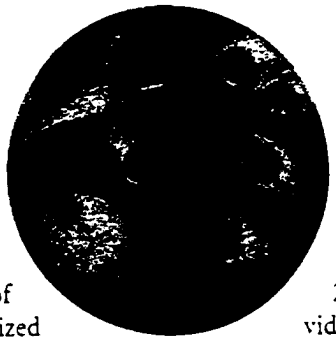
CHAPTER

22

SIGNAL TRANSDUCTION MECHANISMS: I. ELECTRICAL SIGNALS IN NERVE CELLS



In the previous chapter we saw how studies of cytoskeletal structures in muscle cells led to a more general understanding of the molecular mechanisms of motility. This underscores an important principle in biological research: Cellular functions are often best studied in cells that are highly specialized for the function of interest. In the first part of this chapter, we will again be looking at specialized cell functions, but this time in nerve cells. Virtually all cells maintain electrical potentials across their plasma membranes, but nerve cells have special mechanisms for using this potential to transmit information over long distances.

In the second part of the chapter, we will discuss the process by which information is passed between cells in the nervous system. The communication of information always involves at least two components: the sender and the receiver. In the nervous system, the *sender* is a nerve cell or sensory cell, and the *receiver* is a second nerve cell, a gland, or a muscle cell. We will see that nerve cells use specialized processes to deliver information across their junctions with other cells. Such information may be transmitted by direct electrical connection, but more often the process of transmission involves the exocytotic release of chemical *neurotransmitters* at the junction, followed by binding of the neurotransmitters to *receptors* on the plasma membrane of the second cell. Our knowledge of neurotransmitters enables us to understand how pharmaceutical agents interact with the brain and how certain highly toxic compounds affect the nervous system.

The Nervous System

Every animal has a **nervous system,** in which electrical impulses are transmitted along the specialized plasma membranes of nerve cells. The nervous system performs three functions: It *collects* information from the environment ("the light just turned green"), it *processes* that information ("green means go"), and it *elicits responses* to that information by triggering specific effectors, usually muscle tissue or glands ("push on the accelerator").

To accomplish these functions, the nervous system has special components for sensing and processing information and for triggering the appropriate response (Figure 22-1). In vertebrates, the nervous system is divided into two components, the central nervous system and the peripheral nervous system. The **central nervous system (CNS)** consists of the brain and the spinal cord, including both sensory and motor cells; the **peripheral nervous system (PNS)** consists of all other sensory and motor components, including the somatic nervous system and the autonomic nervous system. The **somatic nervous system** controls voluntary movements of skeletal muscles, whereas the **autonomic nervous system** controls the involuntary activities of cardiac muscle, the smooth muscles of the gastrointestinal tract and blood vessels, and a variety of secretory glands.

Cells that make up the nervous system can be broadly divided into two groups: *neurons* or *nerve cells,* and *glial cells.* **Neurons** can be subdivided into three basic types based on function: sensory neurons, motor neurons, and interneurons. **Sensory neurons** are a diverse group of cells specialized for the detection of various types of stimuli. Examples of sensory neurons include the photoreceptors of the retina, olfactory neurons, and the various touch, pressure, pain, and temperature-sensitive neurons located in the skin or joints. Sensory neurons provide a continuous stream of information to the brain about the state of the body and its environment. **Motor neurons** transmit signals from the CNS to muscles or glands, and **interneurons** process signals received from other neurons and relay the information to other parts of the nervous system.

The term **glial cell** (from *glia,* the Greek word for "glue") encompasses a variety of different cell types, including microglia, oligodendrocytes, Schwann cells, and astrocytes. *Microglia* are phagocytic cells that fight infections and remove debris. *Oligodendrocytes* and *Schwann cells* form the

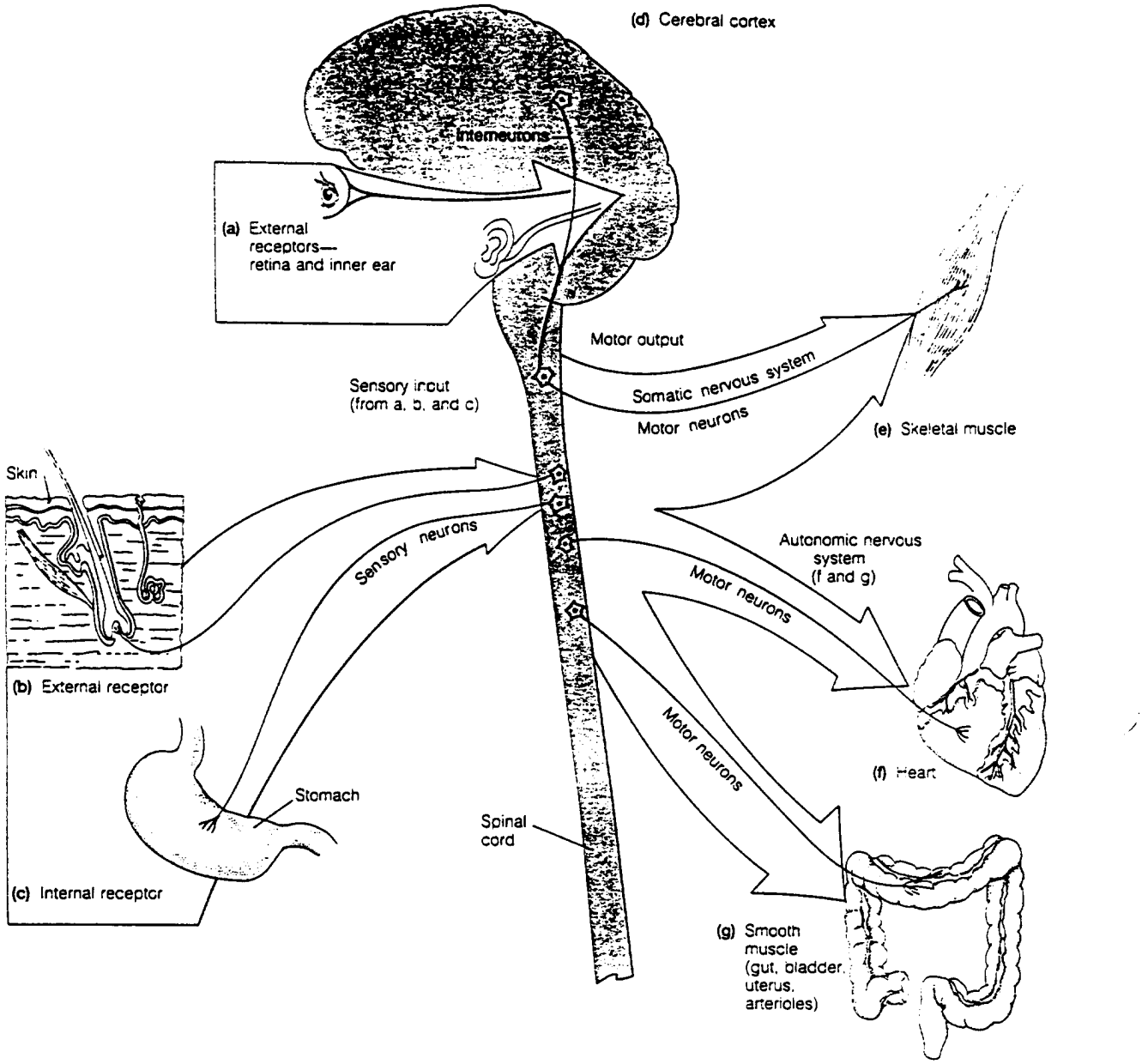


Figure 22-1 The Vertebrate Nervous System. The nervous system consists of the central nervous system (gray) and the peripheral nervous system (yellow). The sensory neurons of the peripheral nervous system receive information from **(a, b, c)** external and internal receptors and transmit it to the CNS. Interneurons in the CNS integrate and coordinate response to the sensory input, a primary example being **(d)** cerebral cortical neurons. Motor responses originate in the CNS and are transmitted to **(e)** skeletal muscles by neurons of the somatic nervous system and to **(f, g)** involuntary muscles and glands by means of the autonomic nervous system.

myelin sheath around neurons of the CNS and those of the peripheral nerves, respectively. The function of the *astrocytes* is still obscure but may involve the maintenance of the potassium concentration in the extracellular fluid surrounding nerves and blood vessels.

Intricate networks of neurons make up the complex tissues of the brain that are responsible for coordinating nervous function. About 10 billion nerve cell bodies are involved in the networks, which sometimes form layers of tissue. Each neuron receives input from thousands of other neurons, so the brain's connections easily number in the trillions. By comparison, computers do not even come close to this number of connections, despite their seeming complexity (Figure 22-2).

Like data in a computer, however, neural information does consist of individual "bits," or *signals*. Our purpose here is not to discuss the overall functioning of the nervous system, but to focus on cellular mechanisms by which the

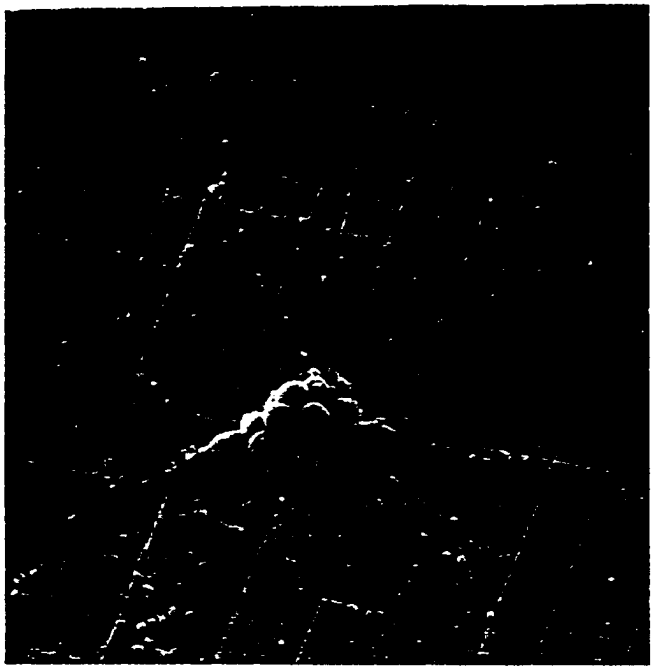


Figure 22-2 A Neuron on a Microprocessor. This micrograph shows a neuron growing on top of a Motorola 68000 microprocessor chip. The neuron is the fundamental information-processing unit of the brain, which might be compared to the transistor as the fundamental processing unit in the computer. However, the brain has 15 billion neurons, whereas microprocessors may have up to a few million transistors (SEM).

series of electrical signals called *nerve impulses* are spread. In addition to understanding the functions of nerve cells specifically, we will also acquire a better appreciation for several general aspects of membrane function, of which nerve cells are a specialized example.

The Structure of a Neuron

The structure of a typical motor neuron is shown in Figure 22-3. The **cell body** of most neurons is similar to that of other cells, consisting of a nucleus and most of the same organelles. In addition, however, neurons contain extensions, or branches, called **processes.** These processes make neurons easy to distinguish from almost any other cell type. There are two types of processes: Those that receive signals and transmit them inward to the cell body are called **dendrites,** and those that conduct signals away from the cell body are called **axons.** The cytoplasm within an axon is commonly referred to as **axoplasm.** A **nerve** is simply a tissue composed of bundles of axons.

Neurons display more structural variability than Figure 22-3 suggests. Some sensory neurons have only one process, which conducts signals both toward and away from the cell body. Moreover, the structure of the dendritic processes is not random; many different classes of neurons in the central

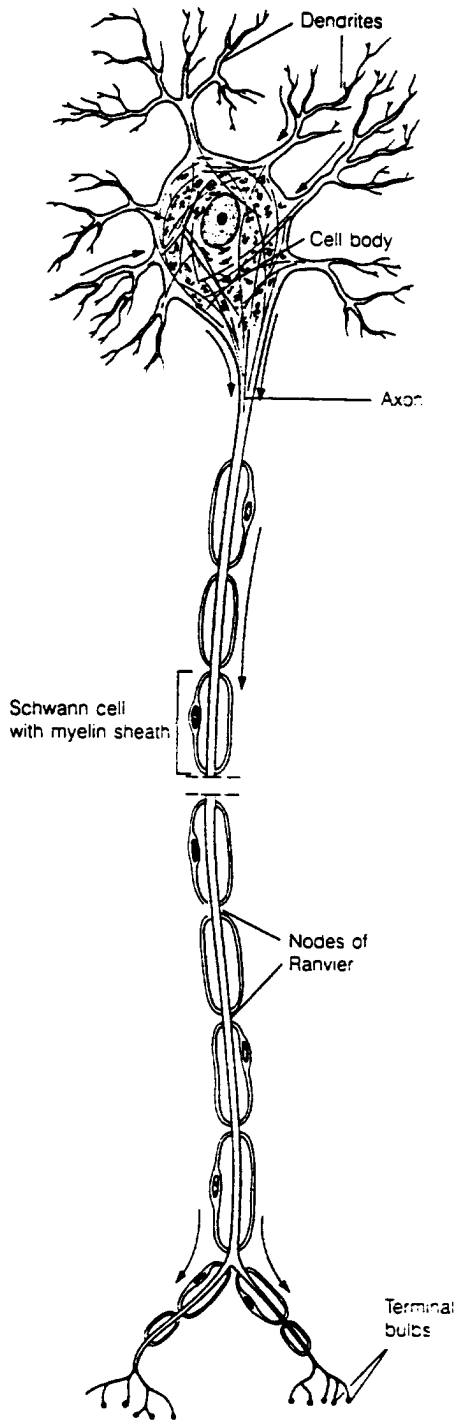


Figure 22-3 The Structure of a Typical Motor Neuron. The cell body contains the nucleus and most of the usual organelles. Dendrites conduct signals passively inward to the cell body, whereas the axon transmits signals actively outward (the direction of transmission is shown by black arrows). At the end of the axon are numerous terminal bulbs. Some, although not all, neurons have a discontinuous myelin sheath around their axons to insulate them electrically. Each segment of the sheath consists of a concentric layer of membranes wrapped around the axon by a Schwann cell (or an oligodendrocyte, in the CNS). The breaks in the myelin sheath, called nodes of Ranvier, are concentrated regions of electrical activity.

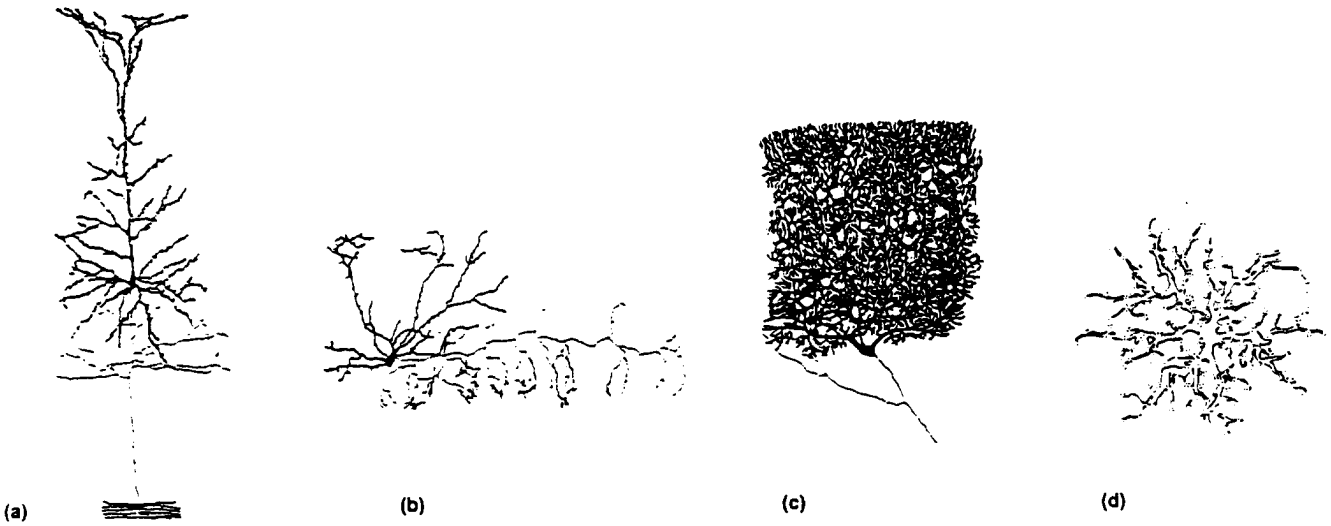


Figure 22-4 Neuron Shapes. Neurons of the central nervous system display a wide variety of characteristic shapes. Axons are shown in pink and dendrites in black. **(a)** A pyramidal neuron from the cerebral cortex. **(b)** Several short-axon cells in the cerebral cortex. **(c)** A Purkinje cell in the cerebellum. **(d)** An axonless horizontal cell in the retina of the eye.

nervous system can be identified by structure alone (Figure 22-4).

As Figure 22-3 illustrates, a motor neuron has multiple, branched dendrites and a single axon leading away from the cell body. The axon of a typical neuron is much longer than the dendrites and forms multiple branches. Each branch terminates in structures called **terminal bulbs,** also known as *synaptic knobs* or *axon terminals.* The terminal bulbs are responsible for transmitting the signal to the next cell, which may be another neuron or a muscle or gland cell. In each case, the junction is called a **synapse.** For neuron-to-neuron junctions, synapses may occur between an axon and a dendrite, between a dendrite and a dendrite, between an axon and a cell body, or even between an axon and an axon. Typically, neurons have synapses with many other neurons.

Axons can be very long—up to several thousand times longer than the diameter of the cell body. For example, a motor neuron that innervates your foot has its cell body in your spinal cord, and its axon extends approximately a meter down a nerve tract in your leg!

