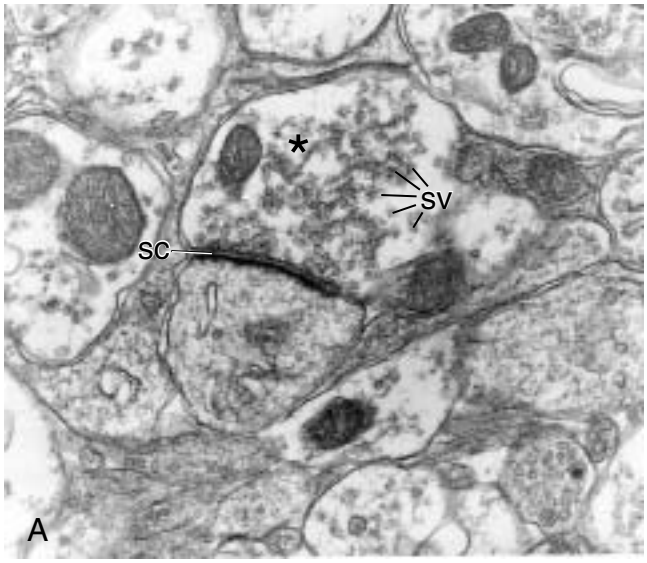


FIGURE 3.7 **Absolute and relative refractory periods.** Immediately after the start of an action potential, a nerve cell is incapable of generating another impulse. This is the absolute refractory period. With time, the neuron can generate another action potential, but only at higher levels of depolarization. The period of increased threshold for impulse initiation is the relative refractory period. Note that action potentials initiated during the relative refractory period have lower-than-normal amplitude.



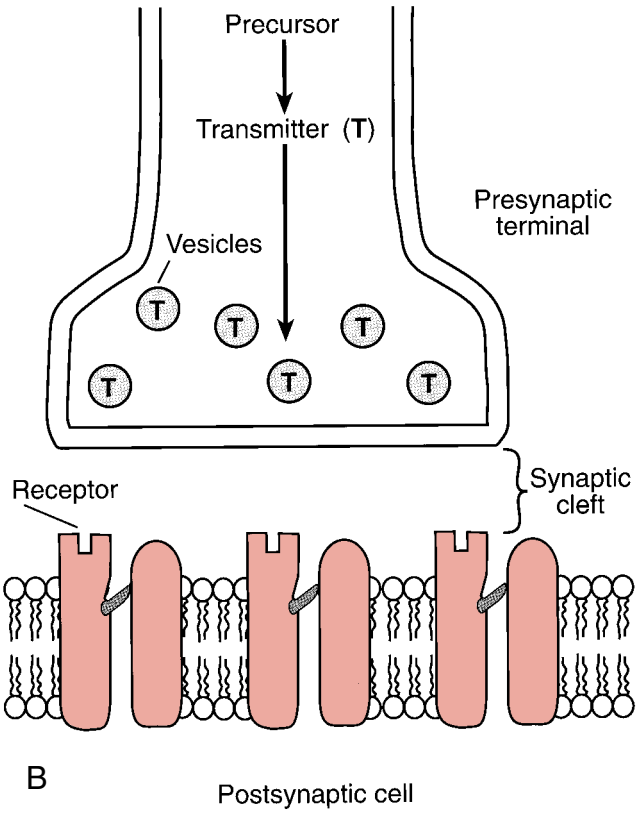


FIGURE 3.8 **A chemical synapse.** **A,** This electron micrograph shows a presynaptic terminal (asterisk) with synaptic vesicles (SV) and synaptic cleft (SC) separating presynaptic and postsynaptic membranes (magnification 60,000×) (Courtesy of Dr. Lazaros Triarhou, Indiana University School of Medicine.) **B,** The main components of a chemical synapse.

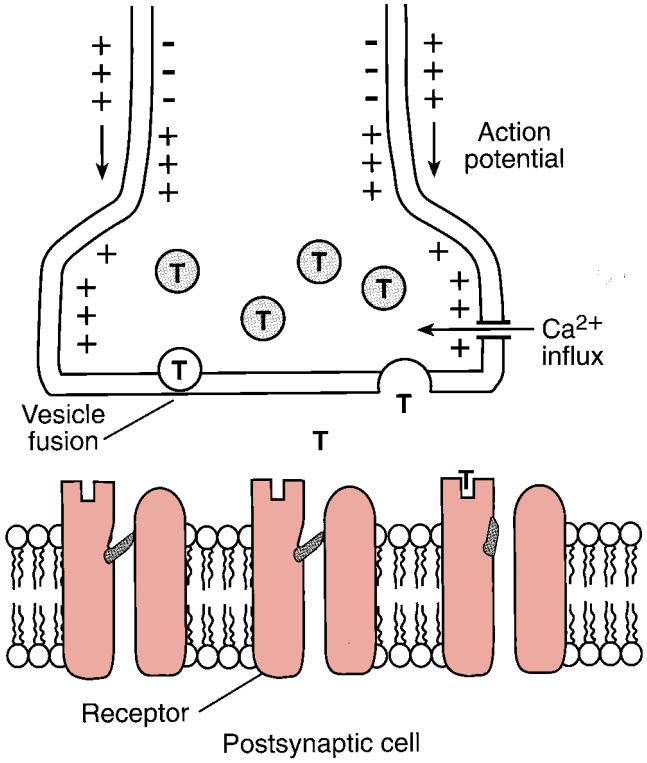


FIGURE 3.9 **The release of neurotransmitter.** Depolarization of the nerve terminal by the action potential opens voltage-gated calcium channels. Increased intracellular Ca^{2+} initiates fusion of synaptic vesicles with the presynaptic membrane, resulting in the release of neurotransmitter molecules into the synaptic cleft and binding with postsynaptic receptors.

Synaptic Transmission Usually Occurs via Chemical Neurotransmitters

At **chemical synapses**, a space called the **synaptic cleft** separates the presynaptic axon terminal from the postsynaptic cell (Fig. 3.8). The presynaptic terminal is packed with vesicles containing chemical neurotransmitters that are released into the synaptic cleft when an action potential enters the terminal. Once released, the chemical neurotransmitter diffuses across the synaptic cleft and binds to receptors on the postsynaptic cell. The binding of the transmitter to its receptor leads to the opening (or closing) of specific ion channels, which, in turn, alter the membrane potential of the postsynaptic cell.

The release of neurotransmitters from the presynaptic terminal begins with the invasion of the action potential into the axon terminal (Fig. 3.9). The depolarization of the terminal by the action potential causes the activation of voltage-gated Ca^{2+} channels. The electrochemical gradients for Ca^{2+} result in forces that drive Ca^{2+} into the terminal. This increase in intracellular ionized calcium causes a fusion of vesicles, containing neurotransmitters, with the presynaptic membrane at **active zones**. The neurotransmitters are then released into the cleft by **exocytosis.** Increasing the amount of Ca^{2+} that enters the terminal increases the amount of transmitter released into the synaptic cleft. The number of transmitter molecules released by any one exocytosed vesicle is called a **quantum,** and the total number of quanta released when the synapse is activated is called the **quantum content**. Under normal conditions, quanta are fixed in size but quantum content varies, particularly with the amount of Ca^{2+} that enters the terminal.

The way in which the entry of Ca^{2+} leads to the fusion of the vesicles with the presynaptic membrane is still being elucidated. It is clear that there are several proteins involved in this process. One hypothesis is that the vesicles are anchored to cytoskeletal components in the terminal by **synapsin,** a protein surrounding the vesicle. The entry of Ca^{2+} ions into the terminal is thought to result in phosphorylation of this protein and a decrease in its binding to the cytoskeleton, releasing the vesicles so they may move to the synaptic release sites.

Other proteins (rab GTP-binding proteins) are involved in targeting synaptic vesicles to specific docking sites in the presynaptic terminal. Still other proteins cause the vesicles to dock and bind to the presynaptic terminal membrane; these proteins are called **SNARES** and are found on both the vesicle and the nerve terminal membrane (called v-SNARES or t-SNARES, respectively). Tetanus toxin and botulinum toxin exert their devastating effects on the nervous system by disrupting the function of SNARES, preventing synaptic transmission. Exposure to these toxins can be fatal because the failure of neurotransmission between neurons and the muscles involved in breathing results in respiratory failure. To complete the process begun by Ca^{2+} entry into the nerve terminal, the docked and bound vesicles must fuse with the membrane and create a pore through which the transmitter may be released into the synaptic cleft. The vesicle membrane is then removed from the terminal membrane and recycled within the nerve terminal.

Once released into the synaptic cleft, neurotransmitter molecules exert their actions by binding to receptors in the postsynaptic membrane. These receptors are of two types. In some, the receptor forms part of an ion channel; in others, the receptor is coupled to an ion channel via a G protein and a second messenger system. In receptors associated with a specific G protein, a series of enzyme steps is initiated by binding of a transmitter to its receptor, producing a second messenger that alters intracellular functions over a longer time than for direct ion channel opening. These membrane-bound enzymes and the second messengers they produce inside the target cells include **adenylyl cyclase,** which produces cAMP; **guanylyl cyclase,** which produces cGMP; and **phospholipase C,** which leads to the formation of two second messengers, diacylglycerol and inositol trisphosphate (see Chapter 1).

When a transmitter binds to its receptor, membrane conductance changes occur, leading to depolarization or hyperpolarization. An increase in membrane conductance to Na^+ depolarizes the membrane. An increase in membrane conductance that permits the efflux of K^+ or the influx of Cl^- hyperpolarizes the membrane. In some cases, membrane hyperpolarization can occur when a decrease in membrane conductance reduces the influx of Na^+. Each of these effects results from specific alterations in ion channel function, and there are many different ligand-gated and voltage-gated channels.

Integration of Postsynaptic Potentials Occurs in the Dendrites and Soma

The transduction of information between neurons in the nervous system is mediated by changes in the membrane potential of the postsynaptic cell. These membrane depolarizations and hyperpolarizations are integrated or summated and can result in activation or inhibition of the postsynaptic neuron. Alterations in the membrane potential that occur in the postsynaptic neuron initially take place in the dendrites and the soma as a result of the activation of afferent inputs.

Since depolarizations can lead to the excitation and activation of a neuron, they are commonly called **excitatory postsynaptic potentials** (EPSPs). In contrast, hyperpolarizations of the membrane prevent the cell from becoming activated and are called **inhibitory postsynaptic potentials** (IPSPs). These membrane potential changes are caused by the influx or efflux of specific ions (Fig. 3.10).

The rate at which the membrane potential of a postsynaptic neuron is altered can greatly influence the efficiency of transducing information from one neuron to the next. If the activation of a synapse leads to the influx of positively charged ions, the postsynaptic membrane will depolarize. When the influx of these ions is stopped, the membrane will repolarize back to the resting level. The rate at which it repolarizes depends on the membrane time constant, τ, which is a function of membrane resistance and capacitance and represents the time required for the membrane potential to decay to 37% of its initial peak value (Fig. 3.11).

The decay rate for repolarization is slower for longer time constants because the increase in membrane resistance and/or capacitance results in a slower discharge of the membrane. The slow decay of the repolarization allows additional time for the synapse to be reactivated and depolarize the membrane. A second depolarization of the mem-

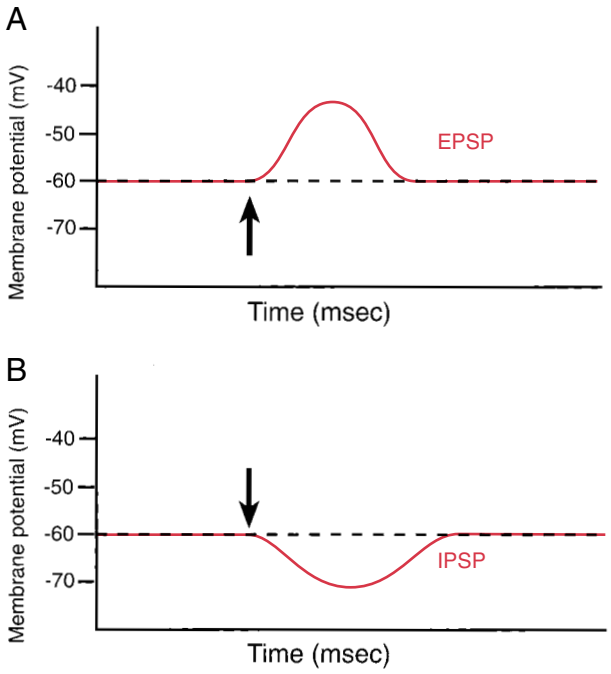


FIGURE 3.10 **Excitatory and inhibitory postsynaptic potentials.** **A,** The depolarization of the membrane (arrow) brings a nerve cell closer to the threshold for the initiation of an action potential and produces an excitatory postsynaptic potential (EPSP). **B,** The hyperpolarization of the membrane produces an inhibitory postsynaptic potential (IPSP).

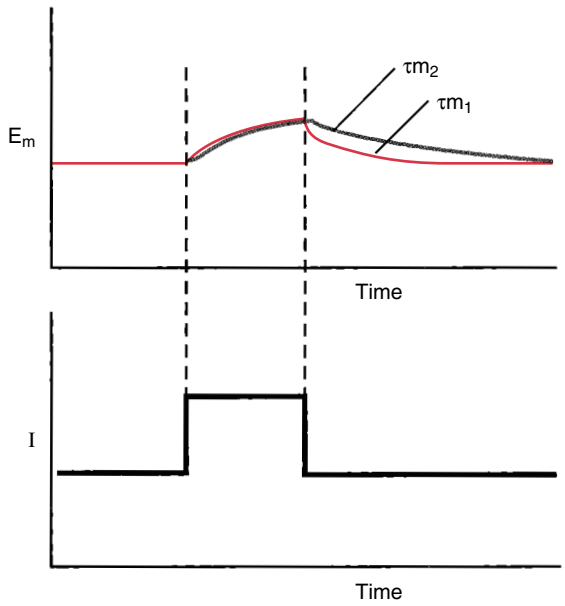


FIGURE 3.11 **Membrane potential decay rate and time constant.** The rate of decay of membrane potential (E_m) varies with a given neuron's membrane time constant. The responses of two neurons to a brief application of depolarizing current (I) are shown here. Each neuron depolarizes to the same degree, but the time for return to the baseline membrane potential differs for each. Neuron 2 takes longer to return to baseline than neuron 1 because its time constant is longer ($\tau_{m2} > \tau_{m1}$).

brane can be added to that of the first depolarization. Consequently, longer periods of depolarization increase the likelihood of summating two postsynaptic potentials. The process in which postsynaptic membrane potentials are added with time is called **temporal summation** (Fig. 3.12). If the magnitude of the summated depolarizations is above a threshold value, as detected at the axon hillock, it will generate an action potential.

The summation of postsynaptic potentials also occurs with the activation of several synapses located at different sites of contact. This process is called **spatial summation**. When a synapse is activated, causing an influx of positively charged ions, a depolarizing **electrotonic potential** develops, with maximal depolarization occurring at the site of synaptic activation. The electrotonic potential is due to the passive spread of ions in the dendritic cytoplasm and across the membrane. The amplitude of the electrotonic potential decays with distance from the synapse activation site (Fig. 3.13). The decay of the electrotonic potential per unit length along the dendrite is determined by the length or space constant, λ, which represents the length required for the membrane potential depolarization to decay to 37% of its maximal value. The larger the space constant value, the smaller the decay per unit length; thus, more charge is delivered to more distant membrane patches.

By depolarizing distal patches of membrane, other electrotonic potentials that occur by activating synaptic inputs at other sites can summate to produce even greater depolarization, and the resulting postsynaptic potentials

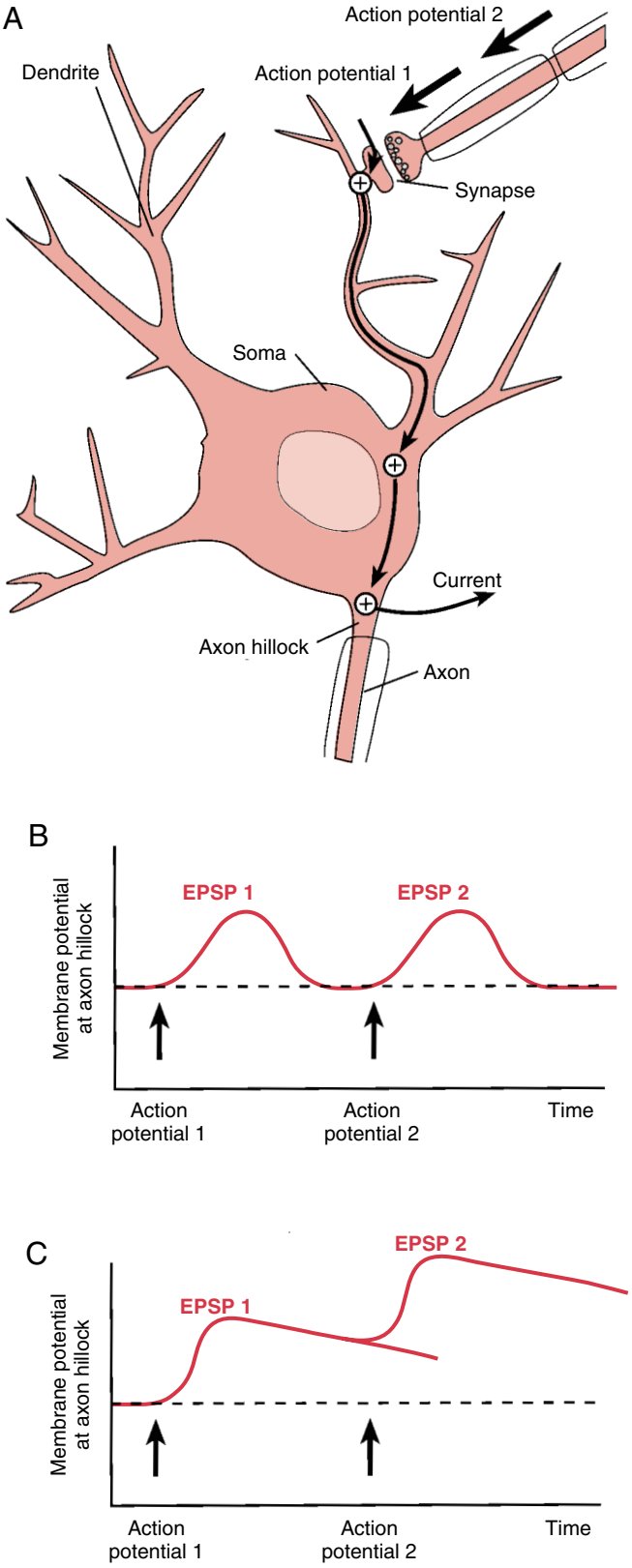


FIGURE 3.12 **A model of temporal summation.** **A**, Depolarization of a dendrite by two sequential action potentials. **B**, A dendritic membrane with a short time constant is unable to summate postsynaptic potentials. **C**, A dendritic membrane with a long time constant is able to summate membrane potential changes.

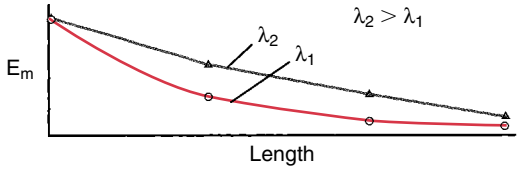


FIGURE 3.13 **A profile of the electrotonic membrane potential produced along the length of a dendrite.** The decay of the membrane potential, E_m, as it proceeds along the length of the dendrite is affected by the space constant, λ_m. Long space constants cause the electrotonic potential to decay more gradually. Profiles are shown for two dendrites with different space constants, λ_1 and λ_2. The electrotonic potential of dendrite 2 decays less steeply than that of dendrite 1 because its space constant is longer.

are added along the length of the dendrite. As with temporal summation, if the depolarizations resulting from spatial summation are sufficient to cause the membrane potential in the region of axon hillock to reach threshold, the postsynaptic neuron will generate an action potential (Fig. 3.14).

Because of the spatial decay of the electrotonic potential, the location of the synaptic contact strongly influences whether a synapse can activate a postsynaptic neuron. For example, axodendritic synapses, located in distal segments of the dendritic tree, are far removed from the axon hillock, and their activation has little impact on the membrane potential near this trigger zone. In contrast, axosomatic synapses have a greater effect in altering the membrane potential at the axon hillock because of their proximal location.

NEUROCHEMICAL TRANSMISSION

Neurons communicate with other cells by the release of chemical neurotransmitters, which act transiently on postsynaptic receptors and then must be removed from the synaptic cleft (Fig. 3.15). Transmitter is stored in synaptic vesicles and released on nerve stimulation by the process of exocytosis, following the opening of voltage-gated calcium ion channels in the nerve terminal. Once released, the neurotransmitter binds to and stimulates its receptors briefly before being rapidly removed from the synapse, thereby allowing the transmission of a new neuronal message. The most common mode of removal of the neurotransmitter following release is called **high-affinity reuptake** by the presynaptic terminal. This is a carrier-mediated, sodium-dependent, secondary active transport that uses energy from the Na^+/K^+- ATPase pump. Other removal mechanisms include enzymatic degradation into a nonactive metabolite in the synapse or diffusion away from the synapse into the extracellular space.