The Myelin Sheath

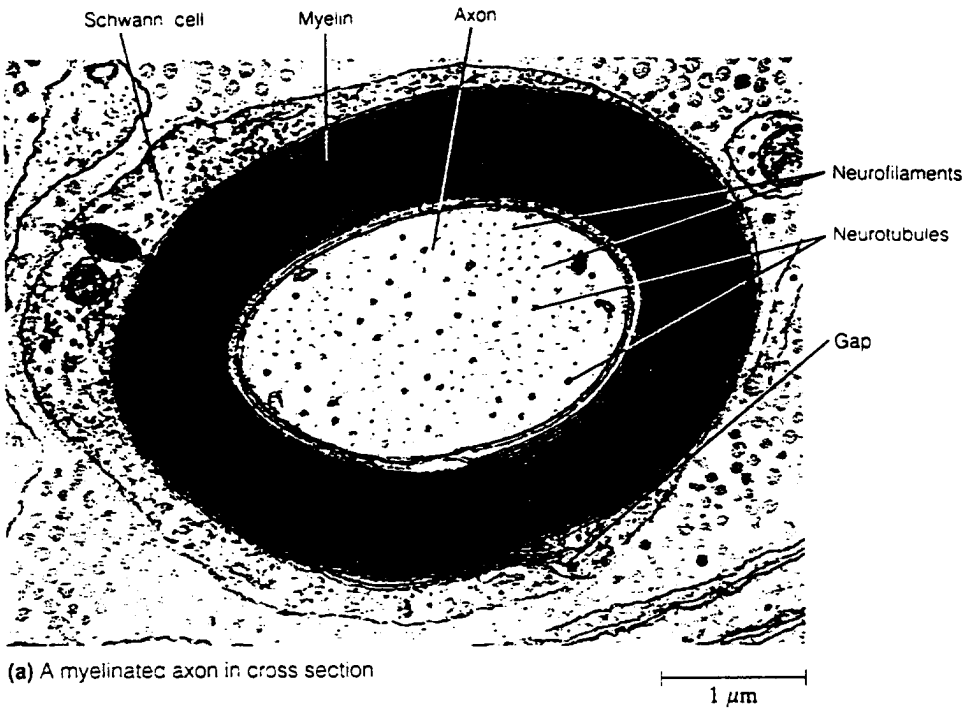
Most axons are surrounded by a discontinuous **myelin sheath** consisting of many concentric layers of membrane. The myelin sheath is a very effective electrical insulation for the segments of the axon that it envelops. As noted, the myelin sheath of neurons in the CNS is formed by **oligodendrocytes,** whereas in the PNS it is formed by **Schwann cells.** Figure 22-5a shows a cross section of a myelinated nerve axon in the peripheral nervous system, and Figure 22-5b illustrates the process of myelination. A Schwann cell envelops an axon and wraps layer after layer of its own plasma membrane around the axon in a tight spiral.

Each Schwann cell is responsible for the myelin sheath around a short segment (about 1 mm) of a single axon. Numerous Schwann cells are therefore required to encase a PNS axon with discontinuous sheaths of myelin. In the CNS, however, a single oligodendrocyte myelinates many axons. The small regions of bare axon between successive segments of the myelin sheath are called **nodes of Ranvier** (see Figure 22-3). These nodes are only about 2 μm long, but they are concentrated regions of electrical activity and therefore play an important role in the transmission of signals, as we shall see shortly.

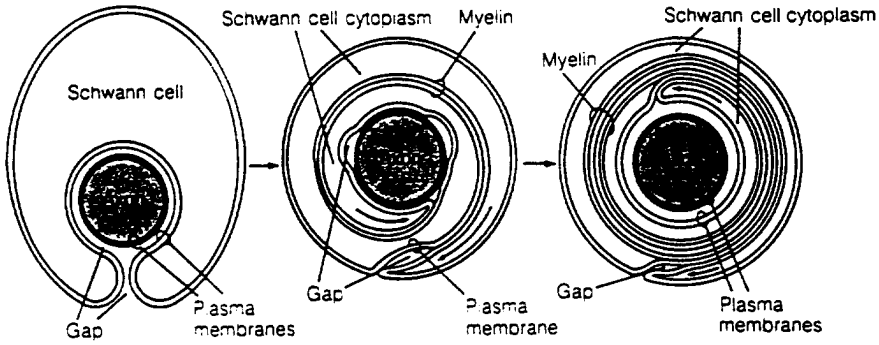
Electrical Properties of Neurons

A **membrane potential** is a fundamental property of essentially all cells. It results from an excess of negative charge on one side of the plasma membrane and an excess of positive charge on the other side. Cells at rest normally have an excess of negative charge inside and an excess of positive charge outside the cell; this is called the **resting membrane potential** (V_m). The resting membrane potential can be measured by placing one tiny electrode inside the cell and another outside the cell. The electrodes compare the ratio of negative to positive charge inside the cell and outside the cell. Because the inside of a cell typically has an excess of negative charge, we say that the cell has a *negative resting membrane potential.* Cell membrane potentials are measured in millivolts (mV).

Nerve, muscle, and certain other cell types such as the islet cells of the pancreas and cells of a water plant called *Nitella* exhibit a special property called **electrical excitability.** In electrically excitable cells, certain types of stimuli



(a) A myelinated axon in cross section



(b) The process of axon myelination

Figure 22-5 Myelination of Axons. **(a)** This cross-sectional view of a myelinated axon from the nervous system of a cat shows the concentric layers of unit membrane that have been wrapped around the axon by the Schwann cell that envelops it. The gap in the plasma membrane of the Schwann cell is the point at which the membrane initially invaginated to begin enveloping the axon. Notice also the neurotubules and neurofilaments in the axoplasm of the myelinated axon. (TEM) **(b)** An axon of the peripheral nervous system being myelinated by a Schwann cell. Each Schwann cell gives rise to one segment of myelin sheath by wrapping its own plasma membrane concentrically around the axon. The myelin layer gets progressively thicker as more layers of unit membrane derived from the plasma membrane of the Schwann cell are added to it, accompanied by the gradual loss of the Schwann cell cytoplasm.

trigger a rapid sequence of changes in the membrane potential known as an *action potential.* During an action potential, the membrane potential changes from negative values to positive values and then back to negative values again, all in little over a millisecond. In nerve cells, the action potential has the specific function of transmitting an electrical signal along the axon.

Understanding Membrane Potentials

To understand how nerve cells use action potentials to transmit signals, we must first comprehend how cells generate a resting membrane potential and how the membrane potential changes during an action potential. Then we will examine how an action potential conveys a signal from one neuron to another.

The Resting Membrane Potential

The resting membrane potential develops because the cytosol of the cell and the extracellular fluid contain different compositions of cations and anions. Extracellular fluid is a watery solution of salts, including sodium chloride and lesser amounts of potassium chloride. The cytosol contains potassium rather than sodium as its main cation because of the action of the sodium-potassium pump (described in Chapter 8). The anions in the cytosol consist largely of macromolecules such as proteins, RNA, and a variety of other molecules that are not present outside the cell. These negatively charged macromolecules cannot pass through the cell membrane and therefore remain inside the cell. The presence of impermeable anions in the cytosol is the main reason that cells develop a resting membrane potential.

To understand how a membrane potential forms, we need to recall a few basic physical principles. First, all sub-

stances tend to diffuse from a higher concentration to a lower concentration. Cells normally have a high concentration of potassium ions inside and a low concentration of potassium ions outside. We refer to this uneven distribution of potassium ions as a *potassium ion gradient.* By convention, the potassium ion gradient is expressed as the molar concentration of potassium ions outside the cell ($[K^-]_{outside}$) divided by the molar concentration of potassium in the cytoplasm ($[K^-]_{inside}$), or $[K^-]_{outside}/[K^-]_{inside}$. Given the large potassium concentration gradient, potassium ions will tend to diffuse out of the cell.

The second basic principle is that of *electroneutrality.* When ions are in solution, they are always present in pairs, one positive ion for each negative ion, so that there is no charge imbalance. For any given ion, which we will call A, there must be an oppositely charged ion B in the solution; therefore, we can refer to B as the *counterion* for A. In the cytosol, potassium ions (K^-) serve as the counterions for the trapped anions. Outside the cell, sodium (Na^-) is the main cation and chloride (Cl^-) is the counterion.

Although a solution must have an equal number of positive and negative charges overall, these charges can be locally separated so that one region has more positive charges while another region has more negative charges. Because it takes work to separate charges, once they have been separated, they tend to move back toward each other. The tendency of oppositely charged ions to flow back toward each other is called a **potential** or **voltage.** When negative or positive ions are actually moving, one toward the other, we say that current is flowing, and this current is measured in amperes (A). Given these principles, we can understand how a resting membrane potential will form as a result of the ionic compositions of the cytosol and the extracellular fluid, and the characteristics of the plasma membrane.

The plasma membrane is normally permeable to potassium because it contains what are commonly known as *potassium leak channels,* which permit potassium ions to diffuse out of the cell. However, there are no channels for negatively charged macromolecules. As potassium leaves the cytosol, increasing numbers of trapped anions are left behind without counterions. Excess negative charge therefore accumulates in the cytosol and excess positive charge accumulates on the outside of the cell, resulting in a membrane potential.

The formation of a membrane potential is illustrated in Figure 22-6, using a container subdivided into two compartments by a semipermeable membrane. The left compartment represents the cytosol of the cell and the right side the extracellular fluid. The semipermeable membrane is permeable to potassium ions but not to negatively charged macromolecules (represented as M^-). The cytosolic compartment contains a mixture of potassium ions and negatively charged macromolecules. For simplicity, we will assume that the extracellular compartment starts with nothing but water.

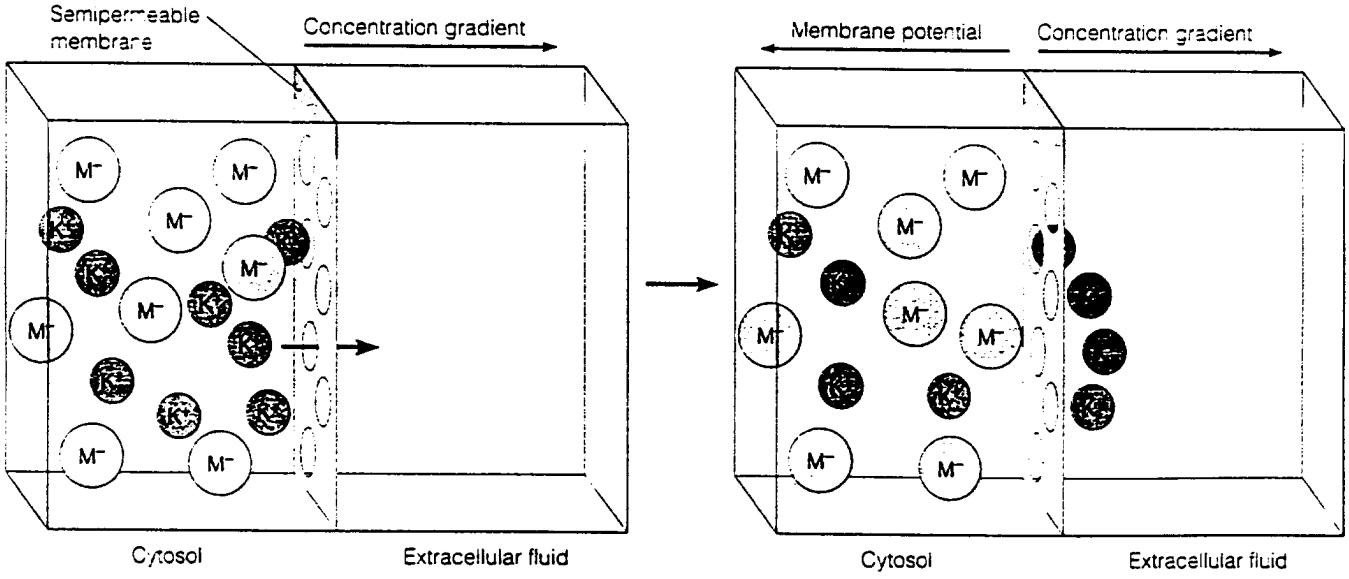


Figure 22-6 Development of the Equilibrium Membrane Potential. A two-compartment container is used to represent a cell, with a semipermeable membrane separating the compartments. In each container, the left-hand compartment represents the cytosol, and the right-hand compartment represents the extracellular fluid. The cytosol contains a high concentration of potassium ions (K^+) and impermeable anions (M^-) relative to their concentrations in the extracellular fluid. As potassium ions diffuse out of the cell (from left to right), the impermeable anions are left behind, creating a membrane potential. The magnitude of the membrane potential increases until an equilibrium is reached in which the electrical attraction of the anions for potassium ions prevents any further net diffusion of potassium ions out of the cell. At this point the membrane potential is in equilibrium with the potassium ion gradient.

Under the pressure of a concentration gradient, potassium ions diffuse across the membrane from the left side to the right side. However, the negatively charged macromolecules are not free to follow. The result is an accumulation of anions on the left side and of cations on the right side. A membrane potential is created by a separation of negative charge from positive charge. The source of work (defined here as force × distance) needed to produce this charge separation is the potassium ion gradient.

Eventually, the membrane potential becomes great enough to prevent further net diffusion of potassium ions across the membrane. As potassium ions diffuse from left to right in Figure 22-6, the left compartment becomes increasingly more negative. This potential ultimately builds to a point at which the positively charged potassium ions are pulled back into the left compartment as fast as they leave. In this way, an equilibrium is reached in which the force of attraction due to the membrane potential balances the tendency of potassium to diffuse down its concentration gradient. This type of equilibrium, in which a chemical gradient is balanced with an electrical potential, is referred to as an **electrochemical equilibrium.** The membrane potential at the point of equilibrium is known as an **equilibrium membrane potential.**

We have seen that the formation of a membrane potential is an important consequence of the potassium ion gradient when potassium ions are free to diffuse out of the cell while anions remain trapped inside. The potassium ion gradient did the work needed to separate negative and positive charges, resulting in an equilibrium membrane potential. Therefore, the magnitude of the potassium ion gradient is related to the magnitude of the equilibrium membrane potential. The Nernst equation provides a mathematical description of this relationship and enables us to estimate the membrane potential.

The Nernst Equation

The **Nernst equation** describes the mathematical relationship between an ion gradient and the equilibrium membrane potential that will form when the membrane is permeable only to that ion:

$$E_X = RT/zF \ln [X]_{outside}/[X]_{inside} \qquad (22\text{–}1)$$

where E_X is the equilibrium membrane potential for ion X (in volts), R is the gas constant (1.987 cal/mol-degree), T is the absolute temperature in kelvin units, z is the valence of the ion, F is the Faraday constant (23,062 cal/V-mol), $[X]_{outside}$ is the concentration of X outside the cell (in M), and X_{inside} is the concentration of X inside the cell (in M). This equation can be simplified if we assume a temperature of 18°C (a value appropriate for marine organisms) and that X is a monovalent cation and therefore has a valence of +1. By substituting into the equation the values for R, T, F, and z and converting from natural logs to $\log_{10}$ ($\log_{10} = 2.3 \ln$) for illustration purposes, the equation reduces to:

$$E_X = 0.058 \log_{10} [X]_{outside}/[X]_{inside} \qquad (22\text{–}2)$$

In this simplified form we can see that for every tenfold increase in the cation gradient, the membrane potential changes by −0.058 V, or −58 mV. This relationship is shown in Figure 22-7 for potassium ions ($X = K^+$).

Diffusible Anions and the Donnan Equilibrium. Figure 22-6 explains the formation of the membrane potential but is incomplete, mainly because it does not take into account diffusible anions that are present on both sides of the membrane. The main anion in the extracellular fluid is chloride, to which the cell membrane is relatively permeable. Now we need to examine how the presence of impermeable anions in the cytosol forces potassium ions and chloride ions to distribute unequally between the cytosol and the extracellular fluid. This unequal distribution is referred to as **Donnan equilibrium,** based on its original description by Frederick Donnan in 1911.

To illustrate how chloride ions distribute between the inside and outside of the cell, we will return to our two-

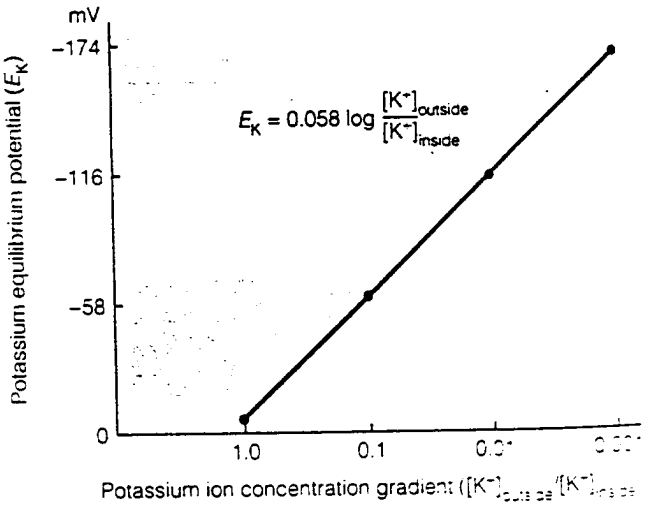


Figure 22-7 The Relationship Between the Potassium Ion Gradient and the Equilibrium Membrane Potential. The Nernst equation was used to calculate equilibrium membrane potential for tenfold changes in the potassium ion concentration gradient across the membrane. By convention, the potassium ion gradient is expressed as the ratio of $[K^+]$ outside the cell to $[K^+]$ inside the cell, or $[K^+]_{outside}/[K^+]_{inside}$. When the ratio is expressed this way, increasing potassium inside the cell relative to outside produces progressively smaller fractions. The result, based on calculations at a temperature of 18°C, shows that for every tenfold change in the potassium ion gradient there is a 58-mV change in membrane potential.

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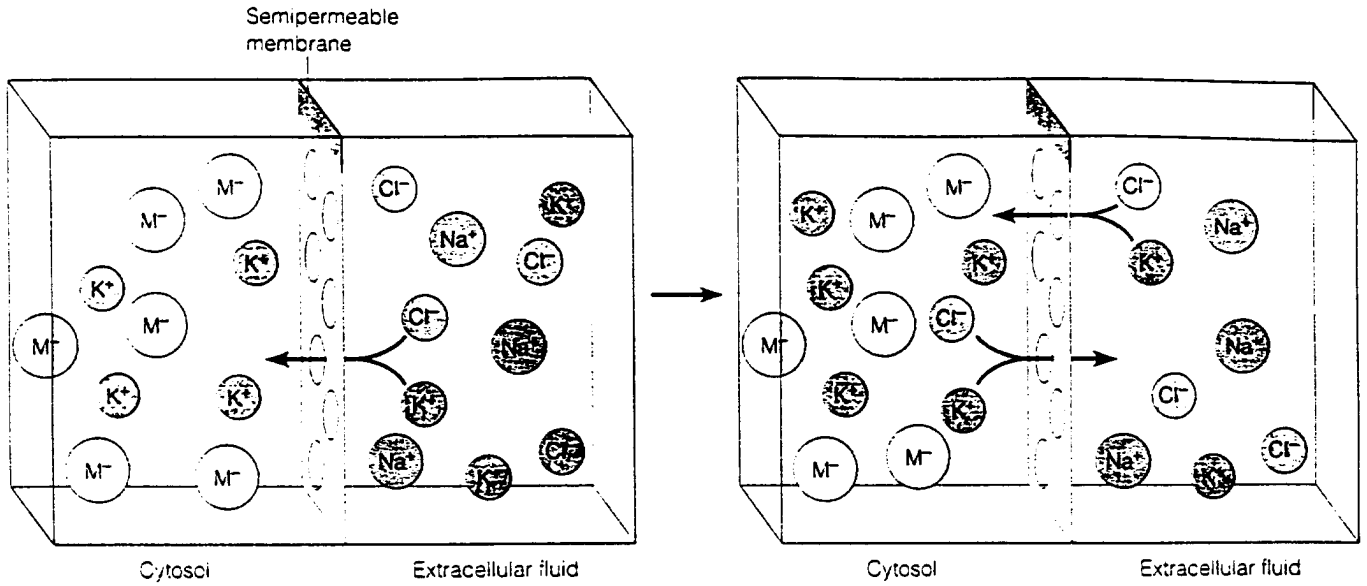

Figure 22-8 Donnan Equilibrium. Donnan equilibrium explains why chloride ions are more concentrated outside the cell than inside, even though the membrane is permeable to both potassium and chloride ions. Chloride ions start out much more concentrated on the outside (right compartment) and will tend to diffuse inward (to the left). Potassium ions are also permeable, and a positively charged potassium ion will diffuse into the cell along with each chloride ion, thereby preserving electrical neutrality. At equilibrium, the chloride ions diffuse across the membrane at the same rate in both directions, but the concentrations of chloride inside and outside the cell are quite different. This is because the high concentration of potassium ions inside the cell leads to the rapid leakage of potassium and chloride ions, even though the concentration of chloride in the cytosol is relatively low.

compartment model (Figure 22-8). As in Figure 22-6, the left compartment represents the cytosol, the right compartment represents the extracellular fluid, and the barrier represents a plasma membrane that is permeable to potassium and chloride ions. Now, however, a solution containing 0.1 *M* potassium ions and negatively charged macromolecules has been added to the left compartment, and a solution containing 0.1 *M* potassium chloride has been added to the right compartment. Even though the concentration of potassium ions is the same on both sides, the system is not at equilibrium because of the large chloride ion concentration gradient. Therefore, chloride ions will diffuse from right to left. A potassium ion will accompany each chloride ion that diffuses across the barrier, thereby preserving electrical neutrality. As chloride diffuses down its concentration gradient from right to left, potassium becomes more concentrated on the left side. This imbalance of potassium is one of the features of Donnan equilibrium.

Eventually, the concentration of potassium chloride will build up in the left compartment until an equilibrium is reached, with potassium and chloride ions diffusing in both directions at the same rate. If we were to measure the concentration of potassium and chloride in both compartments at equilibrium, we would find that potassium is more concentrated on the left side and chloride is more concentrated on the right side. In fact, we would find that

$$[K^-]_{left}/[K^-]_{right} = [Cl^-]_{right}/[Cl^-]_{left} \qquad (22\text{–}3)$$

In other words, the chloride gradient is the reciprocal or opposite of the potassium gradient. Reciprocal concentration gradients of chloride and potassium ions are the hallmark of Donnan equilibrium.

Ion Distribution and the Problem of Cell Swelling. Thus far, we have seen that the presence of negatively charged macromolecules in the cytosol lies at the heart of both the negative equilibrium membrane potential and the reciprocal distribution of potassium ions and chloride ions. Their presence also causes the cytosol to be hypertonic with respect to the extracellular fluid. The cytosol is *hypertonic* because it contains more dissolved substances than the solution outside the cell. This can be demonstrated by summing the ions present inside and outside. The cell contains both impermeable and diffusible anions, and to maintain electrical neutrality, it must also contain a matching number of cations. Outside the cell, there will be only diffusible anions (A^-) with a matching number of cations (C^-). We can express this idea mathematically as:

$$[C^-]_{inside} = [M^-]_{inside} + [A^-]_{inside} \qquad (22\text{–}4)$$

Outside the cell, electrical neutrality is achieved when:

$$[C^-]_{outside} = [A^-]_{outside} \qquad (22\text{–}5)$$

If we were to sum the concentrations of solutes inside the cell, we would find that there are more dissolved substances inside the cell. Therefore, water would tend to enter the cytosol, causing the cell to swell. If this process were to continue unchecked, the cell would eventually burst. 2836

To prevent swelling and rupture, an impermeable solute is needed outside the cell to balance the osmolarity of the cytosol. The high concentration of sodium ions present in the extracellular fluid fulfills this requirement because of the poor permeability of the membrane to sodium ions. In addition, when sodium ions do leak through the membrane, they are removed from the cytosol by the sodium-potassium pump.

The Sodium-Potassium Pump. Although the plasma membrane is relatively impermeable to sodium ions, there is always a small amount of leakage. If sodium continued to leak, eventually the cell would swell and burst. To compensate for this leakage, the **sodium-potassium pump** continually pumps sodium out of the cell while carrying potassium inward (see Figure 8-6). On average, the sodium-potassium pump transports three sodium ions out of the cell and two potassium ions into the cell for every molecule of ATP that is hydrolyzed. This net transport of ions out of the cell dilutes the cytosol, thereby preventing swelling. In addition, the sodium-potassium pump maintains the large potassium ion gradient across the membrane that provides the basis for the resting membrane potential.

Steady-State Ion Concentrations and the Resting Membrane Potential

Sodium, potassium, and chloride ions are the major ionic components present in both the cytosol and the extracellular fluid. Due to their unequal distributions across the cell membrane, each ion has a different impact on the membrane potential. The magnitude of the concentration gradient for each ion is illustrated by the bar graphs in Figure 22-9, in which the height of each bar is proportional to the concentration of a specific ion in the cytosol or the extracellular fluid. Each ion will tend to diffuse down its concentration gradient, and if allowed to do so will produce a change in the membrane potential.

Potassium ions tend to diffuse out of the cell, which makes the membrane potential more negative. Sodium ions tend to flow into the cell, driving the membrane potential in the more positive direction and thereby causing a **depolarization** of the membrane (that is, causing the membrane potential to be less negative). Chloride ions tend to diffuse into the cell slowly which should, in principle, make the membrane potential more negative. However, chloride ions are also repelled by the negative membrane potential, so that chloride ions usually enter the cell in association with positively charged ions such as sodium. This paired movement nullifies the depolarizing effect of sodium entry. Increasing the permeability of cells to chloride can have two effects, both of which decrease neuronal excitability. First, the net entry of chloride ions (chloride entry without a matching cation) causes hyperpolarization of the membrane (that is, the membrane potential becomes more highly negative than usual). Second, when the membrane becomes permeable to sodium ions, some chloride will tend to enter the cell along with sodium. Understanding this effect of chloride entry will be important later when we discuss inhibitory neurotransmitters.

Steady-State Ion Movements and the Goldman Equation

If we want to take into account the relative contributions of each of several ions to the resting membrane potential of a

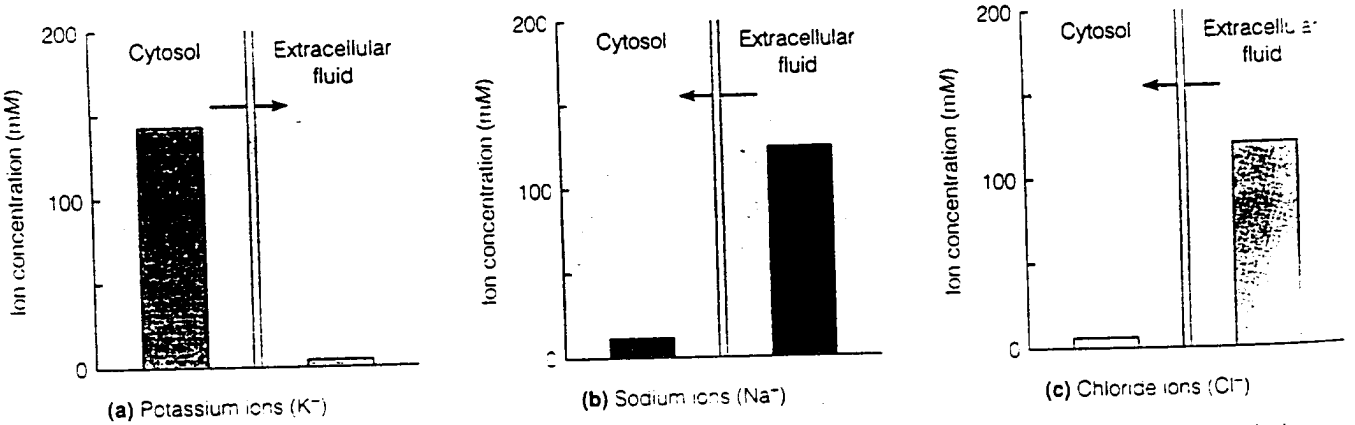

Figure 22-9 Relative Concentrations of Potassium, Sodium, and Chloride Ions Across the Cell Membrane. Each of the major ions in the cytosol exists as a concentration gradient across the plasma membrane, and each is capable of having an effect on the membrane potential. **(a)** Potassium ions are more concentrated in the cytosol than in the extracellular fluid. As a result, potassium ions have a tendency to move out of the cell, leaving behind trapped anions. Therefore, the loss of potassium causes the membrane potential to become more negative. **(b)** Sodium ions are much more concentrated outside the cell than inside; therefore, sodium ions tend to enter the cell. As sodium ions enter, they neutralize some of the excess negative charge in the cytosol. As a result, the membrane potential becomes more positive. **(c)** Chloride ions distribute across the membrane in Donnan equilibrium. Chloride ions usually cross the membrane together with a permeable cation (normally a potassium ion). Although chloride ions are concentrated outside the cell, the extracellular potassium ion concentration is low, which limits the rate of chloride entry. In contrast, the potassium concentration in the cytosol is high, allowing chloride to leave the cell even at low cytosolic chloride concentrations.

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cell, we cannot use the Nernst equation because it deals with only one type of ion at a time, and it assumes that this ion is in electrochemical equilibrium. These relative contributions are important to an understanding of the actual conditions in the cell because even in its resting state, the cell has some permeability to sodium and chloride ions in addition to potassium ions. To take into account the leakage of sodium and chloride ions into the cell, we must move from the more static concept of an equilibrium membrane potential to a consideration of **steady-state ion movements** across the membrane.

We can illustrate the concept of steady-state ion movements by returning to our model of a cell in electrochemical equilibrium (Figure 22-10). As mentioned in our discussion of the Nernst equation, a cell that is permeable only to potassium will have a membrane potential equal to the equilibrium potential for potassium ions. Under these conditions, there will be no net movement of potassium out of the cell. If we now assume that the membrane is slightly permeable to sodium ions, what will happen? We know that the cell will have both a large sodium gradient across the membrane and a negative membrane potential corresponding to the potassium equilibrium potential. These forces tend to drive sodium ions into the cell. As sodium ions leak inward, the membrane is partially depolarized. At the same time, by neutralizing the membrane potential, there is now less restraining force preventing potassium from leaving the cell, so potassium ions diffuse outward to balance the inward movement of sodium. The inward movement of sodium ions shifts the membrane potential in the positive direction, while the outward movement of potassium ions shifts the membrane potential in the negative direction.

The membrane potential now becomes a function not only of ion gradients but also of the rate at which ions can flow through the membrane—a very important new concept. Movements of sodium and potassium ions across the membrane have essentially opposite effects on the membrane potential. For mammalian cells, the sodium ion gradient tends toward a cell membrane potential of about +55 mV, while the potassium ion gradient tends toward a membrane potential of about −90 mV. At what value will the membrane potential come to rest? In principle, it could be anywhere between these points. At any given time, the membrane potential will depend on the outward flux of potassium ions relative to the inward flux of sodium ions. Changes in the permeability of the cell to either ion cause corresponding changes in the membrane potential. In a living cell, sodium ions continually leak into the cell and potassium ions leak out, but steady-state concentrations of the two ions are maintained because the sodium-potassium pump acts to move sodium ions outward and potassium ions inward.

The pioneering neurobiologists David E. Goldman, Alan Lloyd Hodgkin, and Bernard Katz were the first to describe how gradients of several different ions each contribute to the membrane potential as a function of relative ionic permeabilities. The Goldman-Hodgkin-Katz equation, more commonly known as the **Goldman equation,** is as follows:

$$V_m = \frac{RT}{F} \ln \frac{(P_{K})[K^+]_{outside} + (P_{Na})[Na^+]_{outside} + (P_{Cl})[Cl^-]_{inside}}{(P_{K})[K^+]_{inside} + (P_{Na})[Na^+]_{inside} + (P_{Cl})[Cl^-]_{outside}} \qquad (22\text{–}6)$$

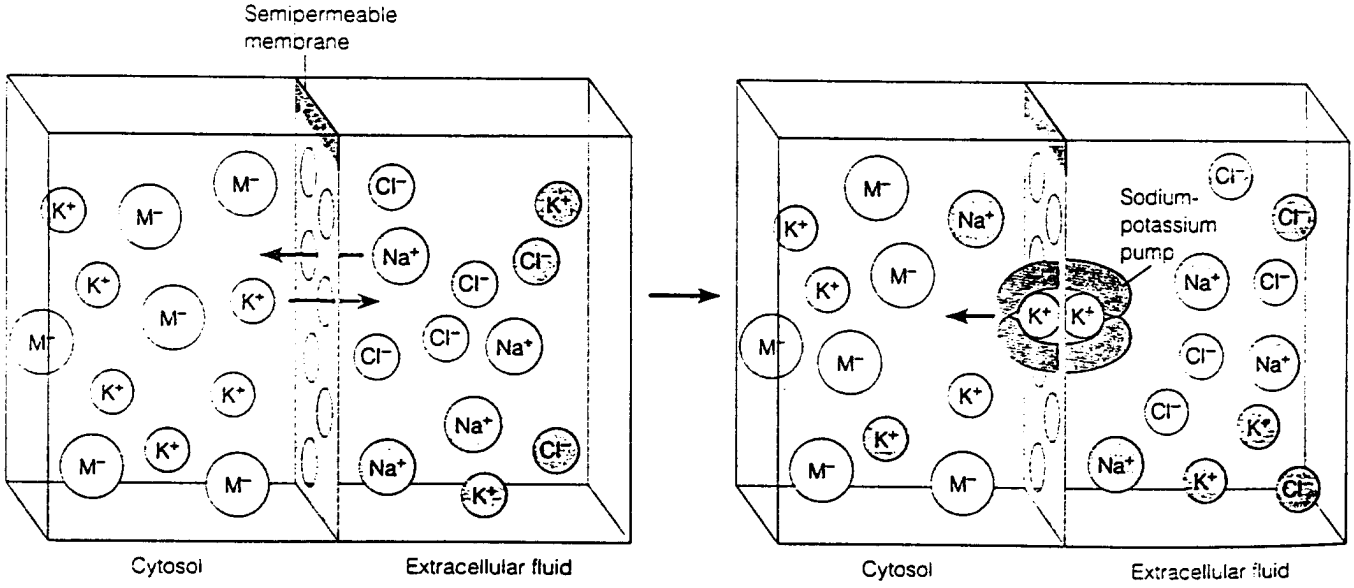

Figure 22-10 Steady-State Ion Movements. The actual membrane potential of a cell depends on the permeability of the membrane to various ions and the steady-state movements of ions across the membrane. As illustrated here with our two-compartment model, a small number of sodium ions continually leak into the cell. This makes the membrane potential more positive, weakening the electrical restraint on the movement of potassium ions. A small number of potassium ions can now leak out of the cell. As sodium ions accumulate in the cytosol, they are pumped outward in exchange for potassium ions by the sodium-potassium pump. The end result is a small, permanent concentration of sodium ions inside the cell. The presence of a small amount of sodium ions in the cytosol causes the membrane potential to be more positive than the equilibrium membrane potential for potassium ions.

One of the key differences between the Nernst equation and the Goldman equation is the incorporation of terms for permeability. Here P_K, P_{Na}, and P_{Cl} are the *relative permeabilities* of the membrane for the respective ions. The use of relative permeabilities circumvents the complicated task of determining the absolute permeability of each ion. Because chloride ions have a negative valence, $[Cl^-]_{inside}$ appears in the numerator and $[Cl^-]_{outside}$ in the denominator. While the equation shown here only takes into account the contributions of potassium, sodium, and chloride ions, other ions could be added as well. Except under special circumstances, however, the permeability of the plasma membrane to other ions is usually so low that their contributions are negligible.

We can use a mammalian neuron to illustrate how one can accurately estimate the resting membrane potential from the known steady-state concentrations of sodium, potassium, and chloride ions as well as their relative permeabilities. To do so, K^- is assigned a permeability value of 1.0, and the permeability values of all other ions are determined relative to that of K^-. The permeability of sodium ions is only about 1% of that for potassium ions, and for chloride ions, the estimated value is 45%. Relative values of P_K, P_{Na}, and P_{Cl} are therefore 1.0, 0.01, and 0.45, respectively. Using these values, a temperature of 37°C, and the intracellular and extracellular concentrations of Na^-, K^-, and Cl^- from Table 22-1, we can estimate the resting membrane potential of a mammalian neuron as follows:

$$V_- = \frac{RT}{F} \ln \left[\frac{(1.0)(5) + (0.01)(145) + (0.45)(10)}{(1.0)(140) + (0.01)(10) + (0.45)(110)} \right]$$
$$= 0.0267 \ln (0.057) = -0.077V = -77\text{mV} \qquad \textbf{(22–7)}$$

Typical measured values for the resting membrane potential of a mammalian neuron are about −80 mV, which is remarkably close to our calculated potential.