The details of synaptic events in chemical transmission were originally described for PNS synapses. CNS synapses appear to use similar mechanisms, with the important difference that muscle and gland cells are the targets of transmission in peripheral nerves, whereas neurons make up the postsynaptic elements at central synapses. In the central nervous system, glial cells also play a crucial role in remov-

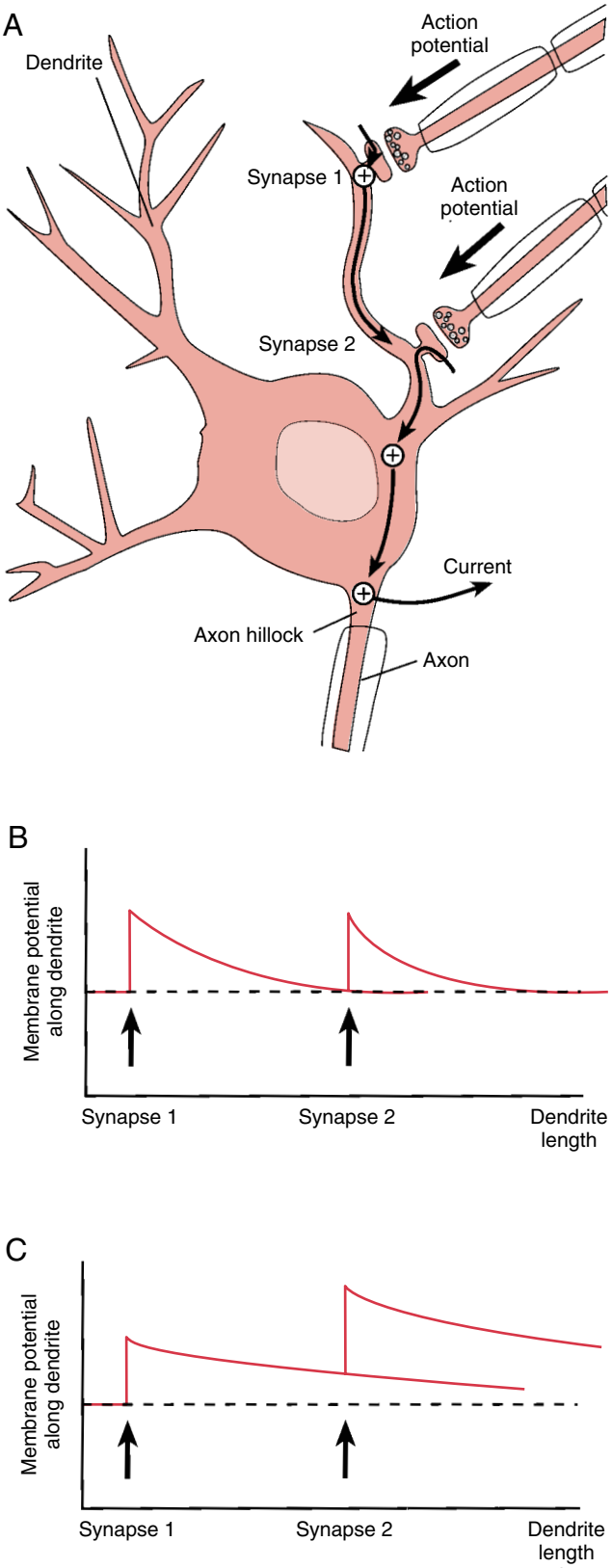


FIGURE 3.14 **A model of spatial summation.** **A**, The depolarization of a dendrite at two spatially separated synapses. **B**, A dendritic membrane with a short space constant is unable to summate postsynaptic potentials. **C**, A dendritic membrane with a long space constant is able to summate membrane potential changes.

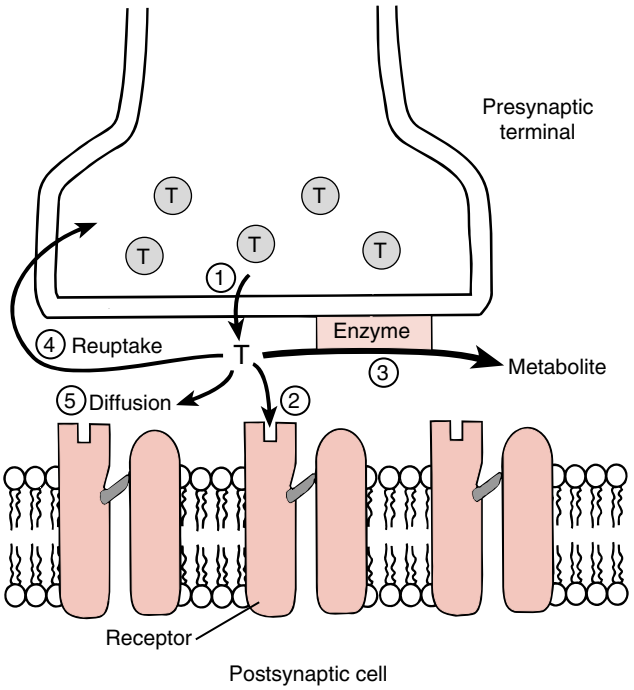


FIGURE 3.15 **The basic steps in neurochemical transmission.** Neurotransmitter molecules (T) are released into the synaptic cleft (1), reversibly bind to receptors on the postsynaptic cell (2), and are removed from the cleft by enzymatic degradation (3), reuptake into the presynaptic nerve terminal (4), or diffusion (5).

ing some neurotransmitters from the synaptic cleft via high-affinity reuptake.

There Are Several Classes of Neurotransmitters

The first neurotransmitters described were acetylcholine and norepinephrine, identified at synapses in the peripheral nervous system. Many others have since been identified, and they fall into three main classes: amino acids, monoamines, and polypeptides. Amino acids and monoamines are collectively termed **small-molecule transmitters.** The monoamines (or biogenic amines) are so named because they are synthesized from a single, readily available amino acid precursor. The polypeptide transmitters (or neuropeptides) consist of an amino acid chain, varying in length from three to several dozen. Recently, a novel set of neurotransmitters has been identified; these are membrane-soluble molecules that may act as both anterograde and retrograde signaling molecules between neurons.

Examples of amino acid transmitters include the excitatory amino acids glutamate and aspartate and the inhibitory amino acids glycine and γ-aminobutyric. (Note that γ-aminobutyric is biosynthetically a monoamine, but it has the features of an amino acid transmitter, not a monoaminergic one.) Examples of monoaminergic neurotransmitters are acetylcholine, derived from choline; the catecholamine transmitters dopamine, norepinephrine, and epinephrine, derived from the amino acid tyrosine; and an indoleamine, serotonin or 5-hydroxytryptamine, derived from tryptophan. Examples of polypeptide transmitters are the opioids and substance P. The best known membrane-soluble neurotransmitters are nitric oxide and arachidonic acid.

The human nervous system has some 100 billion neurons, each of which communicates with postsynaptic targets via chemical neurotransmission. As noted above, there are essentially only a handful of neurotransmitters. Even counting all the peptides known to act as transmitters, the number is well less than 50. Peptide transmitters can be colocalized, in a variety of combinations, with nonpeptide and other peptide transmitters, increasing the number of different types of chemical synapses. However, the specific neuronal signaling that allows the enormous complexity of function in the nervous system is due largely to the specificity of neuronal connections made during development.

There is a pattern to neurotransmitter distribution. Particular sets of pathways use the same neurotransmitter; some functions are performed by the same neurotransmitter in many places (Table 3.1). This redundant use of neurotransmitters is problematic in pathological conditions affecting one anatomic pathway or one neurotransmitter type. A classic example is Parkinson's disease, in which a particular set of dopaminergic neurons in the brain degenerates, resulting in a specific movement disorder. Therapies for Parkinson's disease, such as L-DOPA, that increase dopamine signaling do so globally, so other dopaminergic pathways become overly active. In some cases, patients receiving L-DOPA develop psychotic reactions because of excess dopamine signaling in limbic system pathways. Conversely, antipsychotic medications designed to decrease dopamine signaling in the limbic system may cause parkinsonian side effects. One strategy for decreasing the adverse effects of medications that affect neurotransmission is to target the therapies to specific types of receptors that may be preferentially distributed in one of the pathways that use the same neurotransmitter.

Acetylcholine. Neurons that use **acetylcholine** (ACh) as their neurotransmitter are known as **cholinergic neurons.** Acetylcholine is synthesized in the cholinergic neuron from choline and acetate, under the influence of the enzyme **choline acetyltransferase** or choline acetylase. This enzyme is localized in the cytoplasm of cholinergic neurons, especially in the vicinity of storage vesicles, and it is an identifying marker of the cholinergic neuron.

TABLE 3.1 **General Functions of Neurotransmitters**

Neurotransmitter	Function
Dopamine	Affect, reward, control of movement
Norepinephrine	Affect, alertness
Serotonin	Mood, arousal, modulation of pain
Acetylcholine	Control of movement, cognition
GABA	General inhibition
Glycine	General inhibition
Glutamate	General excitation, sensation
Substance P	Transmission of pain
Opioid peptides	Control of pain
Nitric oxide	Vasodilation, metabolic signaling

All the components for the synthesis, storage, and release of ACh are localized in the terminal region of the cholinergic neuron (Fig. 3.16). The storage vesicles and choline acetyltransferase are produced in the soma and are transported to the axon terminals. The rate-limiting step in ACh synthesis in the nerve terminals is the availability of choline, of which specialized mechanisms ensure a continuous supply. Acetylcholine is stored in vesicles in the axon terminals, where it is protected from enzymatic degradation and packaged appropriately for release upon nerve stimulation.

The enzyme **acetylcholinesterase** (AChE) hydrolyzes ACh back to choline and acetate after the release of ACh. This enzyme is found in both presynaptic and postsynaptic cell membranes, allowing rapid and efficient hydrolysis of extracellular ACh. This enzymatic mechanism is so efficient that normally no ACh spills over from the synapse into the general circulation. The choline generated from ACh hydrolysis is taken back up by the cholinergic neuron by a high-affinity, sodium-dependent uptake mechanism, which ensures a steady supply of the precursor for ACh synthesis. An additional source of choline is the low-affinity transport used by all cells to take up choline from the extracellular fluid for use in the synthesis of phospholipids.

The receptors for ACh, known as **cholinergic receptors**, fall into two categories, based on the drugs that mimic or antagonize the actions of ACh on its many target cell types. In classical studies dating to the early twentieth century, the drugs **muscarine**, isolated from poisonous mushrooms, and **nicotine**, isolated from tobacco, were used to distinguish two separate receptors for ACh. Muscarine stimulates some of the receptors and nicotine stimulates all the others, so receptors were designated as either **muscarinic** or **nicotinic**. It should be noted that ACh has the actions of both muscarine and nicotine at cholinergic receptors (Fig. 3.16); however, these two drugs cause fundamental differences that ACh cannot distinguish.

The **nicotinic acetylcholine receptor** is composed of five components: two α subunits and a β, γ, and δ subunit (Fig. 3.17). The two α subunits are binding sites for ACh. When ACh molecules bind to both α subunits, a conformational change occurs in the receptor, which results in an increase in channel conductance for Na^+ and K^+, leading to depolarization of the postsynaptic membrane. This depolarization is due to the strong inward electrical and chemical gradient for Na^+, which predominates over the outward gradient for K^+ ions and results in a net inward flux of positively charged ions.

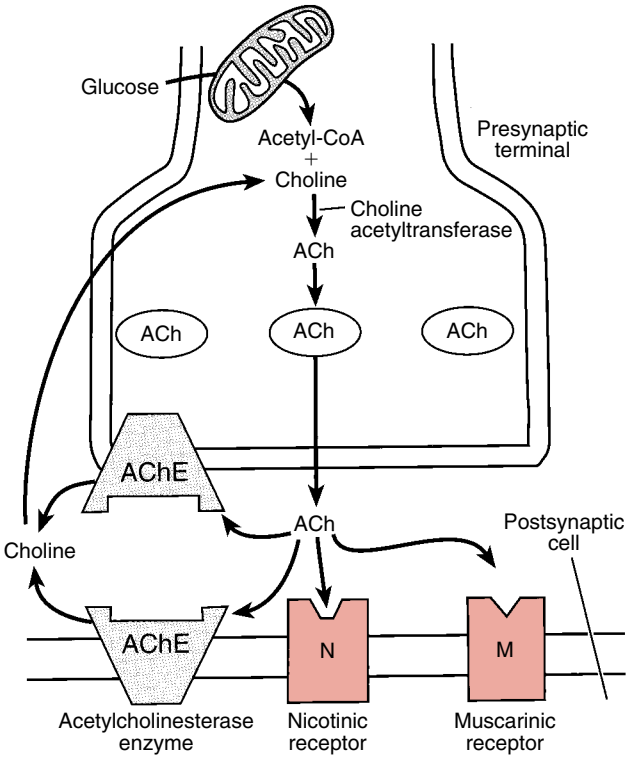


FIGURE 3.16 **Cholinergic neurotransmission.** When an action potential invades the presynaptic terminal, ACh is released into the synaptic cleft and binds to receptors on the postsynaptic cell to activate either nicotinic or muscarinic receptors. ACh is also hydrolyzed in the cleft by the enzyme acetylcholinesterase (AChE) to produce the metabolites choline and acetate. Choline is transported back into the presynaptic terminal by a high-affinity transport process to be reused in ACh resynthesis.

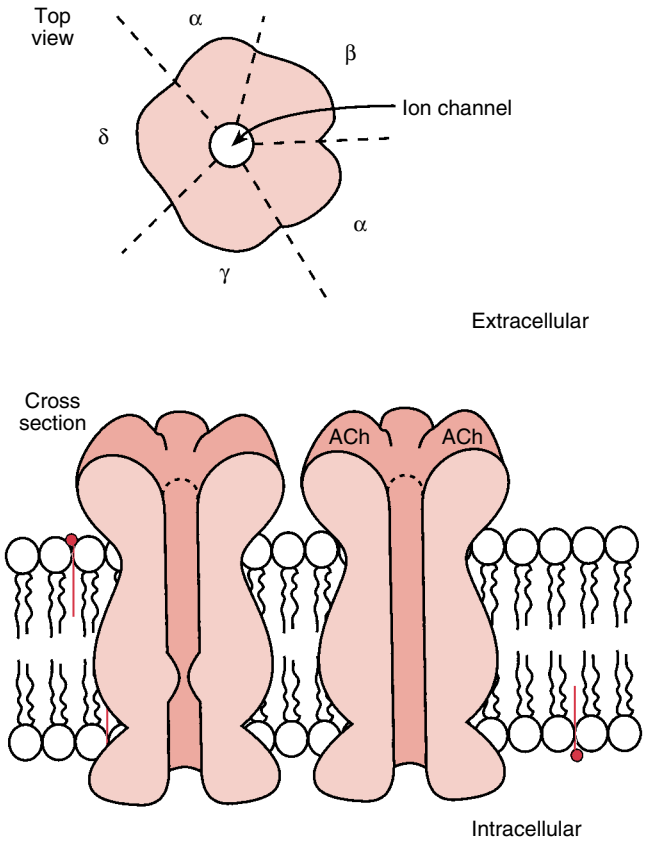


FIGURE 3.17 **The structure of a nicotinic acetylcholine receptor.** The nicotinic receptor is composed of five subunits: two α subunits and β, γ, and δ subunits. The two α subunits serve as binding sites for ACh. Both binding sites must be occupied to open the channel, permitting sodium ion influx and potassium ion efflux.

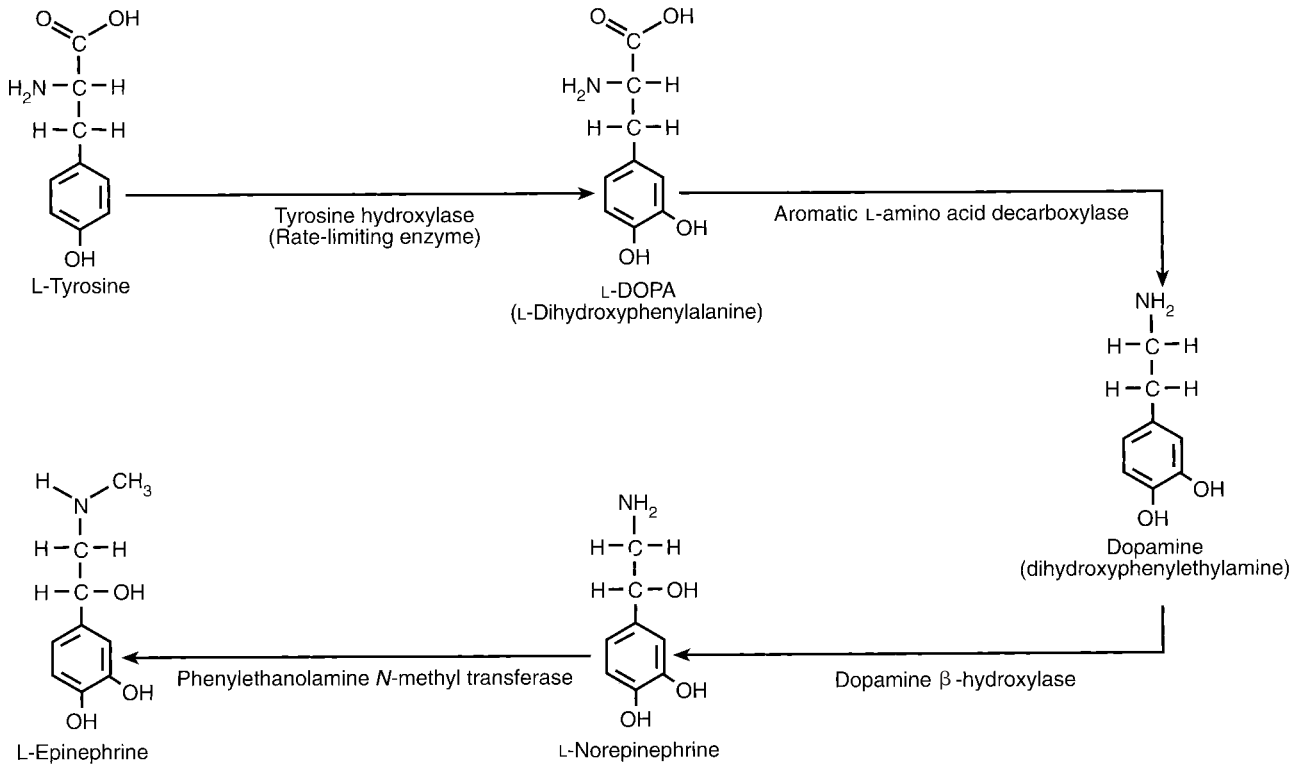


FIGURE 3.18 **The synthesis of catecholamines.** The catecholamine neurotransmitters are synthesized by way of a chain of enzymatic reactions to produce L-DOPA, dopamine, L-norepinephrine, and L-epinephrine.

The structure and the function of the **muscarinic acetylcholine receptor** are different. Five subtypes of muscarinic receptors have been identified. The M_1 and M_2 receptors are composed of seven membrane-spanning domains, with each exerting action through a G protein. The activation of M_1 receptors results in a decrease in K^+ conductance via phospholipase C, and activation of M_2 receptors causes an increase in K^+ conductance by inhibiting adenylyl cyclase. As a consequence, when ACh binds to an M_1 receptor, it results in membrane depolarization; when ACh binds to an M_2 receptor, it causes hyperpolarization.

Catecholamines. The catecholamines are so named because they consist of a catechol moiety (a phenyl ring with two attached hydroxyl groups) and an ethylamine side chain. The catecholamines **dopamine** (DA), **norepinephrine** (NE), and **epinephrine** (EPI) share a common pathway for enzymatic biosynthesis (Fig. 3.18). Three of the enzymes involved—tyrosine hydroxylase (TH), dopamine β-hydroxylase (DBH), and phenylethanolamine *N*-methyl transferase (PNMT)—are unique to catecholamine-secreting cells and all are derived from a common ancestral gene. **Dopaminergic neurons** express only TH, **noradrenergic neurons** express both TH and DBH, and epinephrine-secreting cells express all three. **Epinephrine-secreting cells** include a small population of CNS neurons, as well as the hormonal cells of the adrenal medulla, **chromaffin cells,** which secrete EPI during the fight-or-flight response (see Chapter 6).

The rate-limiting enzyme in catecholamine biosynthesis is **tyrosine hydroxylase**, which converts L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA). Tyrosine hydroxylase is regulated by short-term activation and long-term induction. Short-term excitation of dopaminergic neurons results in an increase in the conversion of tyrosine to DA. This phenomenon is mediated by the phosphorylation of TH via a cAMP-dependent protein kinase, which results in an increase in functional TH activity. Long-term induction is mediated by the synthesis of new TH.

A nonspecific cytoplasmic enzyme, aromatic L-amino acid decarboxylase, catalyzes the formation of dopamine from L-DOPA. Dopamine is then taken up in storage vesicles and protected from enzymatic attack. In NE- and EPI-synthesizing neurons, DBH, which converts DA to NE, is found within vesicles, unlike the other synthetic enzymes, which are in the cytoplasm. In EPI-secreting cells, PNMT is localized in the cytoplasm. The PNMT adds a methyl group to the amine in NE to form EPI.

Two enzymes are involved in degrading the catecholamines following vesicle exocytosis. **Monoamine oxidase** (MAO) removes the amine group, and **catechol-O-methyltransferase** (COMT) methylates the 3-OH group on the catechol ring. As shown in Figure 3.19, MAO is localized in mitochondria, present in both presynaptic and postsynaptic cells, whereas COMT is localized in the cytoplasm and only postsynaptically. At synapses of noradrenergic neurons in the PNS (i.e., postganglionic sympathetic neurons of the autonomic nervous system) (see Chapter 6), the postsynaptic COMT-containing cells are the muscle and gland cells and other nonneuronal tissues that receive sympathetic stimulation. In the CNS, on the other hand, most of the COMT is localized in glial cells (especially astrocytes) rather than in postsynaptic target neurons.