Electrical Excitability

The establishment of a resting membrane potential and its dependence on ion gradients and ion permeability are properties of almost all cells and are not what makes electrically excitable cells unique. The unique feature of electrically excitable cells is their response to membrane depolarization. A nonexcitable cell that has been temporarily and slightly depolarized will simply return to its original resting membrane potential. When an electrically excitable cell is depolarized to the same degree, however, it responds with an *action potential.*

Electrically excitable cells produce an action potential because of the presence of particular types of ion channels in the plasma membrane. As we shall see, ion channels are at the heart of electrical signaling in neurons. Thus, to understand how nerve cells communicate signals electrically, we need to know the characteristics of the ion channels that are present in the membrane.

Ion Channels

Ion channels are integral membrane proteins that form ion-conducting pores through the lipid bilayer. Channel types differ in several ways, including their selectivity for a particular ion and the conditions that determine when the channel is opened or closed to the passage of ions. Channels are generally classified according to the kind of ion they conduct, the most common examples being sodium, potassium, calcium, and chloride channels. Channels also differ in what stimulus causes them to open and how long they stay open in response to a particular stimulus. Controlling the opening and closing of a channel is referred to as *gating* the channel.

As the name suggests, **voltage-gated ion channels** respond to changes in the voltage across a membrane. Voltage-gated sodium and potassium channels are responsible for the action potential. **Ligand-gated ion channels,** however, open when a particular molecule binds to the channel. (*Ligand* is from a Latin word meaning "to bind.") These channels are important in the communication of signals be-

Table 22-1 Ionic Concentrations Inside and Outside Axons, Concentration Ratios, and Resulting Equilibrium Potentials

	Squid Axon				Mammalian Neuron			
Ion	Outide (mM)	Inside (mM)	Ratio*	Potential (mV)	Outside (mM)	Inside (mM)	Ratio*	Potential (mV)
Na^-	440	50	8.8	+55	145	10	14.4	−68
K^-	20	400	0.05	−75	5	140	0.035	−85
Cl^-	560	50	0.09	−61	110	10	0.09	−66

*Concentration ratios are outside/inside for cations, inside/outside for anions.

tween neurons. Finally, some channels appear to be *ungated* and therefore always open. An example of an ungated channel is the potassium leak channel that makes resting cells somewhat permeable to potassium ions.

The Structure and Function of Voltage-Gated Ion Channels. Understanding the structure and function of voltage-gated sodium and potassium channels provides a basis for understanding the events of the action potential. Therefore, before we discuss the events of an action potential, we will first explore the properties of ion channels.

The structure of voltage-gated ion channels follows two different, though similar, models. *Voltage-gated potassium channels* are multimeric proteins that form from four separate protein subunits present in the membrane (Figure 22-11). When these four subunits come together in the membrane, a central pore is formed through which ions can pass. *Voltage-gated sodium channels*, however, are large, monomeric proteins with four separate domains, each of which is similar to one of the subunits of the voltage-gated potassium channel. In both kinds of channels, each subunit or domain contains six transmembrane α helices. One of these transmembrane α helices has positively charged amino acid groups in the middle of its transmembrane segment. These positively charged amino acids probably serve as the *voltage sensor* that makes these channels voltage-sensitive. In some way, changes in voltage across the membrane cause the positions of these amino acids to shift, thereby opening or closing the channel.

The size of the central pore and, more importantly, the way it interacts with an ion, give a channel its ion specificity (Figure 22-12a). In part, channels select for ions of the right charge through electrostatic attraction to, or repulsion from, charged amino acids at the opening of the pore. Ultimately, however, ions must bind to the channel before they can pass through. When an ion binds to a channel, most of the water molecules bound to the ion are released. A channel thus selects for ions that bind strongly enough to displace the water molecules surrounding the ion. Once this happens, the ion can pass through the pore. It is through binding to an ion that a channel exerts its greatest selectivity.

Gated channels have the ability to open in response to some stimulus and then to close again. This open or closed state is an all-or-none phenomenon: When a channel opens, it conducts ions at a maximum, and when it closes, it does not conduct ions at all. However, a channel can go into either of two different closed states. In the case of *channel gating*, the channel closes but remains capable of opening again in response to the appropriate signal (Figure 22-12b). This is due to the voltage gate swinging open or shut.

The other closed state is referred to as **channel inactivation** which is an important feature of voltage-gated sodium channels (Figure 22-12c). When a channel is inactivated, it is closed in such a way that it cannot reopen immediately, even if stimulated to do so. Inactivation is caused by a portion of the channel protein called the *inactivating particle* that protrudes into the cytosol. During inactivation, this particle covers the opening of the channel pore. For such a channel to reactivate and open in response to a stimulus, the inactivating particle must move away from the pore.

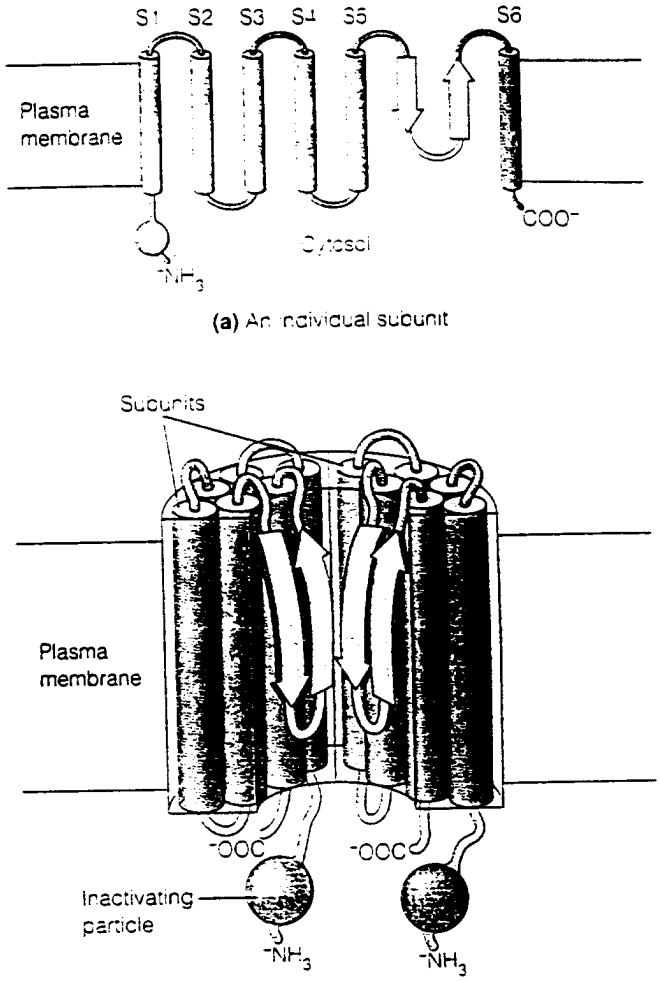

Figure 22-11 The General Structure of Voltage-Gated Ion Channels. The voltage-gated channels for sodium, potassium, and calcium ions all share the same basic structural themes. The channel is essentially a rectangular tube whose four walls are formed from either four subunits, or four domains. **(a)** Each subunit or domain contains six transmembrane α helices labeled S1–S6. The fourth transmembrane α helix, S4, contains many positively charged residues, which make it a good candidate for a voltage sensor and part of the gating mechanism. For voltage-gated sodium channels and some types of potassium channels, a region near the N terminus protrudes into the cytosol and forms an inactivating particle. **(b)** Two of the subunits of a voltage-gated potassium channel are brought together to show how the pore forms in the middle. The inactivating particle (when present) causes channel inactivation by extending over the mouth of the channel to block the passage of ions.

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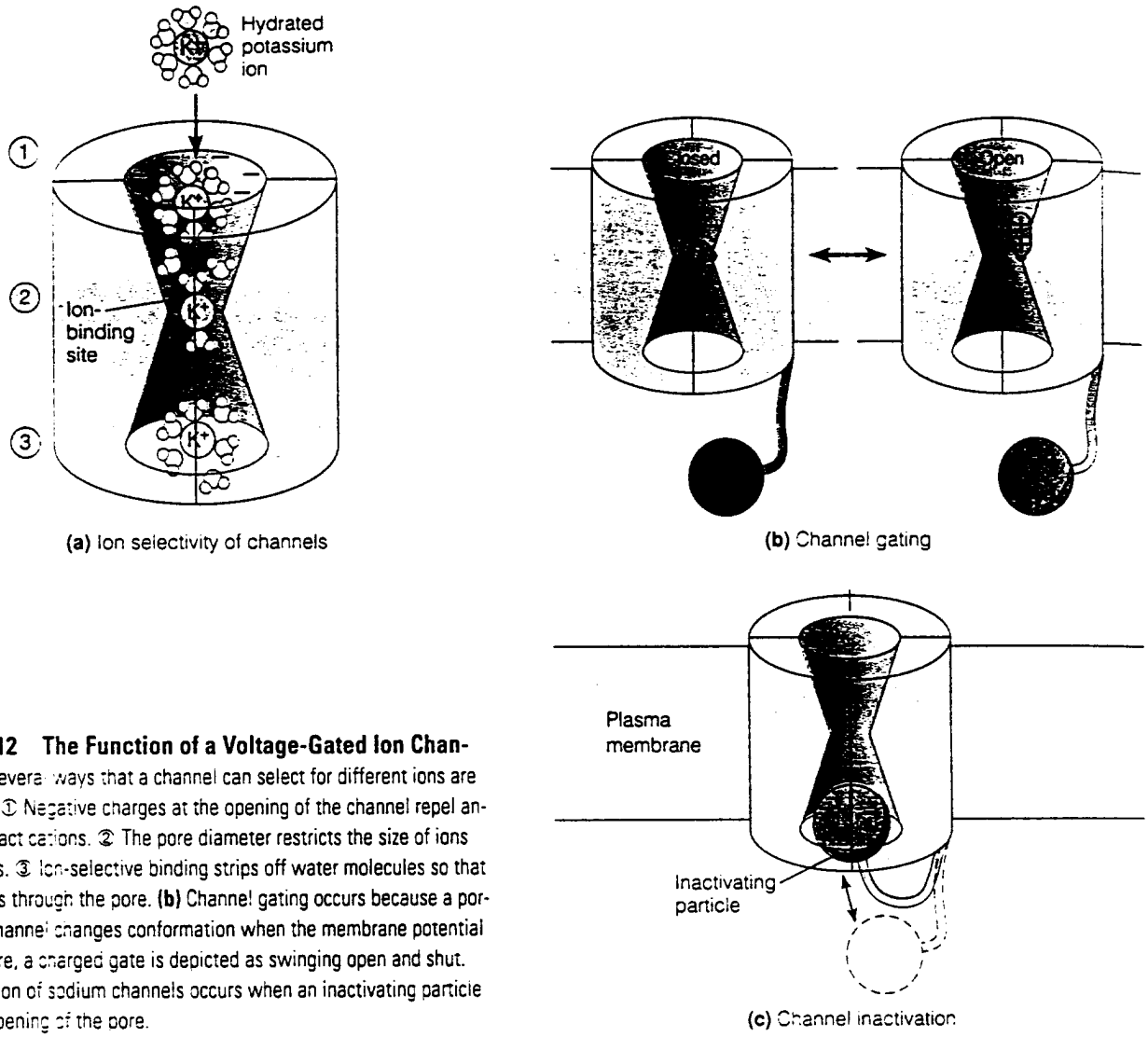

Figure 22-12 The Function of a Voltage-Gated Ion Channel. **(a)** Several ways that a channel can select for different ions are shown here. ① Negative charges at the opening of the channel repel anions and attract cations. ② The pore diameter restricts the size of ions that can pass. ③ Ion-selective binding strips off water molecules so that ions can pass through the pore. **(b)** Channel gating occurs because a portion of the channel changes conformation when the membrane potential changes. Here, a charged gate is depicted as swinging open and shut. **(c)** Inactivation of sodium channels occurs when an inactivating particle blocks the opening of the pore.

Studying a Single Channel: Patch Clamping

Our clearest picture of how channels operate is the result of the development of a technique that permits the recording of ion currents passing through individual channels. This technique, known as *single-channel recording,* or more commonly as **patch clamping** (Figure 22-13), was developed by Erwin Neher and Bert Sackman.

To record single-channel currents, a fire-polished glass micropipette with a tip diameter of approximately 1 μm is carefully pressed up against the surface of a cell such as a neuron (Figure 22-13a). Gentle suction is then applied, so that a tight seal forms between the pipette and the plasma membrane. There is now a "patch" of membrane under the mouth of the micropipette that is sealed off from the surrounding medium (Figure 22-13b).

This patch of membrane is small enough that it will usually contain only one or perhaps a few ion channels. Current can enter and leave the pipette only through these channels, thereby enabling an experimenter to study various properties of the individual channels. The channels can be studied in the intact cell, or the patch can be pulled away from the cell so that the researcher has access to the cytosolic side of the membrane.

During the experimental process, an amplifier maintains voltage across the membrane with the addition of a sophisticated electronic feedback circuit called a *voltage clamp* (hence the term *patch clamp*). The voltage clamp keeps the cell at a fixed membrane potential, regardless of changes in the electrical properties of the plasma membrane, by injecting current as needed to hold the voltage constant. It then measures tiny changes in current flow—actual ionic currents through individual channels—from the patch pipette.

The patch-clamp method has been used to show that when a particular kind of channel opens, it always conducts the same amount of *current*—that is, the same number of ions per unit of time. There are no partially open or closed states in which the channel conducts more or less current. Therefore, we can characterize a particular channel in terms of its conductance. *Conductance* is the amount of current

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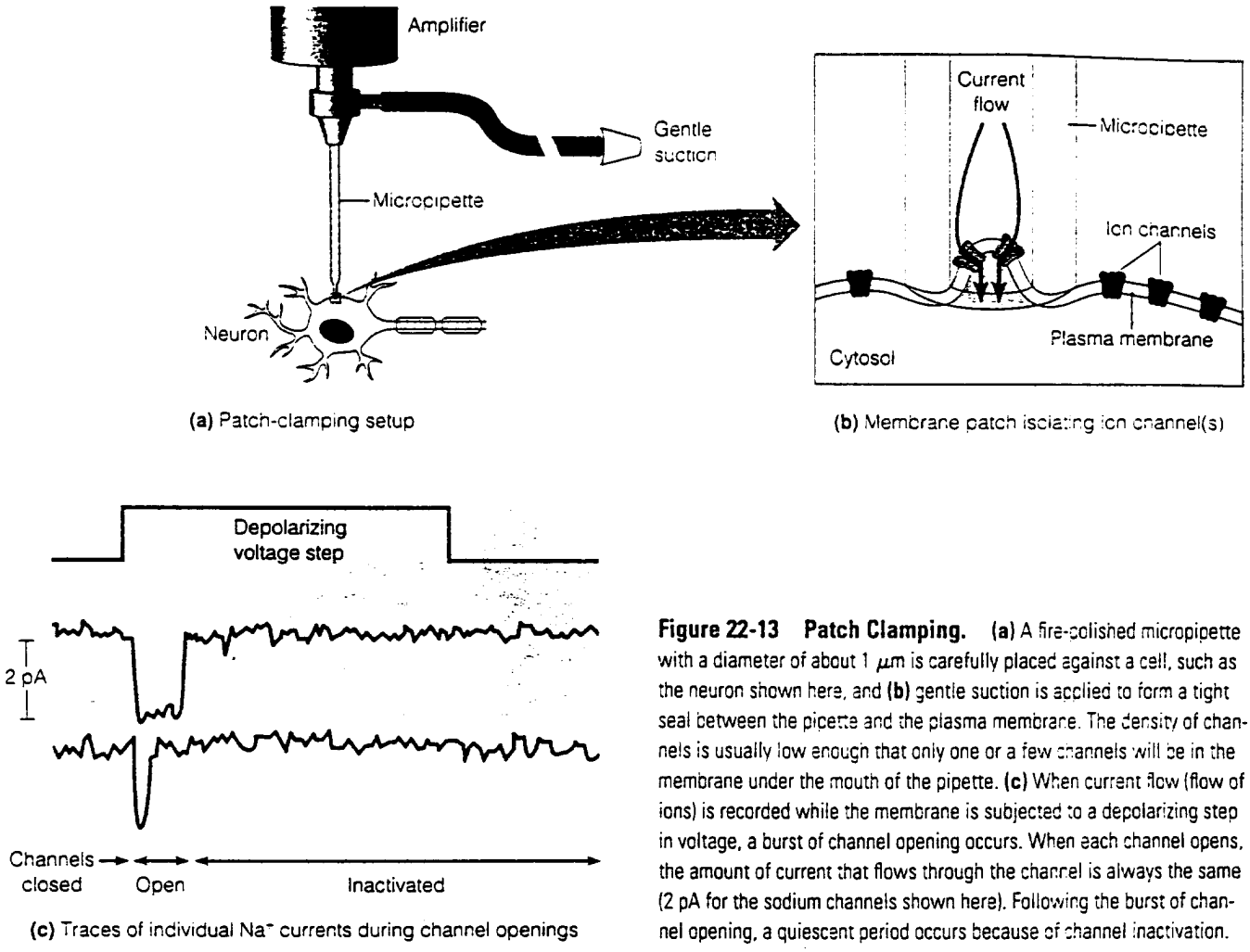

(a) Patch-clamping setup

(b) Membrane patch isolating ion channel(s)

(c) Traces of individual Na^+ currents during channel openings

Figure 22-13 Patch Clamping. **(a)** A fire-polished micropipette with a diameter of about 1 μm is carefully placed against a cell, such as the neuron shown here, and **(b)** gentle suction is applied to form a tight seal between the pipette and the plasma membrane. The density of channels is usually low enough that only one or a few channels will be in the membrane under the mouth of the pipette. **(c)** When current flow (flow of ions) is recorded while the membrane is subjected to a depolarizing step in voltage, a burst of channel opening occurs. When each channel opens, the amount of current that flows through the channel is always the same (2 pA for the sodium channels shown here). Following the burst of channel opening, a quiescent period occurs because of channel inactivation.

flowing through the channel per unit of time when a specified voltage is applied across the membrane. A voltage-gated sodium channel, for example, conducts an electrical current of approximately 2 picoamps (2×10^{-12} A), which corresponds to about 12 million sodium ions flowing through the channel per second. This can be seen in the traces shown in Figure 22-13c.