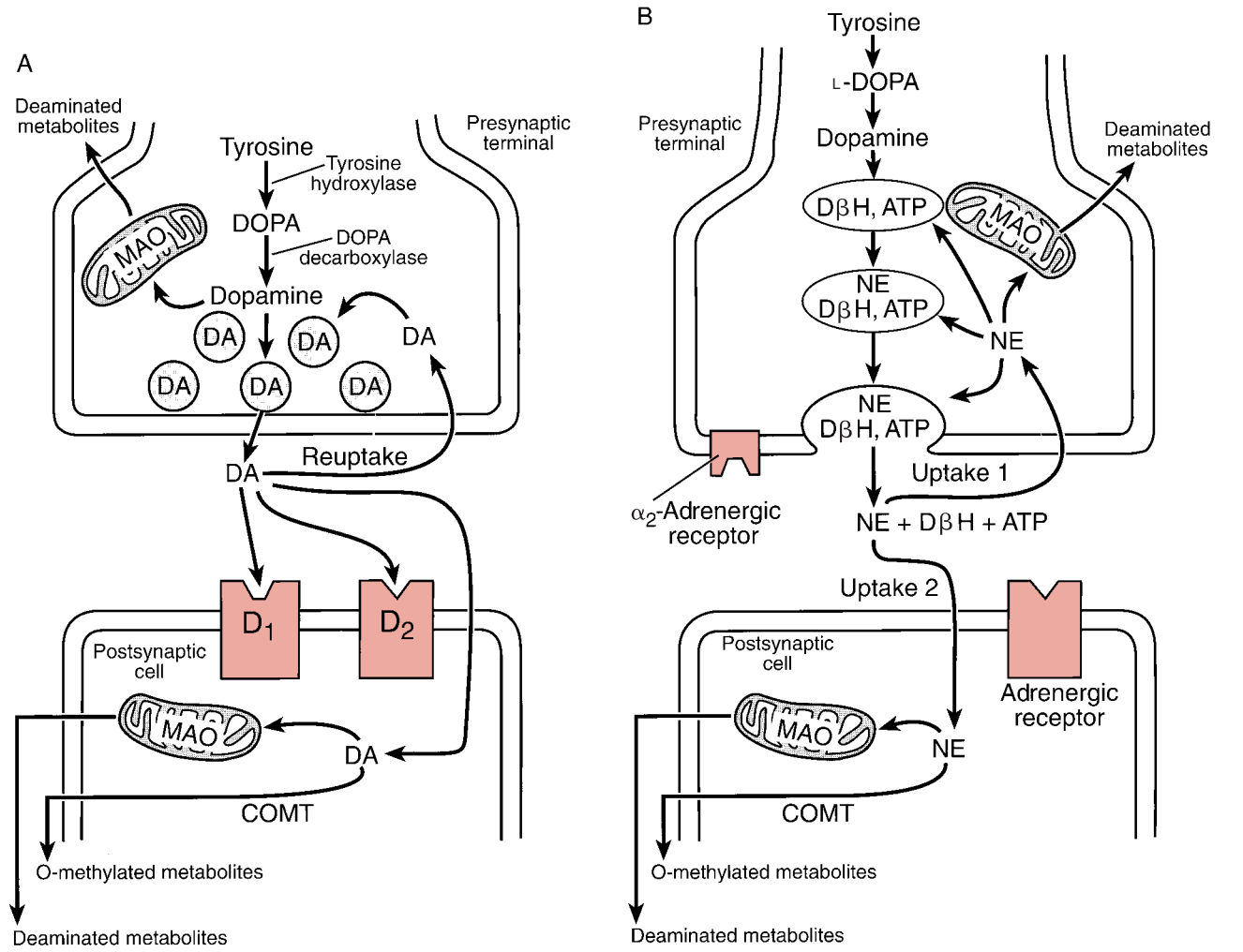


FIGURE 3.19 **Catecholaminergic neurotransmission.** **A,** In dopamine-producing nerve terminals, dopamine is enzymatically synthesized from tyrosine and taken up and stored in vesicles. The fusion of DA-containing vesicles with the terminal membrane results in the release of DA into the synaptic cleft and permits DA to bind to dopamine receptors (D_1 and D_2) in the postsynaptic cell. The termination of DA neurotransmission occurs when DA is transported back into the presynaptic terminal via a high-affinity mechanism. **B,** In norepinephrine (NE)-producing nerve terminals, DA is transported into synaptic vesicles and converted into NE by the enzyme dopamine β-hydroxylase (DBH). On release into the synaptic cleft, NE can bind to postsynaptic α- or β-adrenergic receptors and presynaptic α_2-adrenergic receptors. Uptake of NE into the presynaptic terminal (uptake 1) is responsible for the termination of synaptic transmission. In the presynaptic terminal, NE is repackaged into vesicles or deaminated by mitochondrial MAO. NE can also be transported into the postsynaptic cell by a low-affinity process (uptake 2), in which it is deaminated by MAO and O-methylated by catechol-O-methyltransferase (COMT).

Most of the catecholamine released into the synapse (up to 80%) is rapidly removed by uptake into the presynaptic neuron. Once inside the presynaptic neuron, the transmitter enters the synaptic vesicles and is made available for recycling. In peripheral noradrenergic synapses (the sympathetic nervous system), the neuronal uptake process described above is referred to as **uptake 1,** to distinguish it from a second uptake mechanism, **uptake 2,** localized in the target cells (smooth muscle, cardiac muscle, and gland cells) (Fig. 3.19B). In contrast with uptake 1, an active transport, uptake 2 is a facilitated diffusion mechanism, which takes up the sympathetic transmitter NE, as well as the circulating hormone EPI, and degrades them enzymatically by MAO and COMT localized in the target cells. In the CNS, there is little evidence of an uptake 2 of NE, but glia serve a comparable role by taking up catecholamines and degrading them enzymatically by glial MAO and COMT. Unlike uptake 2 in the PNS, glial uptake of catecholamines has many characteristics of uptake 1.

The catecholamines differ substantially in their interactions with receptors; DA interacts with DA receptors and NE and EPI interact with adrenergic receptors. Up to five subtypes of DA receptors have been described in the CNS. Of these five, two have been well characterized. **D_1 receptors** are coupled to stimulatory G proteins (G_s), which activate adenylyl cyclase, and **D_2 receptors** are coupled to inhibitory G proteins (G_i), which inhibit adenylyl cyclase. Activation of D_2 receptors hyperpolarizes the postsynaptic membrane by increasing potassium conductance. A third subtype of DA receptor postulated to modulate the release of DA is local-

ized on the cell membrane of the nerve terminal that releases DA; accordingly, it is called an **autoreceptor**.

Adrenergic receptors, stimulated by EPI and NE, are located on cells throughout the body, including the CNS and the peripheral target organs of the sympathetic nervous system (see Chapter 6). Adrenergic receptors are classified as either α or β, based on the rank order of potency of catecholamines and related analogs in stimulating each type. The analogs used originally in distinguishing α- from β-adrenergic receptors are NE, EPI, and the two synthetic compounds isoproterenol (ISO) and phenylephrine (PE). Ahlquist, in 1948, designated α as those receptors in which EPI was highest in potency and ISO was least potent (EPI > NE > > ISO). β-Receptors exhibited a different rank order: ISO was most potent and EPI either more potent or equal in potency to NE. Studies with PE further distinguished these two classes of receptors: α-receptors were stimulated by PE, whereas β-receptors were not.

Serotonin. **Serotonin** or **5-hydroxytryptamine** (5-HT) is the transmitter in **serotonergic neurons.** Chemical transmission in these neurons is similar in several ways to that described for catecholaminergic neurons. Tryptophan hydroxylase, a marker of serotonergic neurons, converts tryptophan to 5-hydroxytryptophan (5-HTP), which is then converted to 5-HT by decarboxylation (Fig. 3.20).

5-Hydroxytryptamine is stored in vesicles and is released by exocytosis upon nerve depolarization. The major mode of removal of released 5-HT is by a high-affinity, sodium-dependent, active uptake mechanism. There are several receptor subtypes for serotonin. The 5-HT-3 receptor contains an ion channel. Activation results in an increase in sodium and potassium ion conductances, leading to EPSPs. The remaining well-characterized receptor subtypes appear to operate through second messenger systems. The 5-HT-1A receptor, for example, uses cAMP. Activation of this receptor results in an increase in K^+ ion conductance, producing IPSPs.

Glutamate and Aspartate. Both **glutamate** (GLU) and **aspartate** (ASP) serve as excitatory transmitters of the CNS. These dicarboxylic amino acids are important substrates for transaminations in all cells; but, in certain neurons, they also serve as neurotransmitters—that is, they are sequestered in high concentration in synaptic vesicles, released by exocytosis, stimulate specific receptors in the synapse, and are removed by high-affinity uptake. Since GLU and ASP are readily interconvertible in transamination reactions in cells, including neurons, it has been difficult to distinguish neurons that use glutamate as a transmit-

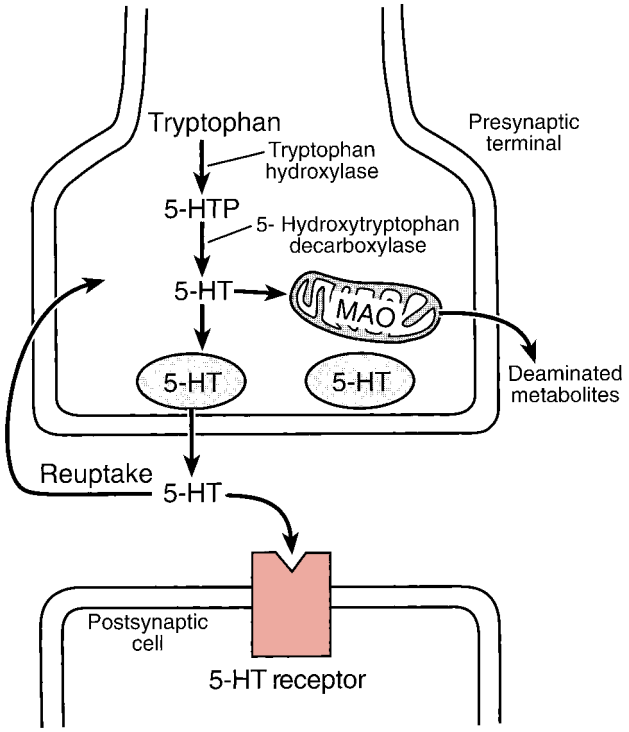


FIGURE 3.20 **Serotonergic neurotransmission.** Serotonin (5-HT) is synthesized by the hydroxylation of tryptophan to form 5-hydroxytryptophan (5-HTP) and the decarboxylation of 5-HTP to form 5-HT. On release into the synaptic cleft, 5-HT can bind to a variety of serotonergic receptors on the postsynaptic cell. Synaptic transmission is terminated when 5-HT is transported back into the presynaptic terminal for repackaging into vesicles.

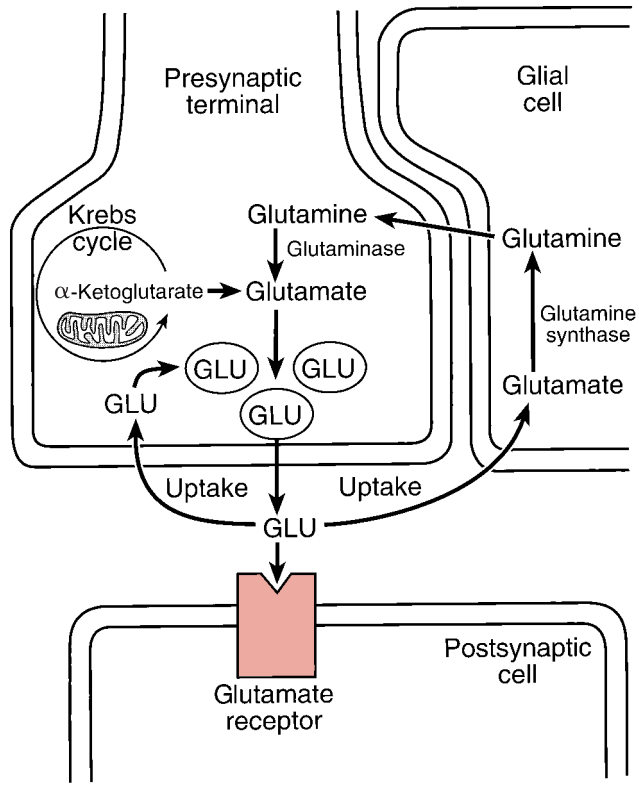


FIGURE 3.21 **Glutamatergic neurotransmission.** Glutamate (GLU) is synthesized from α-ketoglutarate by enzymatic amination. Upon release into the synaptic cleft, GLU can bind to a variety of receptors. The removal of GLU is primarily by transport into glial cells, where it is converted into glutamine. Glutamine, in turn, is transported from glial cells to the nerve terminal, where it is converted to glutamate by the enzyme glutaminase.

ter from those that use aspartate. This difficulty is further compounded by the fact that GLU and ASP stimulate common receptors. Accordingly, it is customary to refer to both as **glutamatergic neurons.**

Sources of GLU for neurotransmission are the diet and mitochondrial conversion of α-ketoglutarate derived from the Krebs cycle (Fig. 3.21). Glutamate is stored in vesicles and released by exocytosis, where it activates specific receptors to depolarize the postsynaptic neuron. Two efficient active transport mechanisms remove GLU rapidly from the synapse. Neuronal uptake recycles the transmitter by re-storage in vesicles and re-release. Glial cells (particularly astrocytes) contain a similar, high-affinity, active transport mechanism that ensures the efficient removal of excitatory neurotransmitter molecules from the synapse (see Fig. 3.21). Glia serves to recycle the transmitter by converting it to **glutamine**, an inactive storage form of GLU containing a second amine group. Glutamine from glia readily enters the neuron, where glutaminase removes the second amine, regenerating GLU for use again as a transmitter.