In single-channel recording, membrane depolarization (triggered by changing the applied voltage to a more positive potential) increases the probability that a channel will open. Even before the membrane is depolarized, a sodium channel will occasionally flicker open and closed. When the membrane is depolarized, a burst of activity occurs, involving much more frequent opening and closing of sodium channels. This channel activity then dies down and cannot resume unless the membrane potential is restored to a more negative level. The cessation of channel activity that occurs while the membrane is still depolarized is due to channel inactivation.

Mode of Action of Sodium Channels. Much of the current research using patch clamping focuses on the mechanism that enables ion channels of excitable membranes to sense and respond to changes in membrane potential. Our understanding in this area has been greatly enhanced by studies of **gating currents.** These are small currents that last only about 0.1 msec and precede the opening of the sodium channels. Gating currents are thought to reflect changes in the positions of charged amino acids within the channel. Any movement of charge over a distance is a current. Here, the movement of charge that makes up the gating current is due to the gate of the sodium channel protein swinging open in response to membrane depolarization.

Our understanding of how these channels function has been greatly aided by the isolation and cloning of the gene that encodes the sodium channel protein. This has made it possible to synthesize large amounts of the channel protein and to study its functions in lipid bilayers. In addition, specific molecular modifications or mutations to the channel can be used to determine how various regions of the channel protein are involved in channel function. This approach has been used to study the parts of the channel protein responsible for voltage-gating. Each of the four domains of the sodium channels has six transmembrane helices, called S1–S6. One of these helices, S4, has a conspicuous series of positively charged amino acids. When these positively

charged amino acids are replaced with neutral amino acids, gating currents are abolished, and the channel does not open. This suggests that the transmembrane helix S4 functions as the voltage sensor and gate.

Molecular studies have also identified the mechanism of channel inactivation. The current model of inactivation suggests something like a ball tethered on a chain (the inactivating particle) that swings over the cytosolic opening of the channel to block conductance (see Figure 22-12c). Several lines of evidence support this conclusion. When the cytosolic side of the channel is treated with a protease, channels can no longer be inactivated. Treatment of channels with antibodies prepared against the fragment of the channel thought to be responsible for inactivation also prevents inactivation.

Kinds of Potassium Channels. There are many different kinds of potassium channels. The delayed potassium channels play an important role in action potentials. These channels respond to depolarization as the sodium channels do, but they open more slowly. Other potassium channels are activated by internal calcium and may play a role in the regulation of membrane potential.

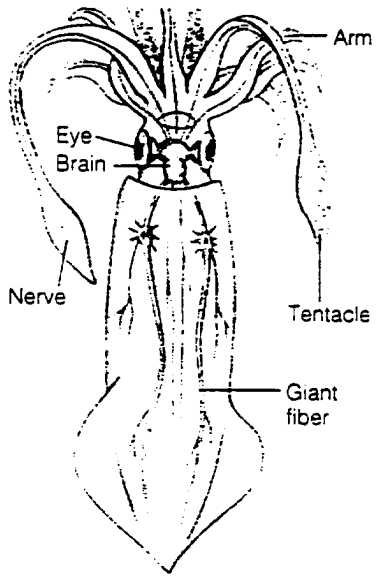

Figure 22-14 Squid Giant Axons. The squid nervous system includes motor nerves that control swimming movements. The nerves contain giant axons (fibers) with diameters ranging up to 1 mm, providing a convenient system for studying resting and action potentials in a biological membrane.

The Action Potential

We have seen how an ion gradient across a selectively permeable membrane can generate a membrane potential, and how, according to the Goldman equation, membrane potential will change in response to changes in ion permeability. We have also examined the nature of ion channels in the membrane, which are responsible for regulating the permeability of the membrane to the different ions. Now we are ready to explore how the coordinated opening and closing of ion channels can lead to an electrical impulse called an action potential. To do this, we will first examine how the membrane potential is measured and how it changes during an action potential, using the squid giant axon as a model system. Then we will discuss how the opening and closing of sodium and potassium channels account for these changes in membrane potential.

The Squid Giant Axon as an Experimental Model

Progress in science is often associated with technological breakthroughs. One of the great advances in understanding the electrical events in neurons came with the discovery of the *giant neurons* of the squid in the 1930s. Since that time, the squid giant axon has become one of the most extensively studied and well characterized of all neurons. In the squid, these giant nerve fibers are used to expel water explosively from the mantle cavity of the animal, enabling it to propel itself quickly backward to escape predators (Figure 22-14). The axons involved in triggering this "jet propulsion" system are very large, with diameters of about 0.5–1.0 mm. This size allows microelectrodes to be inserted readily into the axon, thereby making it possible to measure and control electrical potentials and ionic currents across the axonal membrane. Because the squid giant axon has been studied so intensively, we will use it to illustrate the properties of an action potential.

Measuring the Resting Membrane Potential

We have seen how the ion currents flowing through a single channel can be measured using patch clamping. To measure the resting membrane potential of the cell, we use a slightly different apparatus, such as that shown in Figure 22-15a. Here, a *recording electrode* is implanted in the axon and a *reference electrode* is placed in the electrolyte solution surrounding the membrane. Wires run from the electrodes to an electronic amplifier to amplify the signals, and then to an oscilloscope or computer screen that displays the strength of the signal over time. As we will discuss later, additional electrodes can be inserted into the neuron for special purposes.

The Sequence of Events During an Action Potential

A resting neuron is a system poised for electrical action. As already mentioned, the membrane potential of the cell is set by a delicate balance of ion gradients and ion permeability. Depolarization of the membrane upsets this balance. If the level of depolarization is small—less than about 20 mV—the membrane potential will normally recover without event. Further depolarization brings the membrane to the

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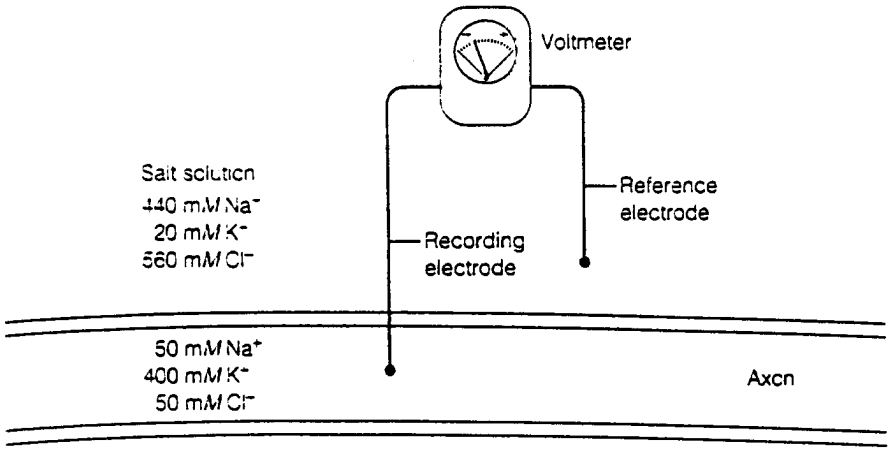
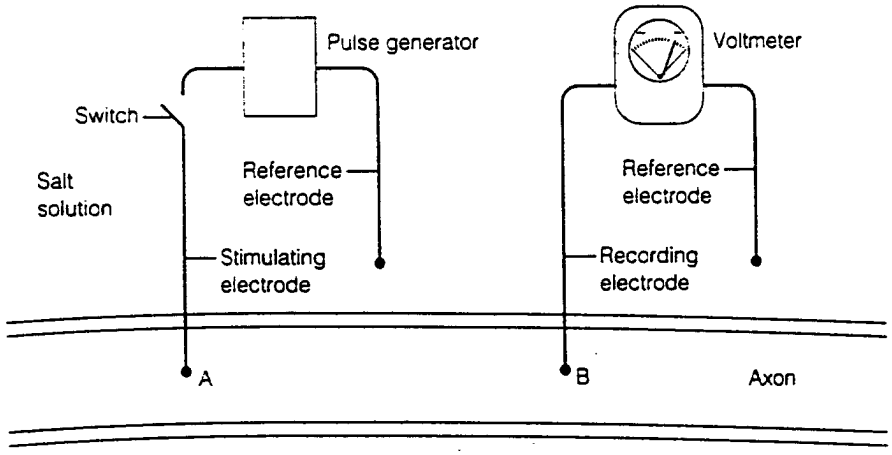


(a) Measuring the resting membrane potential in a squid axon



(b) Measuring an action potential in a squid axon

Figure 22-15 An Apparatus for Measuring Membrane Potentials.
(a) Measurement of the resting membrane potential requires two electrodes, one inserted inside the axon (the recording electrode) and one placed in the fluid surrounding the cell (the reference electrode). Differences in potential between the recording and reference electrodes are amplified by a voltage amplifier and displayed on a voltmeter, an oscilloscope, or a computer monitor. **(b)** Measurement of an action potential requires four electrodes, one in the axon for stimulation, another in the axon for recording, and two in the fluid surrounding the cell for reference. The stimulating electrode is connected to a pulse generator, which delivers a pulse of current to the axon when the switch is momentarily closed. The nerve impulse this generates is propagated down the axon and can be detected a few milliseconds later by the recording electrode. The impulse is detected as a transient change in transmembrane potential, measured with respect to the reference electrodes.

threshold potential, where the events of the action potential take control.

An **action potential** is a brief but large electrical depolarization and repolarization of the neuronal plasma membrane caused by the inward movement of sodium ions followed by the outward movement of potassium ions. These ion movements are, in turn, controlled by the opening and closing of voltage-gated sodium and potassium channels. In fact, we can explain the development of an action potential solely in terms of the behavior of these channels. Once an action potential is initiated in one region of the membrane, it will travel along the membrane away from the site of origin by a process called **propagation.**

Measuring an Action Potential

The development and propagation of an action potential can be readily studied in large axons such as those of the squid. To do so using the apparatus shown in Figure 22-15b, an additional electrode called the *stimulating electrode* is connected to a power source and inserted into the axon some distance from the recording electrode. A brief impulse from this stimulating electrode can be used to locally depolarize the neuron beyond the threshold potential. This requires an electrical impulse from the stimulating electrode sufficient to depolarize the membrane by about 20 mV (i.e., from −60 to about −40 mV). This triggers an action potential that spreads out, or propagates away from, the stimulating electrode. As the action potential passes the recording electrode, the voltmeter or oscilloscope will display the characteristic pattern of potential changes shown in Figure 22-16.

In less than a millisecond, such an apparatus will record the membrane potential rising dramatically from the resting membrane potential to about +40 mV—the interior of the membrane actually becomes positive for a brief period. The potential then falls somewhat more slowly, dropping to about −75 mV (hyperpolarization) before stabilizing again

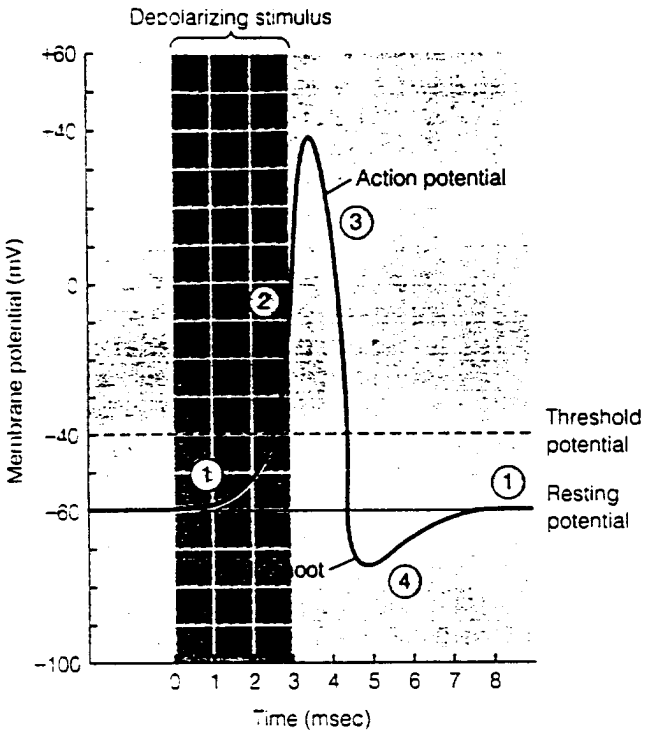


Figure 22-16 The Action Potential of the Squid Axon.
① The resting potential prior to the start of the action potential is approximately −60 mV. ② An action potential begins when the neuron is depolarized by about 20 mV to a point known as the threshold potential. Once the action potential is initiated, the potential swings rapidly in the positive direction. At the peak of the positive swing, the membrane potential reaches a value of about +40 mV. ③ Once the cell reaches the peak positive potential, it begins to repolarize, returning to a negative membrane potential. ④ Repolarization often leads to a membrane potential that is actually hyperpolarized or more negative than the resting potential. This is referred to as the undershoot. The membrane potential then returns to its resting state.

at the resting potential of about −60 mV. As Figure 22-16 indicates, the complete sequence of events during an action potential takes place within a few milliseconds.

The apparatus shown in Figure 22-15 can also be used to measure the ion currents that flow through the membrane at different phases of an action potential. To do so, an additional electrode known as the *holding electrode* is inserted into the cell and connected to a voltage clamp, thereby enabling the investigator to set and hold the membrane at a particular potential, regardless of changes in the membrane's electrical properties. Using the voltage-clamp apparatus, a researcher can measure the current flowing through the membrane at any given membrane potential. Such experiments have contributed fundamentally to our current understanding of the mechanism that causes an action potential.

Understanding the Action Potential in Terms of Ion Channels and Currents

In a resting neuron, the voltage-dependent sodium and potassium channels are usually closed. Therefore, the cell is roughly 100 times more permeable to potassium than to sodium ions because of the potassium leak channels. When a region of the nerve cell is slightly depolarized, a fraction of the sodium channels respond and open. As they do, the increased sodium current acts to depolarize the membrane. Thus, increasing depolarization causes a larger sodium current to flow, which further depolarizes the cell. This relationship between depolarization, the opening of voltage-gated sodium channels, and an increased sodium current constitutes a positive feedback loop known as the *Hodgkin cycle* (Figure 22-17).

Subthreshold and Threshold Depolarization. If the Hodgkin cycle were not opposed by other forces, even a small amount of sodium entry would always lead to complete depolarization of the cell membrane. However, the events of the Hodgkin cycle meet with resistance due to the efflux of potassium ions, which tends to restore the resting membrane potential. As mentioned earlier, when the membrane is depolarized by a small amount, the membrane potential recovers and no action potential is generated. Levels

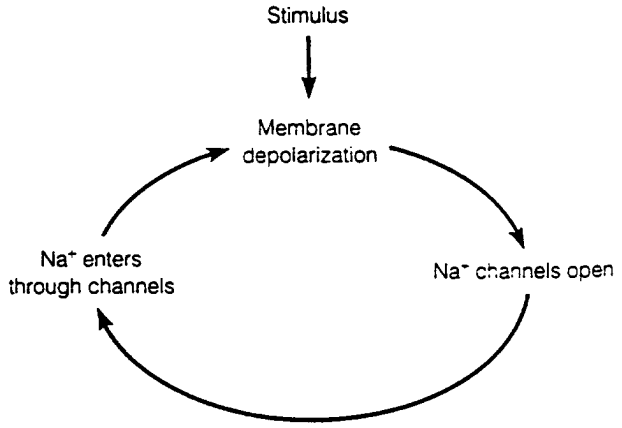


Figure 22-17 The Hodgkin Cycle. This diagram illustrates the positive feedback relationship between depolarization, the opening of sodium channels, and the corresponding increase in sodium current. A small depolarization causes sodium channels to open. This in turn lets sodium ions flow into the cell, which depolarizes the membrane even more. As long as the membrane's permeability to potassium ions is greater than its permeability to sodium ions, diffusion of potassium ions out of the cell will counteract the Hodgkin cycle. However, when the membrane's permeability to sodium ions approaches its permeability to potassium ions, the Hodgkin cycle will operate unopposed, leading to maximum sodium permeability.

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of depolarization that are too small to produce an action potential are referred to as **subthreshold depolarizations.**

To understand why subthreshold depolarizations lead to recovery while larger depolarizations lead to an action potential, we need to consider how potassium ions respond to depolarization. When sodium ions enter a cell and depolarize the membrane, the electrical restraint that keeps potassium ions from diffusing out of the cell is weakened. In response to a depolarization of the membrane, potassium ions diffuse outward, thereby making the membrane potential more negative again.

This efflux of potassium ions can effectively oppose the Hodgkin cycle as long as its rate is greater than or equal to the rate of sodium influx. The rate of sodium influx varies with the degree of depolarization: The greater the depolarization, the faster sodium enters. Up to a point, increasing rates of sodium entry are matched by increasing rates of potassium efflux. For subthreshold levels of depolarization, the rate of potassium efflux can compensate for the rate of sodium entry.

The Depolarizing Phase. If all the voltage-dependent sodium channels in the membrane were to open at once, the cell would suddenly become ten times more permeable to sodium than to potassium. Because sodium would then be the more permeable ion, the membrane potential would be largely a function of the sodium ion gradient. This is effectively what happens when the membrane is depolarized past the threshold potential (Figure 22-18, steps 1 and 2). Once the threshold potential is reached, potassium efflux can no longer compensate for the rate of sodium entry. At this point, the membrane potential shoots rapidly upward, peaking at approximately +40 mV. When the rate of sodium entry slightly exceeds the maximum rate of potassium efflux, an action potential is triggered. Note that at this peak, the action potential approaches, although it does not actually reach, the equilibrium potential for sodium ions (about +55 mV).

The Repolarizing Phase Once the membrane potential has risen to its peak, it quickly repolarizes (Figure 22-18, step 3). This is due to a combination of the inactivation of sodium channels and the opening of voltage-gated potassium channels. When sodium channels are inactivated, they close and remain closed until the membrane potential becomes negative again. Channel inactivation thus stops the inward flow of sodium ions and temporarily blocks the Hodgkin cycle. The cell will now automatically repolarize as potassium ions leak out.

Voltage-gated potassium channels in neurons differ kinetically from voltage-gated sodium channels in that, when the cell is depolarized, the potassium channels open more slowly. As a result, an action potential begins with an increase in the membrane's permeability to sodium, followed by an increased permeability to potassium. The increased permeability to sodium depolarizes the membrane, and the increased permeability to potassium ions that follows repolarizes the membrane.

The Hyperpolarizing Phase (Undershoot). At the end of an action potential, most neurons show a transient **hyperpolarization**, or **undershoot**, in which the membrane potential briefly becomes even more negative than it normally is at rest (Figure 22-18, step 4). The undershoot occurs because of the increased potassium permeability that exists while voltage-gated potassium channels remain open. Note that the potential of the undershoot closely approximates the equilibrium potential for potassium ions (about −75 mV for the squid axon). As the voltage-gated potassium channels close, the membrane potential returns to its original resting state.

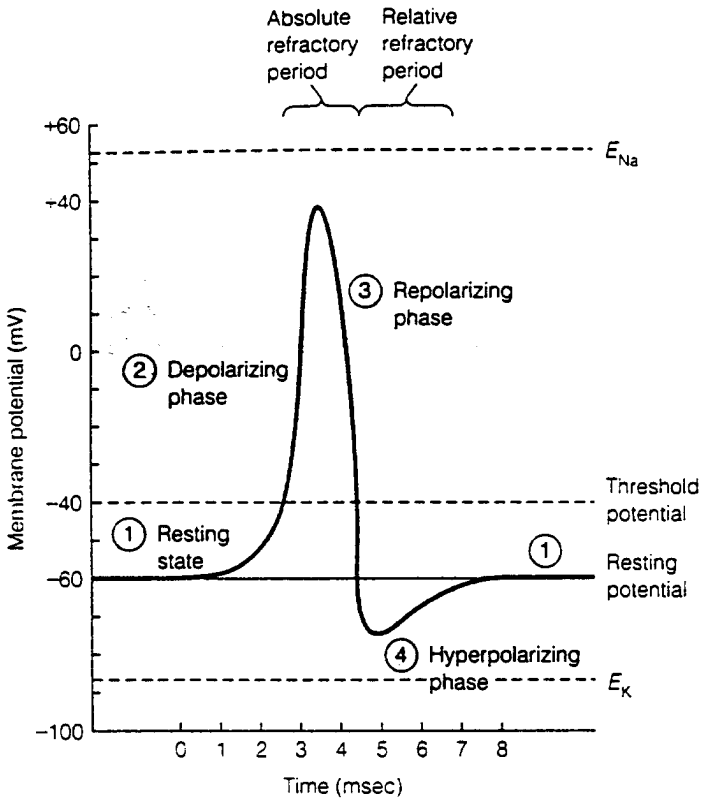
The Refractory Periods. For a few milliseconds after an action potential, it is impossible to trigger a new action potential. This interval, the **absolute refractory period,** is due to sodium channel inactivation. As long as the channels are inactivated, they cannot open, even if the membrane is depolarized. In addition, the undershoot makes it more difficult to stimulate an action potential, even after sodium channels have reactivated and are ready to open again. During this interval, the **relative refractory period,** it is possible but difficult to trigger an action potential.

Changes in Ion Concentrations Due to an Action Potential. Our discussion of ion movements might give the impression that an action potential involves large changes in the cytosolic concentrations of sodium and potassium ions. In fact, during a single action potential, the cellular concentrations of sodium and potassium ions hardly change at all. Remember that the membrane potential is due to a slight excess of negative charge on one side and of positive charge on the other side of the membrane. The number of excess charges is a tiny fraction of the total ions in the cell, and the number of ions that must cross the membrane to neutralize or alter the balance of charge is likewise tiny.

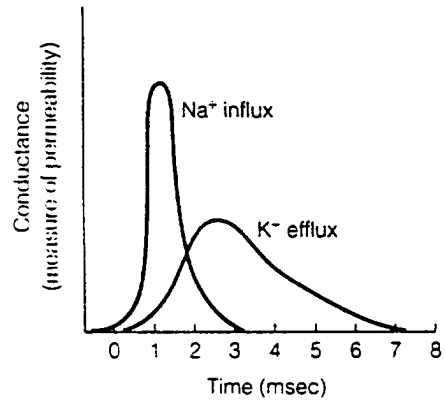
However, intense neuronal activity can lead to significant changes in the overall ion concentrations. For example, as a neuron continues to generate large numbers of action potentials, the concentration of potassium outside the cell will begin to rise perceptibly. This can affect the membrane potential of both the neuron itself and surrounding cells. Astrocytes are thought to control this problem by taking up excess potassium ions.

The Propagation of an Action Potential

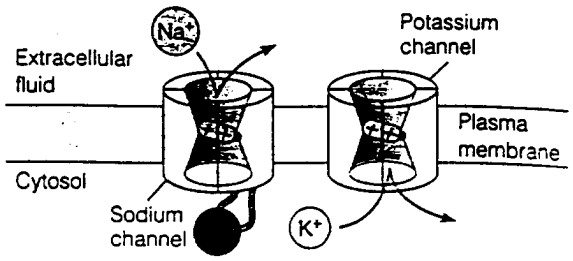
In order for neurons to transmit signals to one another, the transient depolarization and repolarization that occur during an action potential must travel along the neuronal membrane. The depolarization at one point on the membrane



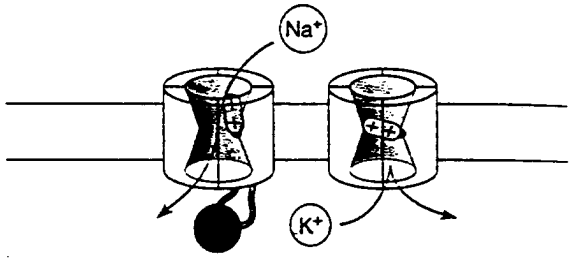
(a) Changes in ion channels and membrane potential



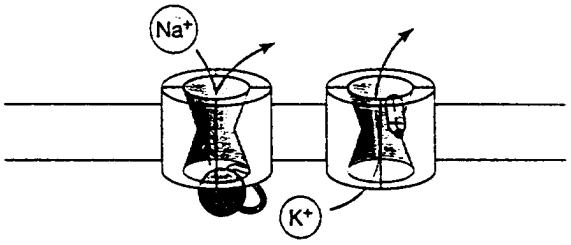
(b) Change in membrane conductance



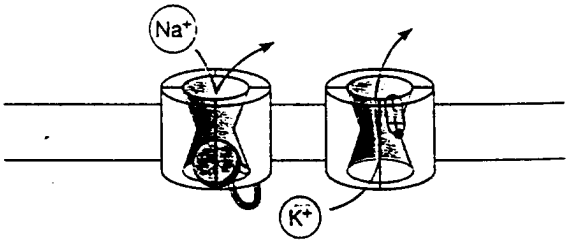
1 Resting state: All gated Na^+ and K^+ channels closed



2 Depolarizing phase: Na^+ channels open



3 Repolarizing phase: Na^+ channels inactivated and K^+ channels open



4 Hyperpolarizing phase (undershoot): K^+ channels remain open and Na^+ channels inactivated

Figure 22-18 Changes in Ion Channels and Currents in the Membrane of a Squid Axon During an Action Potential.
(a) The change in membrane potential caused by movement of Na^+ and K^+ through their voltage-gated channels, which are shown at each step of the action potential at right. The absolute refractory period is caused by sodium channel inactivation. Notice that, at the peak of the action potential, the membrane potential approaches the E_{Na} (sodium equilibrium potential) value of about +55 mV; similarly, the potential undershoots nearly to the E_K (potassium equilibrium potential) value of about −75 mV. **(b)** The change in membrane conductance (permeability of the membrane to specific ions). The depolarized membrane initially becomes very permeable to sodium ions, facilitating a large inward rush of sodium. Thereafter, as permeability to sodium declines, the permeability of the membrane to potassium increases transiently, causing the membrane potential to hyperpolarize.

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spreads to adjacent regions through a process called the **passive spread of depolarization.** This passive spread is due to the movement of cations (mostly potassium ions) away from the site of depolarization to regions under the membrane where the potential is more negative. As a wave of depolarization spreads passively away from the site of origin, it also decreases in magnitude, however. The fact that the depolarization fades with distance from the source makes it difficult for signals to travel very far by passive means only. For signals to travel longer distances, an action potential must be propagated, or actively regenerated, from point to point along the membrane.

To illustrate the difference between the passive spread of depolarization and the propagation of an action potential, consider how a signal travels along the nerve from the site of origin at the dendrites to the end of the axon (Figure 22-19). Incoming signals are transmitted to a nerve at synapses that form points of contact between the terminal bulbs of the transmitting neuron and the dendrites of the receiving neuron. When these incoming signals depolarize the dendrites of the receiving neuron, the depolarization spreads passively over the membrane from the dendrites to the base of the axon, the **axon hillock.** The axon hillock is the region where action potentials are initiated most easily. This is because sodium channels are distributed sparsely over the dendrites and cell body but are concentrated at the axon hillock and nodes of Ranvier. A given amount of depolarization will produce the greatest amount of sodium entry at sites where sodium channels are abundant. The depolarization that spreads passively from the dendrites initiates action potentials at the axon hillock, which are then propagated along the axon.

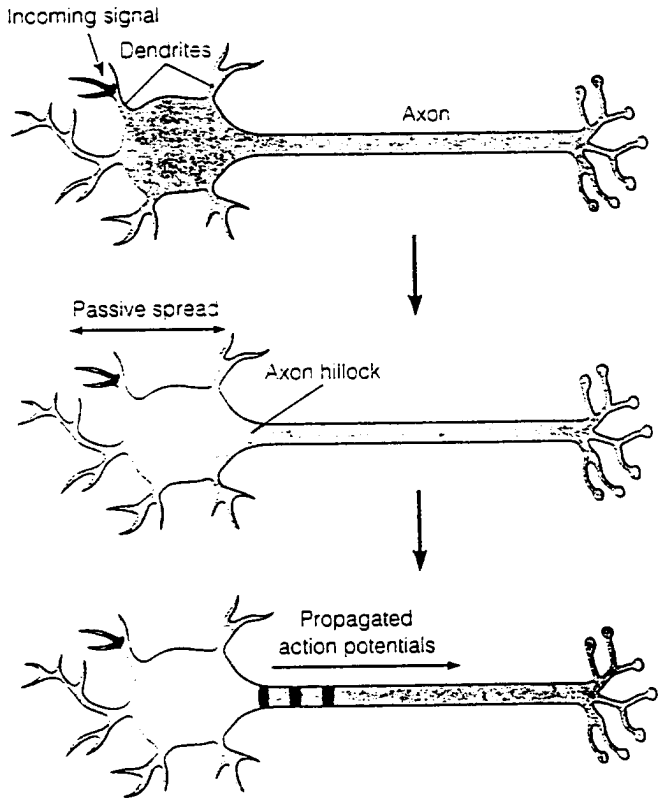

Figure 22-19 The Passive Spread of Depolarization and Propagated Action Potentials in a Neuron. The transmission of a nerve impulse along a neuron depends on both the passive spread of depolarization and the propagation of action potentials. A neuron is stimulated when its dendrites receive a depolarizing stimulus from other neurons. A depolarization starting at a dendrite will spread passively over the cell body to the axon hillock, where an action potential will form. This action potential will then be propagated down the axon.

The mechanism for propagating an action potential in nonmyelinated nerve cells is illustrated in Figure 22-20. Stimulation of a resting membrane at point *P* results in a depolarization of the membrane and a sudden rush of sodium ions into the axon at that location. Membrane polarity is temporarily reversed at that point, and this depolarization then spreads passively over a short distance to an adjacent point *Q*. Passive depolarization at point *Q* is sufficient to bring it above the threshold potential, triggering the inward rush of sodium ions. By this time, the membrane at point *P* has become highly permeable to potassium ions. As potassium ions rush out of the cell, negative polarity is restored, and that portion of the membrane returns to its resting state.

Meanwhile, the events at *Q* have stimulated the membrane in the neighboring region at *R*, initiating the same sequence of events there, which then moves on to point *S*. In this way, the signal moves along the membrane as a ripple of depolarization-repolarization events, with the membrane polarity reversed in the immediate vicinity of the signal, but returned to normal again as the signal travels down the axon. The propagation of this cycle of events along the nerve fiber is called a *propagated action potential* or **nerve impulse.** The nerve impulse can only move away from the initial site of depolarization because the sodium channels that have just been depolarized are in the inactivated state and cannot respond immediately to further stimulation.

The Energetics and Rate of Impulse Transmission

We can establish that an action potential is propagated by showing that it does not fade as it travels. This can be demonstrated by measuring changes in membrane potential from two recording electrodes, each inserted at a different distance from a stimulating electrode. The stimulating electrode will trigger an action potential, which will then travel along the axon, first passing by recording electrode 1 and

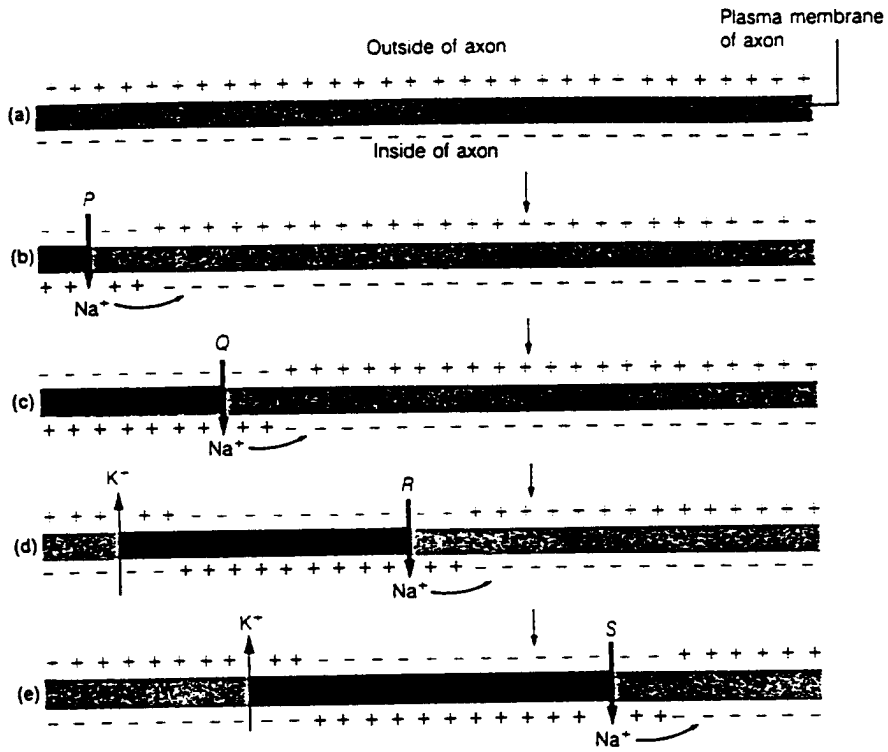

Figure 22-20 The Transmission of an Action Potential Along a Nonmyelinated Axon. A nonmyelinated axon might be viewed as an infinite string of points, each capable of undergoing an action potential. For simplicity, we will consider only the four points *P*, *Q*, *R*, and *S*, which represent adjacent regions along the plasma membrane of the axon. **(a)** At the start, the membrane is completely polarized. **(b)** When an action potential is initiated at point *P*, this region of the membrane depolarizes and briefly has a positive potential. The positively charged sodium ions will be drawn along the membrane to adjacent regions where the potential is negative. As this happens, the adjacent regions become depolarized. **(c)** When the adjacent point *Q* is depolarized to its threshold, an action potential starts here. **(d)** Meanwhile, point *P* is recovering from its action potential and has repolarized because of the outward flow of potassium ions. The action potential at point *Q* continues to propagate in the direction of point *R*. (It cannot propagate backward toward *P* because sodium channels are in a refractory, or inactivated, state, and the membrane in this region has become hyperpolarized.) The depolarization spreading from point *Q* will trigger an action potential at *R*. **(e)** Likewise, the depolarization at point *R* will eventually trigger an action potential at point *S*.

then by recording electrode 2. The magnitude of response detected by the two electrodes will be the same, even though the signal has had to travel further along the membrane to reach the second electrode.

A nerve impulse can be propagated along the membrane with no reduction in amplitude because it is constantly being renewed along the way. It is generated anew as an all-or-none event at each successive point along the membrane, using energy provided by the electrochemical ion gradients. Thus, a nerve impulse can be transmitted over essentially any distance with no decrease in strength.

The rate of action potential propagation determines how fast a signal can be transmitted through a nerve. This can be a critical issue in some situations—when an animal needs to respond quickly to danger, for example. The rate-limiting step for the speed of propagation is the passive spread of depolarization. The rate at which a depolarization event spreads passively depends, in turn, on several properties of the plasma membrane and the cytosol, including resistance of the cytosol and the capacitance of the plasma membrane (Figure 22-21).

The **resistance** of the cytosol determines how easily positively charged ions can move laterally along the inside of the membrane away from the site of depolarization. Larger axons have less resistance and thus conduct signals more rapidly. This principle is exploited in the squid giant axon, which controls the muscles involved in propelling the squid away from danger. The faster the squid can respond to danger, the better chance it has of escaping.