At least five subtypes of GLU receptors have been described, based on the relative potency of synthetic analogs in stimulating them. Three of these, named for the synthetic analogs that best activate them—kainate, quisqualate, and *N*-methyl-D-aspartate (NMDA) receptors—are associated with cationic channels in the neuronal membrane. Activation of the **kainate** and **quisqualate receptors** produces EPSPs by opening ion channels that increase Na^+ and K^+ conductance. Activation of the **NMDA receptor** increases Ca^{2+} conductance. This receptor, however, is blocked by Mg^{2+} when the membrane is in the resting state and becomes unblocked when the membrane is depolarized. Thus, the NMDA receptor can be thought of as both a ligand-gated and a voltage-gated channel. Calcium gating through the NMDA receptor is crucial for the development of specific neuronal connections and for neural processing related to learning and memory. In addition, excess entry of Ca^{2+} through NMDA receptors during ischemic disorders of the brain is thought to be responsible for the rapid death of neurons in stroke and hemorrhagic brain disorders (see Clinical Focus Box 3.2).

γ-Aminobutyric Acid and Glycine. The inhibitory amino acid transmitters **γ-aminobutyric acid** (GABA) and **glycine** (GLY) bind to their respective receptors, causing hyperpolar-

CLINICAL FOCUS BOX 3.2

The Role of Glutamate Receptors in Nerve Cell Death in Hypoxic/Ischemic Disorders

Excitatory amino acids (EAA), GLU and ASP, are the neurotransmitters for more than half the total neuronal population of the CNS. Not surprisingly, most neurons in the CNS contain receptors for EAA. When transmission in glutamatergic neurons functions normally, very low concentrations of EAA appear in the synapse at any time, primarily because of the efficient uptake mechanisms of the presynaptic neuron and neighboring glial cells.

In certain pathological states, however, extraneuronal concentrations of EAA exceed the ability of the uptake mechanisms to remove them, resulting in cell death in a matter of minutes. This can be seen in severe **hypoxia,** such as during respiratory or cardiovascular failure, and in **ischemia,** where the blood supply to a region of the brain is interrupted, as in stroke. In either condition, the affected area is deprived of oxygen and glucose, which are essential for normal neuronal functions, including energy-dependent mechanisms for the removal of extracellular EAA and their conversion to glutamine.

The consequences of prolonged exposure of neurons to EAA has been described as **excitotoxicity**. Much of the cytotoxicity can be attributed to the destructive actions of high intracellular calcium brought about by stimulation of the various subtypes of glutamatergic receptors. One subtype, a presynaptic kainate receptor, opens voltage-gated calcium channels and promotes the further release of GLU. Several postsynaptic receptor subtypes depolarize the nerve cell and promote the rise of intracellular calcium via ligand-gated and voltage-gated channels and second messenger-mediated mobilization of intracellular calcium stores. The spiraling consequences of increased extracellular GLU, leading to the further release of GLU, and of increased calcium entry, leading to the further mobilization of intracellular calcium, bring about cell death, resulting from the inability of ischemic/hypoxic conditions to meet the high metabolic demands of excited neurons and the triggering of destructive changes in the cell by increased free calcium.

Intracellular free calcium is an activator of calcium-dependent proteases, which destroy microtubules and other structural proteins that maintain neuronal integrity. Calcium activates phospholipases, which break down membrane phospholipids and lead to lipid peroxidation and the formation of oxygen-free radicals, which are toxic to cells. Another consequence of activated phospholipase is the formation of arachidonic acid and metabolites, including prostaglandins, some of which constrict blood vessels and further exacerbate hypoxia/ischemia. Calcium activates cellular endonucleases, leading to DNA fragmentation and the destruction of chromatin. In mitochondria, high calcium induces swelling and impaired formation of ATP via the Krebs cycle. Calcium is the primary toxic agent in EAA-induced cytotoxicity.

In addition to calcium, nitric oxide (NO) is known to mediate EAA-induced cytotoxicity. Nitric oxide synthase (NOS) activity is enhanced by NMDA receptor activation. Neurons that exhibit NOS and, therefore, synthesize NO are protected from NO, but NO released from NOS-expressing neurons in response to NMDA receptor activation kills adjacent neurons.

Proposed new treatment strategies promise to enhance survival of neurons in brain ischemic/hypoxic disorders. These therapies include drugs that block specific subtypes of glutamatergic receptors, such as the NMDA receptor, which is most responsible for promoting high calcium levels in the neuron. Other strategies include drugs that destroy oxygen-free radicals, calcium ion channel blocking agents, and NOS antagonists.

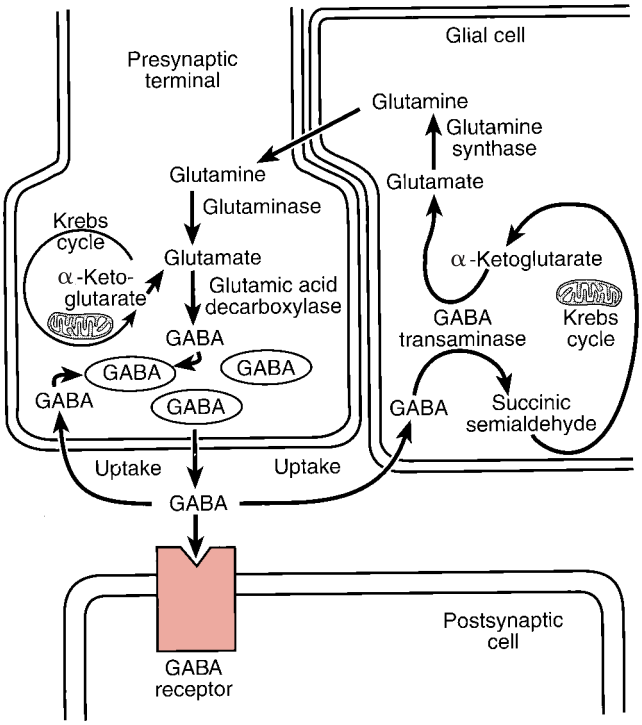


FIGURE 3.22 **GABAergic neurotransmission.** γ-Aminobutyric acid (GABA) is synthesized from glutamate by the enzyme glutamic acid decarboxylase. Upon release into the synaptic cleft, GABA can bind to GABA receptors ($GABA_A$, $GABA_B$). The removal of GABA from the synaptic cleft is primarily by uptake into the presynaptic neuron and surrounding glial cells. The conversion of GABA to succinic semialdehyde is coupled to the conversion of α-ketoglutarate to glutamate by the enzyme GABA-transaminase. In glia, glutamate is converted into glutamine, which is transported back into the presynaptic terminal for synthesis into GABA.

ization of the postsynaptic membrane. **GABAergic neurons** represent the major inhibitory neurons of the CNS, whereas **glycinergic neurons** are found in limited numbers, restricted only to the spinal cord and brainstem. Glycinergic transmission has not been as well characterized as transmission using GABA; therefore, only GABA will be discussed here.

The synthesis of GABA in neurons is by decarboxylation of GLU by the enzyme glutamic acid decarboxylase, a marker of GABAergic neurons. GABA is stored in vesicles and released by exocytosis, leading to the stimulation of postsynaptic receptors (Fig. 3.22).

There are two types of GABA receptors: $GABA_A$ and $GABA_B$. The **$GABA_A$ receptor** is a ligand-gated Cl^- channel, and its activation produces IPSPs by increasing the influx of Cl^- ions. The increase in Cl^- conductance is facilitated by **benzodiazepines,** drugs that are widely used to treat anxiety. Activation of the **$GABA_B$ receptor** also produces IPSPs, but the IPSP results from an increase in K^+ conductance via the activation of a G protein. Drugs that inhibit GABA transmission cause seizures, indicating a major role for inhibitory mechanisms in normal brain function.

GABA is removed from the synaptic cleft by transport into the presynaptic terminal and glial cells (astrocytes) (Fig. 3.22). The GABA enters the Krebs cycle in both neuronal and glial mitochondria and is converted to succinic semialdehyde by the enzyme GABA-transaminase. This enzyme is also coupled to the conversion of α-ketoglutarate to glutamate. The glutamate produced in the glial cell is converted to glutamine. As in the recycling of glutamate, glutamine is transported into the presynaptic terminal, where it is converted into glutamate.

Neuropeptides. Neurally active peptides are stored in synaptic vesicles and undergo exocytotic release in common with other neurotransmitters. Many times, vesicles containing neuropeptides are colocalized with vesicles containing another transmitter in the same neuron, and both can be shown to be released during nerve stimulation. In these colocalization instances, release of the peptide-containing vesicles generally occurs at higher stimulation frequencies than release of the vesicles containing nonpeptide neurotransmitters.

The list of candidate peptide transmitters continues to grow; it includes well-known gastrointestinal hormones, pituitary hormones, and hypothalamic-releasing factors. As a class, the neuropeptides fall into several families of peptides, based on their origins, homologies in amino acid composition, and similarities in the response they elicit at common or related receptors. Table 3.2 lists some members of each of these families.

TABLE 3.2 **Some Recognized Neuropeptide Neurotransmitters**

Neuropeptide	Amino Acid Composition
Opioids	
Met-enkephalin	Tyr-Gly-Gly-Phe-Met-OH
Leu-enkephalin	Tyr-Gly-Gly-Phe-Leu-OH
Dynorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile
β-Endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-His-Lys-Gly-Gln-OH
Gastrointestinal peptides	
Cholecystokinin octapeptide (CCK-8)	Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2
Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met
Vasoactive intestinal peptide	His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH_2
Hypothalamic and pituitary peptides	
Thyrotropin-releasing hormone (TRH)	Pyro-Glu-His-Pro-NH_2
Somatostatin	Ala-Gly-Cys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys
Luteinizing hormone-releasing hormone (LHRH)	Pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly
Vasopressin	Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2
Oxytocin	Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2

Peptides are synthesized as large prepropeptides in the endoplasmic reticulum and are packaged into vesicles that reach the axon terminal by **axoplasmic transport.** While in transit, the prepropeptide in the vesicle is posttranslationally modified by proteases that split it into small peptides and by other enzymes that alter the peptides by hydroxylation, amidation, sulfation, and so on. The products released by exocytosis include a neurally active peptide fragment, as well as many unidentified peptides and enzymes from within the vesicles.

The most common removal mechanism for synaptically released peptides appears to be diffusion, a slow process that ensures a longer-lasting action of the peptide in the synapse and in the extracellular fluid surrounding it. Peptides are degraded by proteases in the extracellular space; some of this degradation may occur within the synaptic cleft. There are no mechanisms for the recycling of peptide transmitters at the axon terminal, unlike more classical transmitters, for which the mechanisms for recycling, including synthesis, storage, reuptake, and release, are contained within the terminals. Accordingly, classical transmitters do not exhaust their supply, whereas peptide transmitters can be depleted in the axon terminal unless replenished by a steady supply of new vesicles transported from the soma.

Peptides can interact with specific peptide receptors located on postsynaptic target cells and, in this sense, are considered to be true neurotransmitters. However, peptides can also modify the response of a coreleased transmitter interacting with its own receptor in the synapse. In this case, the peptide is said to be a **modulator** of the actions of other neurotransmitters.

Opioids are peptides that bind to opiate receptors. They appear to be involved in the control of pain information. Opioid peptides include met-enkephalin, leu-enkephalin, dynorphins, and β-endorphin. Structurally, they share homologous regions consisting of the amino acid sequence Tyr-Gly-Gly-Phe. There are several opioid receptor subtypes: β-endorphin binds preferentially to **μ receptors**, enkephalins bind preferentially to **μ** and **δ receptors;** and dynorphin binds preferentially to **κ receptors**.

Originally isolated in the 1930s, **substance P** was found to have the properties of a neurotransmitter four decades later. Substance P is a polypeptide consisting of 11 amino acids, and is found in high concentrations in the spinal cord and hypothalamus. In the spinal cord, substance P is localized in nerve fibers involved in the transmission of pain information. It slowly depolarizes neurons in the spinal cord and appears to use inositol 1,4,5-trisphosphate as a second messenger. Antagonists that block the action of substance P produce an analgesic effect. The opioid enkephalin also diminishes pain sensation, probably by presynaptically inhibiting the release of substance P.

Many of the other peptides found throughout the CNS were originally discovered in the hypothalamus as part of the neuroendocrine system. Among the hypothalamic peptides, somatostatin has been fairly well characterized in its role as a transmitter. As part of the neuroendocrine system, this peptide inhibits the release of growth hormone by the anterior pituitary (see Chapter 32). About 90% of brain somatostatin, however, is found outside the hypothalamus. Application of somatostatin to target neurons inhibits their electrical activity, but the ionic mechanisms mediating this inhibition are unknown.

Nitric Oxide and Arachidonic Acid. Recently a novel type of neurotransmission has been identified. In this case, membrane-soluble molecules diffuse through neuronal membranes and activate "postsynaptic" cells via second messenger pathways. **Nitric oxide (NO)** is a labile free-radical gas that is synthesized on demand from its precursor, L-arginine, by nitric oxide synthase (NOS). Because NOS activity is exquisitely regulated by Ca^{2+}, the release of NO is calcium-dependent even though it is not packaged into synaptic vesicles.

Nitric oxide was first identified as the substance formed by macrophages that allow them to kill tumor cells. NO was also identified as the endothelial-derived relaxing factor in blood vessels before it was known to be a neurotransmitter. It is a relatively common neurotransmitter in peripheral autonomic pathways and **nitrergic neurons** are also found throughout the brain, where the NO they produce may be involved in damage associated with hypoxia (see Clinical Focus Box 3.2). The effects of NO are mediated through its activation of second messengers, particularly guanylyl cyclase.

Arachidonic acid is a fatty acid released from phospholipids in the membrane when phospholipase A2 is activated by ligand-gated receptors. The arachidonic acid then diffuses retrogradely to affect the presynaptic cell by activating second messenger systems. Nitric oxide can also act in this retrograde fashion as a signaling molecule.

THE MAINTENANCE OF NERVE CELL FUNCTION

Neurons are highly specialized cells and, thus, have unique metabolic needs compared to other cells, particularly with respect to their axonal and dendritic extensions. The axons of some neurons can exceed 1 meter long. Consider the control of toe movement in a tall individual. Neurons in the motor cortex of the brain have axons that must connect with the appropriate motor neurons in the lumbar region of the spinal cord; these motor neurons, in turn, have axons that connect the spinal cord to muscles in the toe. An enormous amount of axonal membrane and intraaxonal material must be supported by the cell bodies of neurons; additionally, a typical motor neuron soma may be only 40 μm in diameter and support a total dendritic arborization of 2 to 5 mm.

Another specialized feature of neurons is their intricate connectivity. Mechanisms must exist to allow the appropriate connections to be made during development.

Proteins Are Synthesized in the Soma of Neurons

The nucleus of a neuron is large, and a substantial portion of the genetic information it contains is continuously transcribed. Based on hybridization studies, it is estimated that one third of the genome in brain cells is actively transcribed, producing more mRNA than any other kind of cell in the

body. Because of the high level of transcriptional activity, the nuclear chromatin is dispersed. In contrast, the chromatin in nonneuronal cells in the brain, such as glial cells, is found in clusters on the internal face of the nuclear membrane.

Most of the proteins formed by free ribosomes and polyribosomes remain within the soma, whereas proteins formed by rough endoplasmic reticulum (rough ER) are exported to the dendrites and the axon. Polyribosomes and rough ER are found predominantly in the soma of neurons. Axons contain no rough ER and are unable to synthesize proteins. The smooth ER is involved in the intracellular storage of calcium. Smooth ER in neurons binds calcium and maintains the intracellular cytoplasmic concentration at a low level, about 10^{-7} M. Prolonged elevation of intracellular calcium leads to neuronal death and degeneration (see Clinical Focus Box 3.2).

The Golgi apparatus in neurons is found only in the soma. As in other types of cells, this structure is engaged in the terminal glycosylation of proteins synthesized in the rough ER. The Golgi apparatus forms export vesicles for proteins produced in the rough ER. These vesicles are released into the cytoplasm, and some are carried by axoplasmic transport to the axon terminals.

The Cytoskeleton Is the Infrastructure for Neuron Form

The transport of proteins from the Golgi apparatus and the highly specialized form of the neuron depend on the internal framework of the cytoskeleton. The neuronal cytoskeleton is made of microfilaments, neurofilaments, and microtubules. **Microfilaments** are composed of actin, a contractile protein also found in muscle. They are 4 to 5 nm in diameter and are found in dendritic spines. **Neurofilaments** are found in both axons and dendrites and are thought to provide structural rigidity. They are not found in the growing tips of axons and dendritic spines, which are more dynamic structures. Neurofilaments are about the size of intermediate filaments found in other types of cells (10 nm in diameter). In other cell types, however, intermediate filaments consist of one protein, whereas neurofilaments are composed of three proteins. The core of neurofilaments consists of a 70 kDa protein, similar to intermediate filaments in other cells. The two other neurofilament proteins are thought to be side arms that interact with microtubules.

Microtubules are responsible for the rapid movement of material in axons and dendrites. They are 23 nm in diameter and are composed of tubulin. In neurons, microtubules have accessory proteins, called **microtubule-associated proteins** (MAPs), thought to be responsible for the specific distribution of material to dendrites or axons.

Mitochondria Are Important for Synaptic Transmission

Mitochondria in neurons are highly concentrated in the region of the axon terminals. They produce ATP, which is required as a source of energy for many cellular processes. In the axon terminal, mitochondria provide both a source of energy for processes associated with synaptic transmission and substrates for the synthesis of certain neurotransmitter chemicals, such as the amino acid glutamate. In addition, mitochondria contain enzymes for degrading neurotransmitter molecules, such as MAO, which degrades catecholamines and 5-HT, and GABA-transaminase, which degrades GABA.

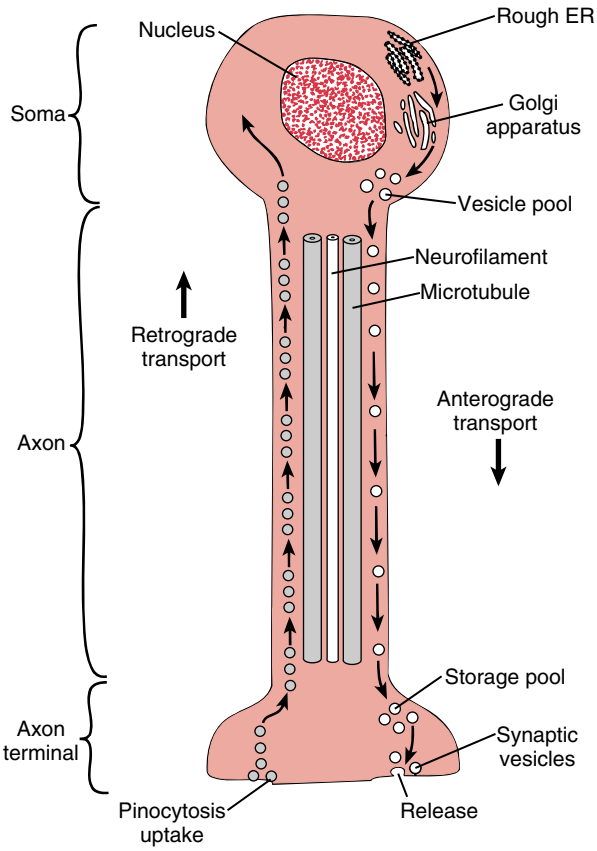


FIGURE 3.23 **Anterograde and retrograde axoplasmic transport.** Transport of molecules in vesicles along microtubules is mediated by kinesin for anterograde transport and by dynein for retrograde transport.

Transport Mechanisms Distribute Material Needed by the Neuron and Its Fiber Processes

The shape of most cells in the body is relatively simple, compared to the complexity of neurons, with their elaborate axons and dendrites. Neurons have mechanisms for transporting the proteins, organelles, and other cellular materials needed for the maintenance of the cell along the length of axons and dendrites. These transport mechanisms are capable of moving cellular components in an **anterograde** direction, away from the soma, or in a **retrograde** direction, toward the soma (Fig. 3.23). **Kinesin,** an MAP, is involved in anterograde transport of organelles and vesicles via the hydrolysis of ATP. Retrograde transport of organelles and vesicles is mediated by **dynein,** another MAP.

In the axon, anterograde transport occurs at both slow and fast rates. The rate of **slow axoplasmic transport** is 1 to 2 mm/day. Structural proteins, such as actin, neurofilaments,

and microtubules, are transported at this speed. Slow axonal transport is rate limiting for the regeneration of axons following neuronal injury. The rate of **fast axoplasmic transport** is about 400 mm/day. Fast transport mechanisms are used for organelles, vesicles, and membrane glycoproteins needed at the axon terminal. In dendrites, anterograde transport occurs at a rate of approximately 0.4 mm/day. Dendritic transport also moves ribosomes and RNA, suggesting that protein synthesis occurs within dendrites.

In retrograde axoplasmic transport, material is moved from terminal endings to the cell body. This provides a mechanism for the cell body to sample the environment around its synaptic terminals. In some neurons, maintenance of synaptic connections depends on the **transneuronal transport** of trophic substances, such as nerve growth factor, across the synapse. After retrograde transport to the soma, nerve growth factor activates mechanisms for protein synthesis.

Nerve Fibers Migrate and Extend During Development and Regeneration

One of the major features that distinguishes differentiation and growth in nerve cells from these processes in other types of cells is the outgrowth of the axon that extends along a specific pathway to form synaptic connections with appropriate targets. Axonal growth is determined largely by interactions between the growing axon and the tissue environment. At the leading edge of a growing axon is the **growth cone**, a flat structure that gives rise to protrusions called **filopodia**. Growth cones contain actin and are motile, with filopodia extending and retracting at a velocity of 6 to 10 μm/min. Newly synthesized membranes in the form of vesicles are also found in the growth cone and fuse with the growth cone as it extends. As the growth cone elongates, microtubules and neurofilaments are added to the distal end of the fiber and partially extend into the growth cone. They are transported to the growth cone by slow axoplasmic transport.

The direction of axonal growth is dictated, in part, by **cell adhesion molecules** (CAMs), plasma membrane glycoproteins that promote cell adhesion. Neuron-glia-CAM (N-CAM) is expressed in postmitotic neurons and is particularly prominent in growing axons and dendrites, which migrate along certain types of glial cells that provide a guiding path to target sites. The secretion of tropic factors by target cells also influences the direction of axon growth. When the proper target site is reached and synaptic connections are formed, the processes of growth cone elongation and migration are terminated.

During the formation and maturation of specific neuronal connections, the initial connections made are more widespread than the final outcome. Some connections are lost, concomitant with a strengthening of other connections. This pruning of connections is a result of a selection process in which the most electrically active inputs predominate and survive and the less active contacts are lost. While the number of connections between different neurons decreases during this process, the total number of synapses increases dramatically as the remaining connections grow stronger.