Membrane capacitance is another factor controlling the rate at which a depolarization event spreads passively along the membrane. **Capacitance** is the ability of the membrane to store or accumulate ions when a potential exists. When a negative membrane potential occurs, the excess negatively charged ions accumulate on the inside of the membrane, and an equal amount of positively charged ions line up along the outside of the membrane. In effect, these oppositely charged ions are attracted to each other even though

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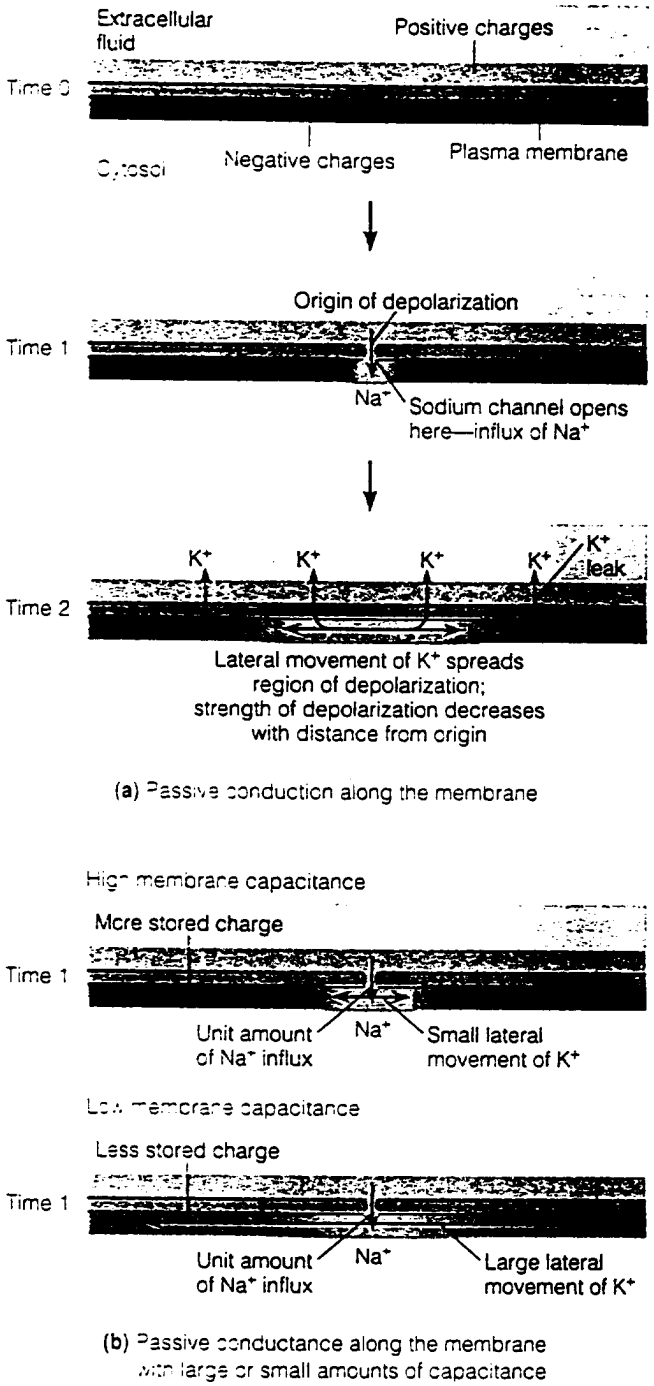

Figure 22-21 Factors Affecting the Rate of the Passive Spread of Depolarization. The rate at which depolarization spreads passively is a function of the resistance of the cytosol and the capacitance of the membrane. Reducing either resistance or capacitance will allow depolarization to spread passively both further and faster along the membrane. **(a)** A depolarization at one point on the membrane will spread passively to adjacent points on the membrane against the resistance of the cytosol. For example, where sodium enters (blue arrow), the membrane potential is depolarized. In this depolarized region, any positive ions (primarily potassium) will be drawn laterally (pink arrows) to adjacent regions where the membrane potential is more negative. As this occurs, the regions next to the point of sodium entry are also depolarized. However, due to the leakage of potassium ions from the cell and resistance, the strength of the depolarization fades with increasing distance from the site of sodium entry. **(b)** Low amounts of capacitance (charge stored in the membrane) allow a faster passive spread of depolarization.

they are separated by the lipid bilayer. The larger the capacitance, the more ions accumulate per unit area of the membrane at any given membrane potential.

To understand how capacitance affects the passive conduction of depolarization, we can ask what happens during the transition of the membrane from a negative potential to a positive potential. When, for example, sodium channels open and sodium ions rush in, each incoming sodium ion neutralizes one of the excess negative charges. A membrane potential of zero is reached when all of the excess negative charges have been matched with sodium ions. Any excess sodium ions beyond this point will drive the potential to positive values. When the capacitance of a membrane is large, there are more negative charges to neutralize, which requires a greater amount of sodium influx. Therefore, a given amount of sodium influx will cause less change in membrane potential when the membrane capacitance is large than it will when the capacitance is small. Capacitance, in other words, has the effect of dampening and slowing the passive spread of depolarization.

Accelerating Signal Transmission by Myelination. Myelination decreases the capacitance of the neuronal membrane. This reduction in membrane capacitance permits a depolarization event to spread further and faster than it would without myelination. However, myelination does not eliminate the need for propagation. For depolarization to spread from

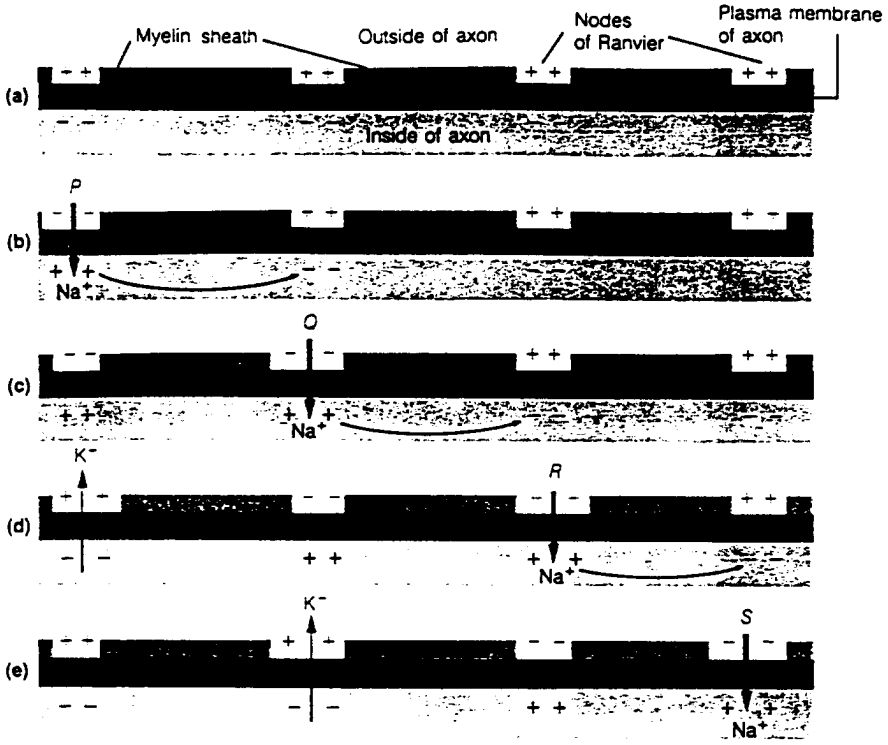

Figure 22-22 The Transmission of an Action Potential Along a Myelinated Axon. Myelination reduces membrane capacitance, thereby allowing a given amount of sodium current, entering at one point of the membrane, to spread much farther along the membrane than it would in the absence of myelin. Thus, there is much less need to regenerate the signal by the relatively slow process of generating an action potential. **(a)** In myelinated neurons an action potential is usually triggered at the axon hilliock, just before the start of the myelin sheath. The depolarization then spreads along the axon. Action potentials can only be generated at nodes of Ranvier, here represented by points *P*, *Q*, *R*, and *S*. **(b)** With myelination, the depolarization at point *P* spreads passively all the way to point *Q* and **(c)** brings *Q* to its threshold. Here a new action potential is generated that **(d)** triggers point *R* to undergo an action potential and **(e)** so on to point *S*. A nerve impulse consists of a wave of depolarization-repolarization events that is propagated along the axon from node to node.

one site to the rest of the neuron, the action potential must still be renewed periodically down the axon. The only places along a myelinated axon that can support an action potential are the nodes of Ranvier.

Nodes of Ranvier are interruptions in the myelin layer that are spaced just close enough together (1–2 mm) to ensure that the depolarization spreading out from an action potential at one node brings an adjacent node above its threshold potential. Voltage-gated sodium channels are concentrated at the nodes and therefore can generate a large response. Thus, action potentials "jump" from node to node along myelinated axons, rather than moving as a steady ripple along the membrane. Nerve impulses are thereby transmitted in a *saltatory* manner along myelinated axons, as illustrated in Figure 22-22. (*Saltatory* is derived from the Latin word for "dancing.") Saltatory propagation is much more rapid than the continuous propagation that occurs in nonmyelinated axons.

Synaptic Transmission

Nerve cells communicate with one another and with glands and muscles at synapses. There are two structurally different types of synapses, electrical and chemical. In an **electrical synapse,** the axon of one neuron, called the **presynaptic neuron,** is connected to another cell, the **postsynaptic neuron,** by gap junctions. These junctions allow ions to move back and forth between the two cells (Figure 22-23). As a result, the depolarization in one cell spreads passively to the connected cell. Electrical synapses provide for transmission with no delay and tend to occur in places in the nervous system where speed of transmission is of the essence.

In a **chemical synapse,** the presynaptic and postsynaptic neurons are close to each other but not directly connected (Figure 22-24). Typically, the synaptic terminals at the end of an axon are separated from the synaptic membrane of the dendrites by a gap of about 20–50 nm known as the **synaptic cleft.** A nerve signal arriving at the terminals of the presynaptic neuron cannot bridge the synaptic cleft as an electrical impulse. For synaptic transmission to take place, the electrical signal must be converted at the presynaptic neuron to the chemical signal of a **neurotransmitter.** Neurotransmitter molecules are stored in secretory vesicles in the synaptic knobs or terminal bulbs of the presynaptic neuron and can diffuse across the synaptic cleft when released into it. An action potential arriving at the terminal causes the neurotransmitter to be secreted into the synaptic cleft. The chemical signal must then be converted back to an electrical signal at the postsynaptic neuron. This takes place when neurotransmitter molecules bind to their receptors on the postsynaptic neuron.

Understanding how a nerve signal is transmitted across a synapse requires that we know the nature of neurotransmitters and their respective receptors. Specifically, we need to comprehend how the binding of neurotransmitter molecules to their receptors can alter the electrical activity of the postsynaptic cell, either to excite it to the threshold point or to inhibit its electrical activity. Finally, we need to understand how an action potential regulates the secretion of neurotransmitter into the synaptic cleft and the processes that terminate the signal by removing the neurotransmitter from the synaptic cleft.

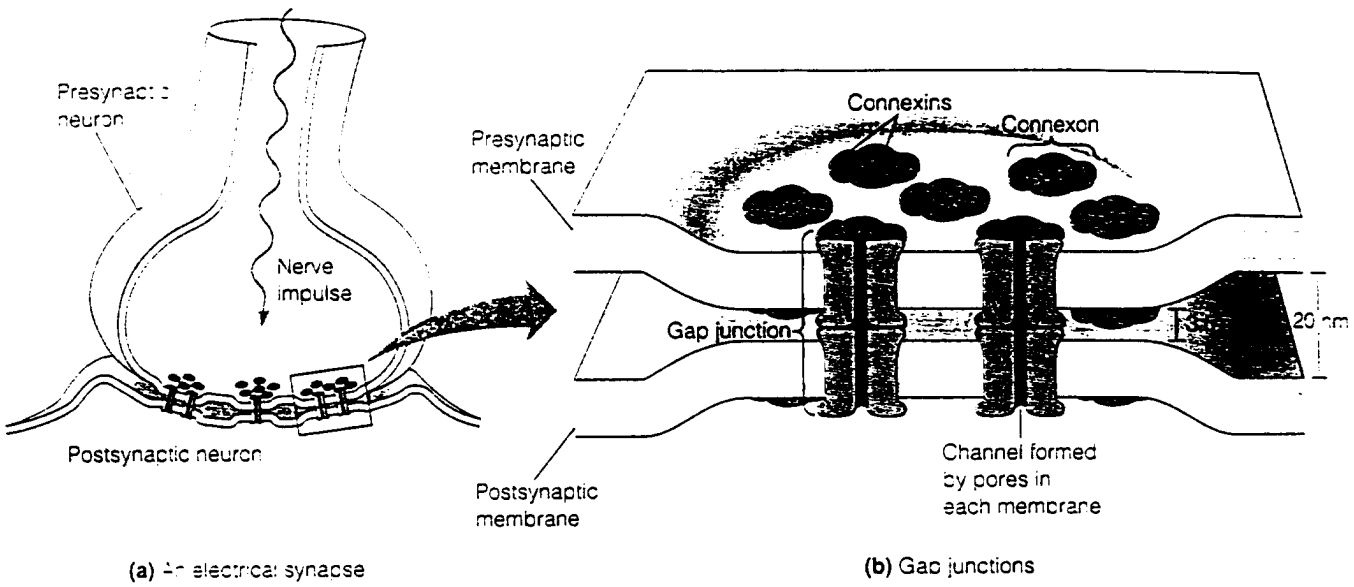

Figure 22-23 An Electrical Synapse. **(a)** In electrical synapses, the presynaptic and postsynaptic neurons are coupled by gap junctions. Gap junctions allow small molecules and ions to pass freely from the cytosol of one cell to the next. Therefore, when an action potential arrives at the presynaptic side of an electrical synapse, the depolarization spreads passively, due to the flow of positively charged ions, across the gap junction. **(b)** The gap junction is composed of sets of channels. Each channel is made up of six protein subunits called connexins. The entire set of six subunits together is called a connexon. Two connexons, one in the presynaptic membrane and one in the postsynaptic membrane, make up a gap junction.

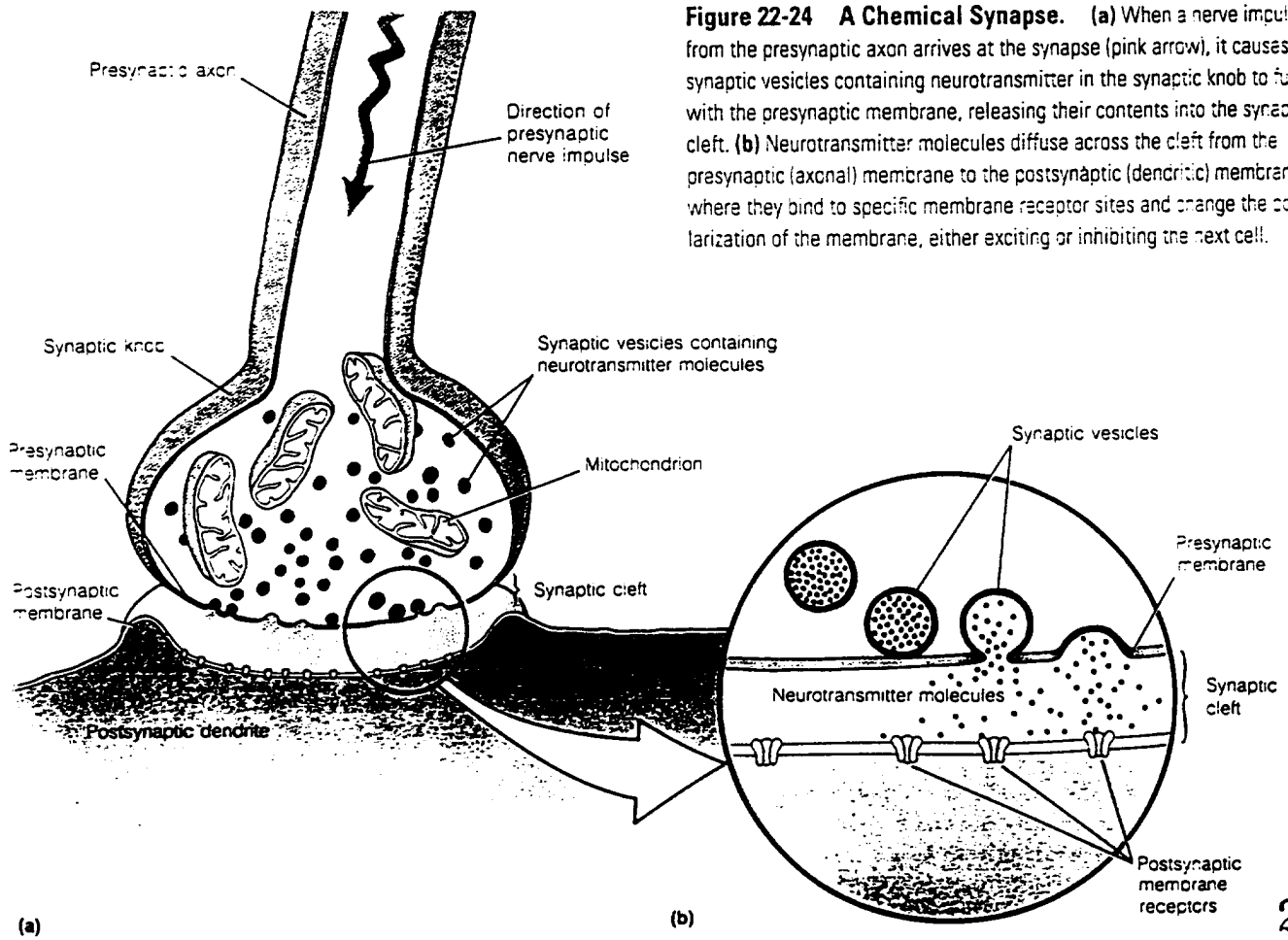

Figure 22-24 A Chemical Synapse. **(a)** When a nerve impulse from the presynaptic axon arrives at the synapse (pink arrow), it causes synaptic vesicles containing neurotransmitter in the synaptic knob to fuse with the presynaptic membrane, releasing their contents into the synaptic cleft. **(b)** Neurotransmitter molecules diffuse across the cleft from the presynaptic (axonal) membrane to the postsynaptic (dendritic) membrane, where they bind to specific membrane receptor sites and change the polarization of the membrane, either exciting or inhibiting the next cell.

Neurotransmitters

A neurotransmitter is a small molecule whose function is to bind to a receptor. Many kinds of molecules act as neurotransmitters, each with at least one specific type of receptor; some neurotransmitters have more than one type of receptor. When a neurotransmitter molecule binds to its receptor, the properties of the receptor are altered. One might compare receptors and neurotransmitters to a lock and key. The neurotransmitter, by virtue of its unique chemical structure, is the key that fits into the receptor lock. Its function is typically to turn the receptor from an "off" state to an "on" state. For a particular receptor, however, the specific meanings of "off" and "on" lie in the properties of that receptor.

Neurotransmitters can be classified as excitatory or inhibitory, depending on what happens when they bind to their receptors. An *excitatory neurotransmitter* causes depolarization of the postsynaptic neuron. The binding of an *inhibitory neurotransmitter* to its receptor, however, causes the postsynaptic cell to hyperpolarize. This can be accomplished by opening either potassium or chloride ion channels.