Growth cones are also present in axons that regenerate following injury. When axons are severed, the distal portion—that is, the portion cut off from the cell body—degenerates. The proximal portion of the axon then develops a growth cone and begins to elongate. The signal to the cell body that injury has occurred is the loss of retrogradely transported signaling molecules normally derived from the axon terminal. The success of neuronal regeneration depends on the severity of the damage, the proximity of the damage to the cell body, and the location of the neurons. Axons in the CNS regenerate less successfully than axons in the PNS. Neurons damaged close to the cell body often die rather than regenerate because so much of their membrane and cytoplasm is lost.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A pharmacological or physiological perturbation that increases the resting P_K/P_{Na} ratio for the plasma membrane of a neuron would
   (A) Lead to depolarization of the cell
   (B) Lead to hyperpolarization of the cell
   (C) Produce no change in the value of the resting membrane potential
2. The afterhyperpolarization phase of the action potential is caused by
   (A) An outward calcium current
   (B) An inward chloride current
   (C) An outward potassium current
   (D) An outward sodium current
3. Saltatory conduction in myelinated axons results from the fact that
   (A) Salt concentration is increased beneath the myelin segments
   (B) Nongated ion channels are present beneath the segments of myelin
   (C) Membrane resistance is decreased beneath the segments of myelin
   (D) Voltage-gated sodium channels are concentrated at the nodes of Ranvier
   (E) Capacitance is decreased at the nodes of Ranvier
4. In individuals with multiple sclerosis, regions of CNS axons lose their myelin sheath. When this happens, the space constant of these unmyelinated regions would
   (A) Not change
   (B) Increase
   (C) Decrease
5. Tetanus toxin and botulinum toxin exert their effects by disrupting the function of SNARES, inhibiting
   (A) Propagation of the action potential
   (B) The function of voltage-gated ion channels
   (C) The docking and binding of synaptic vesicles to the presynaptic membrane
   (D) The binding of transmitter to the postsynaptic receptor
   (E) The reuptake of neurotransmitter by the presynaptic cell
6. What property of the postsynaptic neuron would optimize the effectiveness of two closely spaced axodendritic synapses?
   (A) A high membrane resistance
   (B) A high dendritic cytoplasmic resistance
   (C) A small cross-sectional area

(continued)

(D) A small space constant
(E) A small time constant

7. A gardener was accidentally poisoned by a weed killer that inhibits acetylcholinesterase. Which of the following alterations in neurochemical transmission at brain cholinergic synapses is the most likely result of this poisoning?
(A) Blockade of cholinergic receptors
(B) A pileup of choline outside the cholinergic neuron (in the synaptic cleft)
(C) A pileup of acetylcholine outside the cholinergic neuron (in the synaptic cleft)
(D) Up-regulation of postsynaptic cholinergic receptors
(E) Increased synthesis of choline acetyltransferase
8. The major mode of removal of catecholamines from the synaptic cleft is
(A) Diffusion
(B) Breakdown by MAO
(C) Reuptake by the presynaptic nerve terminal
(D) Breakdown by COMT
(E) Endocytosis by the postsynaptic neuron
9. A patient in the emergency department exhibits psychosis. Pharmacological intervention to decrease the psychosis would most likely involve
(A) Blockade of dopaminergic neurotransmission
(B) Stimulation of dopaminergic neurotransmission
(C) Blockade of nitrergic neurotransmission
(D) Stimulation of nitrergic neurotransmission
(E) Blockade of cholinergic neurotransmission
(F) Stimulation of cholinergic transmission
10. Which class of neurotransmitter would be most affected by a toxin that disrupted microtubules within neurons?
(A) Amino acid transmitters
(B) Catecholamine transmitters
(C) Membrane-soluble transmitters
(D) Peptide transmitters
(E) Second messenger transmitters
11. A teenager in the emergency department exhibits convulsions. The friend who accompanied her indicated that she does not have a seizure disorder. The friend also indicated that the patient had ingested an unknown substance at a party. From her symptoms, you suspect the substance interfered with
(A) Epinephrine receptors
(B) GABA receptors
(C) Nicotinic receptors
(D) Opioid receptors
(E) Serotonin receptors
12. A 45-year-old lawyer complains of nausea, vomiting, and a tingling feeling in his extremities. He had dined on red snapper with a client at a fancy seafood restaurant the night before. His client also became ill with similar symptoms. Which of the following is the most likely cause of his problem?
(A) Chronic demyelinating disorder
(B) Ingestion of a toxin that activates sodium channels
(C) Ingestion of a toxin that blocks sodium channels
(D) Ingestion of a toxin that blocks nerve-muscle transmission
(E) Cerebral infarct (stroke)
13. A summated (compound) action potential is recorded from the affected peripheral nerve of a patient with a demyelinating disorder. Compared to a recording from a normal nerve, the recording from the patient will have a
(A) Greater amplitude
(B) Increased rate of rise
(C) Lower conduction velocity
(D) Shorter duration afterhyperpolarization
14. A syndrome of muscle weakness associated with certain types of lung cancer is caused by antibodies against components of the cancer plasma membrane that cross-react with voltage-gated calcium channels. The interaction of the antibodies impairs ion channel opening and would likely cause
(A) Decreased nerve conduction velocity
(B) Delayed repolarization of axon membranes
(C) Impaired release of acetylcholine from motor nerve terminals
(D) More rapid upstroke of the nerve action potential
(E) Repetitive nerve firing

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CASE STUDIES FOR PART I • • •

Case Study for Chapter 1

Severe, Acute Diarrhea

A 29-year-old woman had spent the past 2 weeks visiting her family in southern Louisiana. On the last night of her visit, she consumed a dozen fresh oysters. Twenty-four hours later, following her return home, she awoke with nausea, vomiting, abdominal pain, and profuse watery diarrhea. She went into shock and was transported to the emergency department, where she was found to be dehydrated and lethargic. She does not have an elevated temperature, but her abdomen is distended. There is no tenderness to the abdomen, and her bowel sounds are hyperactive. Laboratory results show she is hypokalemic, with a plasma potassium level of 1.4 mEq/L (normal values, 3.5 to 5.0 mEq/L). Plasma sodium and chloride levels are slightly lower than normal, and plasma bicarbonate is 11 mEq/L (normal values, 22 to 28 mEq/L). After oral rehydration and antibiotic therapy, she rapidly improves and is discharged on the fourth hospital day.

Questions

1. What disease is consistent with this patient's symptoms?
2. Describe the pathophysiology associated with this disease.

Answers to Case Study Questions for Chapter 1

1. The disease consistent with the symptoms of this patient is cholera. Cholera is a self-limiting disease characterized by acute diarrhea and dehydration without febrile symptoms (no fever). The microorganism responsible for this disease is *Vibrio cholerae*. The ingestion of water or food that has been contaminated with feces or vomitus of an individual transmits the bacterium, causing the disease.
2. The pathophysiology associated with this disease is related to the production of a toxin by the *V. cholerae* bacterium. The toxin has two subunits (α and β). The α subunit causes the activation of adenylyl cyclase (AC) and the β subunit recognizes and binds to an apical (facing the lumen of the intestine) membrane component of intestinal epithelial cells, causing the toxin to become engulfed into the cell. Inside the cell, the toxin is transported to the basolateral membrane, where the α subunit ADP-ribosylates the G_s protein. ADP-ribosylation of G_s results in inhibition of the GTPase activity of the G_s subunit and the stabilization of the G protein in an active or "on" conformation. The continuous stimulation of AC and concomitant sustained production of cAMP result in opening of a chloride channel in the apical plasma membrane. This produces net chloride secretion, with sodium and water following. Bicarbonate and potassium ions are also lost in the stool. The loss of water and electrolytes in diarrheal fluid can be so severe (20 L/day) that it may be fatal.

Case Study for Chapter 2

Cystic Fibrosis

A 12-month-old baby is brought to a pediatrician's office because the parents are concerned about a recurrent cough and frequent foul-smelling stools. The doctor has followed the child from birth and notices that the baby's weight has remained below the normal range. A chest X-ray reveals hyperinflation consistent with the obstruction of small airways.

Questions

1. What is the explanation for the frequent stools and poor growth?
2. What is causing obstruction of the small airways?
3. What is the fundamental defect at the molecular level that underlies these symptoms?

Answers to Case Study Questions for Chapter 2

1. Impaired secretion of chloride ions by epithelial cells of pancreatic ducts limits the function of a Cl^-/HCO_3^- exchanger to secrete bicarbonate. Secretion of Na^+ is also impaired, and the resultant failure to secrete $NaHCO_3$ retards water movement into the ducts. Mucus in the ducts becomes dehydrated and thick and blocks the delivery of pancreatic enzymes. The deficiency of pancreatic enzymes in the intestinal lumen leads to malabsorption of protein and fats, hence, the malnutrition and frequent malodorous stools.
2. An analogous mechanism in the epithelial cells of small airways results in reduced secretion of NaCl and retardation of water movement. The dehydrated mucus cannot be cleared from the small airways and not only obstructs them but also traps bacteria that initiate localized infections.
3. The defect in chloride transport is a result of mutations in the gene for the chloride channel known as the **cystic fibrosis transmembrane regulator** (CFTR). Some mutated forms of the CFTR protein are destroyed in the epithelial cell before they reach the apical plasma membrane; other mutations result in a CFTR protein that is inserted in the plasma membrane but functions abnormally.

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Case Study for Chapter 3

Episodic Ataxia

A 3-year-old child was brought to the pediatrician because of visible muscle twitching. The parents described the twitches as looking like worms crawling under the skin. The child also periodically complained that her legs hurt, and the mother reported she could feel that the child's leg muscles were somewhat rigid at these times. Occasionally, the child would exhibit a loss of motor coordination (ataxia) that lasted 20 to 30 minutes; these episodes sometimes followed exertion or startle. Neurological function seemed normal between these episodes; the parents reported that the child's motor development seemed similar to that of their older child. The neurological examination confirms the parents' perception. Electromyographic analysis of the child's leg muscles indicate no abnormality in muscle membrane responses and a muscle biopsy is histologically normal. Spinal anesthesia eliminated the muscle twitching. The child's mother indicates that one of the child's sisters also had frequent muscle twitches as a child, but did not have episodes of ataxia.

Questions

1. What is the likely source of the abnormal muscle activity?
2. What information in the presentation supports your answer to question 1?
3. Spontaneous muscle twitches indicate hyperexcitability of nerve or muscle. If this hyperexcitability is a result of an abnormality in action potential repolarization, what channels associated with the nerve action potential might lead to this condition?

Answers to Case Study Questions for Chapter 3

1. The abnormal muscle activity derives from the motor neurons.
2. Spontaneous muscle twitching could be a result of a defect in the muscle, the motor neurons that control the muscle, the neuromuscular junction (synapse), or the central nervous system elements that control spinal motor neurons. The description of muscle twitches that look like worms crawling under the skin indicates that individual motor units are firing randomly and spontaneously. (A motor unit is one motor neuron and all of the muscle fibers it innervates.) The muscle biopsy and electromyographic studies indicate it is not the muscle. Spinal anesthesia eliminates the muscle twitching indicating that the defect is at the level of the motor neurons.
3. The nerve action potential may fail to repolarize properly if there is a defect in the inactivation of voltage-gated sodium channels or in the activation of voltage-gated potassium channels. Genetic analysis in this individual, whose diagnosis is episodic ataxia with myokymia, would indicate a mutation in the potassium channel.

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