To qualify as a neurotransmitter, a compound must satisfy the following three criteria: (1) It must elicit the appropriate response when microinjected into the synaptic cleft, (2) it must occur naturally in the presynaptic axon, and (3) it must be released at the right time when the presynaptic membrane is stimulated. At present, molecules that meet these criteria include acetylcholine, a group of biogenic amines called the catecholamines, certain other amino acids and their derivatives, and perhaps some of the neuropeptides (see below). Figure 22-25 shows several common neurotransmitters.

Acetylcholine. In vertebrates, **acetylcholine** (Figure 22-25a) is the most common neurotransmitter for synapses between neurons outside the central nervous system, as well as for neuromuscular junctions (see Chapter 20). Acetylcholine is an excitatory neurotransmitter. Bernard Katz and his collaborators were the first to make the important observation that acetylcholine increases the permeability of the postsynaptic membrane to sodium within 0.1 msec of binding to its receptor. Synapses that use acetylcholine as their neurotransmitter are called **cholinergic synapses.**

Catecholamines. Another family of neurotransmitters is referred to as the **catecholamines** (Figure 22-25b). Catecholamines include *dopamine* and the hormones *norepinephrine* and *epinephrine*, all derivatives of the amino acid tyrosine. Because the hormones are also synthesized in the adrenal gland, synapses that use them as neurotransmitters are termed **adrenergic synapses.** Adrenergic synapses are found at the junctions between nerves and smooth muscles in internal organs such as the intestines, as well as at nerve-nerve junctions in the brain. The mode of action of the adrenergic hormones will be considered in Chapter 23.

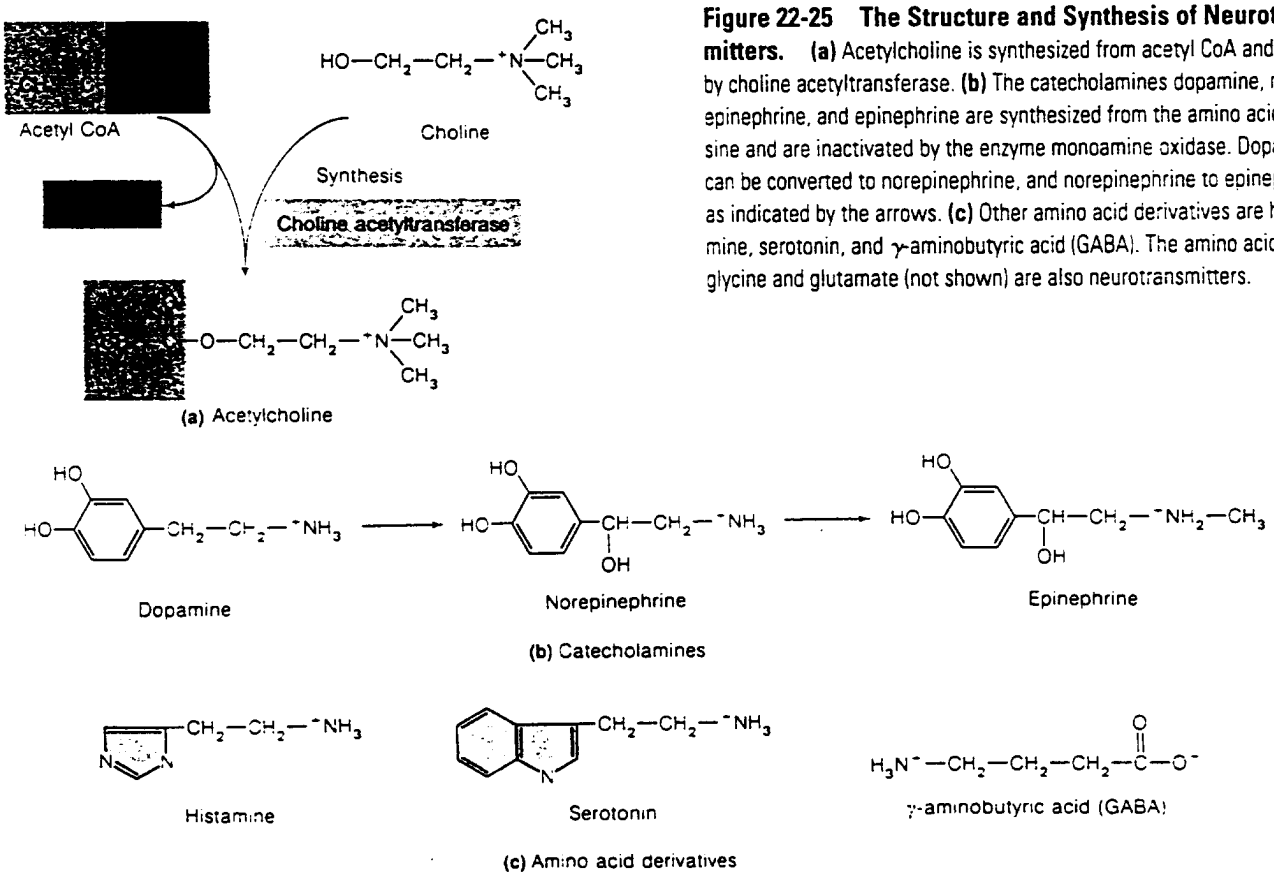

Figure 22-25 The Structure and Synthesis of Neurotransmitters. **(a)** Acetylcholine is synthesized from acetyl CoA and choline by choline acetyltransferase. **(b)** The catecholamines dopamine, norepinephrine, and epinephrine are synthesized from the amino acid tyrosine and are inactivated by the enzyme monoamine oxidase. Dopamine can be converted to norepinephrine, and norepinephrine to epinephrine, as indicated by the arrows. **(c)** Other amino acid derivatives are histamine, serotonin, and γ-aminobutyric acid (GABA). The amino acids glycine and glutamate (not shown) are also neurotransmitters.

Other Amino Acids and Derivatives. Other neurotransmitters that consist of amino acids and derivatives include *histamine, serotonin, γ-aminobutyric acid (GABA), glycine,* and *glutamate* (Figure 22-25c). Serotonin functions in the central nervous system. It is considered an excitatory neurotransmitter because it indirectly causes potassium channels to close, which has an effect similar to opening sodium channels in that the postsynaptic cell is depolarized. However, its effect is exerted much more slowly than that of sodium channels. GABA and glycine are inhibitory neurotransmitters, while glutamate has an excitatory effect.

Neuropeptides. In addition to the neurotransmitters described above, neurons can secrete short chains of amino acids called **neuropeptides.** Neuropeptides are formed by proteolytic cleavage of precursor proteins and can be stored in the secretory vesicles similar to those that hold neurotransmitters. At present, over 50 different neuropeptides have been identified. Some neuropeptides exhibit characteristics similar to neurotransmitters in that they excite, inhibit, or modify the activity of other neurons in the brain. However, they differ from typical neurotransmitters in that they act on groups of neurons and have long-lasting effects. Examples of this group of neuropeptides include *substance P* and the *enkaphalins,* which target regions of the brain involved with the perception of pain. Other neuropeptides act on tissues outside of the brain and are often classified as *endocrine hormones* (see Chapter 23). Examples of this group of neuropeptides are *prolactin, growth hormone,* and *leutinizing hormone.*

Neurotransmitter Receptors

Neurotransmitter receptors fall into two broad groups: ligand-gated ion channels, in which activation has a direct effect on the cell, and receptors that exert their effects indirectly through a system of intracellular messengers. We will focus here on the ligand-gated channels and leave the other category for Chapter 23.

Ligand-gated channels are ion channels in the plasma membrane that open in response to the binding of a neurotransmitter. Functionally, the ligand-gated channel class of neurotransmitter receptors can mediate either excitatory or inhibitory responses in the postsynaptic cell.

The Acetylcholine Receptor. Acetylcholine binds to the ligand-gated sodium channel known as the *nicotinic acetylcholine receptor.* When two molecules of acetylcholine bind, the channel opens and lets sodium ions rush into the postsynaptic neuron, causing a depolarization.

Our understanding of synaptic transmission has been greatly aided by the ease with which membranes rich in acetylcholine receptors can be isolated from the electric organs of the electric ray (*Torpedo californica*), an organism that is also useful as a source of sodium channel protein. The electric organ consists of *electroplaxes*—stacks of cells that are innervated on one side but not on the other. The innervated side of the stack can undergo a potential change from about −90 mV to about +60 mV upon excitation, whereas the noninnervated side stays at −90 mV. A potential difference of about 150 mV can therefore be built up across a single electroplax at the peak of an action potential. Because the electric organ contains thousands of electroplaxes arranged in series, their voltages are additive, allowing the organism to deliver a jolt of several hundred volts.

When electroplax membranes are examined under the electron microscope, they are found to be rich in rosettelike particles about 8 nm in diameter (Figure 22-26a). Each such particle consists of five subunits arranged around a central axis, which is assumed to be the ion channel. Their size and reaction with antibodies indicate that these structures are the acetylcholine receptors.

The acetylcholine receptor from the electric ray can be purified by solubilizing electroplax membranes with nonionic detergents, followed by several chromatographic procedures. Purification of the acetylcholine receptor was greatly aided by the availability of several substances from snake venom, including *α-bungarotoxin* and *cobratoxin* (see Box 22A, page 744). These toxins serve as a highly specific means of locating and quantifying acetylcholine receptors, because they can be made highly radioactive and they bind to the receptor protein very tightly and specifically. The radioactive toxin can therefore be used as an assay for the acetylcholine receptor after each step in the purification procedure.

The purified acetylcholine receptor has a molecular weight of about 300,000 and consists of four kinds of subunits—α, β, γ, and δ—each containing about 500 amino acids. The transmembrane segment of each subunit includes sequences of relatively hydrophobic amino acids, which probably form α helices grouped together in the plane of the bilayer. The intact receptor contains the subunits in the ratio 2:1:1:1 (Figure 22-26b and c), so the simplest empirical formula for the receptor protein is $\alpha_2\beta\gamma\delta$.

The GABA Receptor. The GABA receptor is also a ligand-gated channel, but when open, it conducts chloride ions rather than sodium ions (Figure 22-27). By opening chloride channels, the activated GABA receptor inhibits formation of an action potential.

To understand this mechanism, we need to see how increasing permeability to chloride opposes the depolarization of the membrane caused by sodium influx. Sodium ions depolarize the membrane as long as they enter the cell unaccompanied by a negatively charged ion. As we discussed previously, if a chloride ion entered at the same time as a sodium ion, there would be no net effect on the membrane potential. Sodium ions normally diffuse across the membrane much faster than chloride ions, but increasing the permeability of the membrane to chloride ions tends to negate this difference. When the membrane is depolarized and sodium ions enter, more chloride ions enter also.

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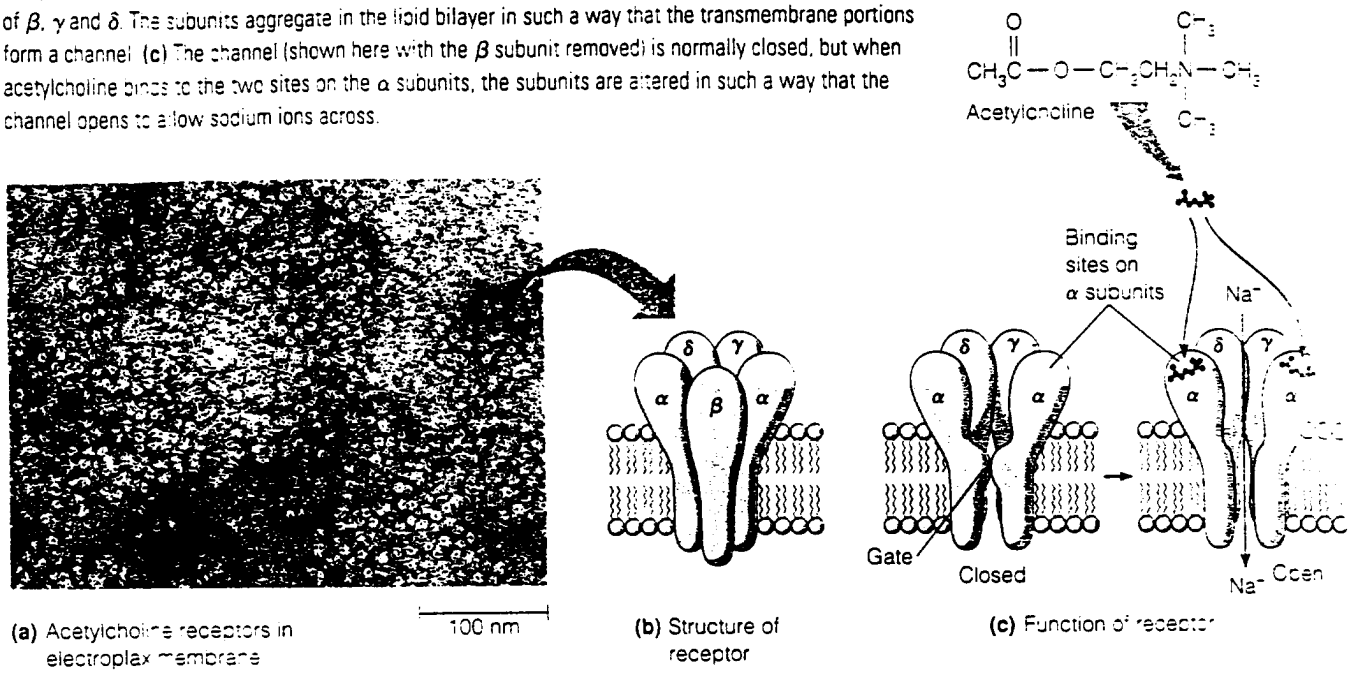
Figure 22-26 The Acetylcholine Receptor. The acetylcholine receptor is the primary excitatory receptor of the central nervous system. **(a)** This micrograph of an electroplax postsynaptic membrane shows the rosette like particles thought to be the acetylcholine receptors of the membrane (TEM). **(b)** This receptor contains five subunits, including two α subunits with binding sites for acetylcholine and one each of β, γ and δ. The subunits aggregate in the lipid bilayer in such a way that the transmembrane portions form a channel. **(c)** The channel (shown here with the β subunit removed) is normally closed, but when acetylcholine binds to the two sites on the α subunits, the subunits are altered in such a way that the channel opens to allow sodium ions across.



(a) Acetylcholine receptors in electroplax membrane

(b) Structure of receptor

(c) Function of receptor

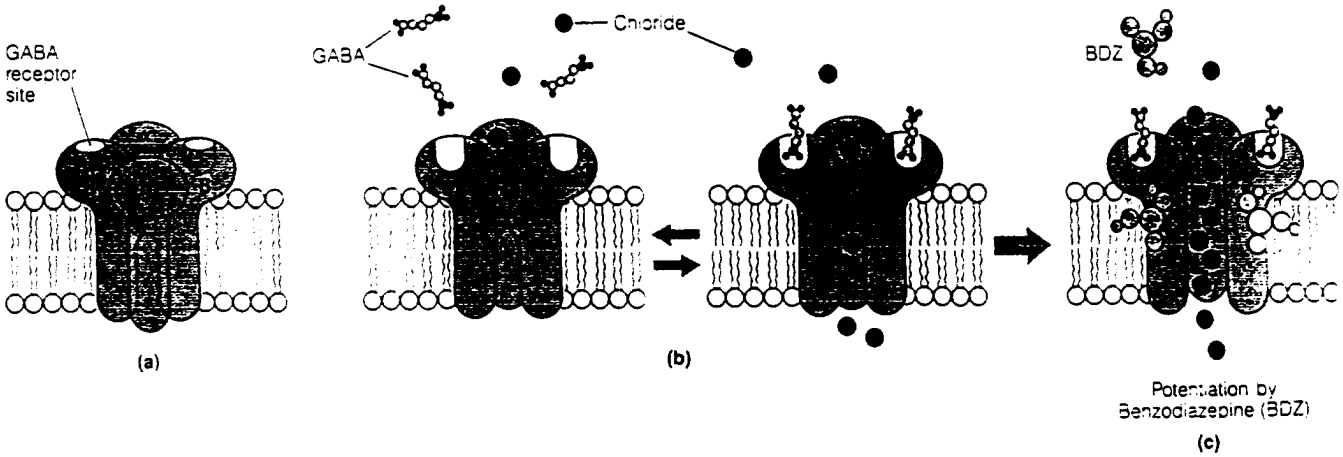


Figure 22-27 The GABA Receptor. The GABA receptor is the primary inhibitory receptor of the central nervous system. **(a)** It is composed of two α subunits and two β subunits, and each β subunit has binding sites for GABA. **(b)** When GABA is present, the channel assumes a configuration that permits chloride ions to enter the cell down their concentration gradient. This increased chloride permeability can lead to both a small hyperpolarization and chloride entry along with sodium ions. Both effects raise the threshold for stimulating an action potential and thus decrease neuronal excitability. Several pharmacologically active agents act at the GABA receptor. For instance, **(c)** when benzodiazepines (BDZ) bind to the receptor, the effect of GABA is enhanced and the overall level of excitability is reduced. Presumably, this produces the tranquilizing effect of benzodiazepine drugs such as Valium and Librium.

Neurotransmitter Secretion

Neurotransmitter molecules are stored in small membrane-bounded **neurosecretory vesicles** in the terminal bulbs. For the neurotransmitter to act on the postsynaptic cell, it must be secreted by the process of exocytosis (see Chapter 5). During this process, the membrane of the vesicles moves into close contact with the plasma membrane of the axon

terminal and then fuses with it to release the contents of the vesicle.

As we learned in Chapter 9, secretory processes are either constitutive or regulated. *Constitutive secretion* is an unregulated, ongoing process, whereas *regulated secretion* occurs only in response to a specific signal, which is needed to induce fusion. In a wide variety of cell types, the immediate signal for regulated secretion is an increase in intracellular calcium. This can be demonstrated experimentally using a compound called a *calcium ionophore*. Ionophores are molecules that carry a normally impermeable ion across a lipid bilayer, such as the plasma membrane (see Box 8B, p. 209). Several different ionophores have been isolated from bacteria and fungi, each exhibiting selectivity for a particular kind of ion. For example, a calcium ionophore carries calcium ions into the cytosol from the extracellular medium, causing the cytosolic calcium concentration to increase. In cells capable of regulated secretion, experimental application of a calcium ionophore stimulates such secretion.

The secretion of neurotransmitter by the presynaptic cell is directly controlled by the concentration of calcium ions in the terminal bulb (Figure 22-28). Each time an ac-

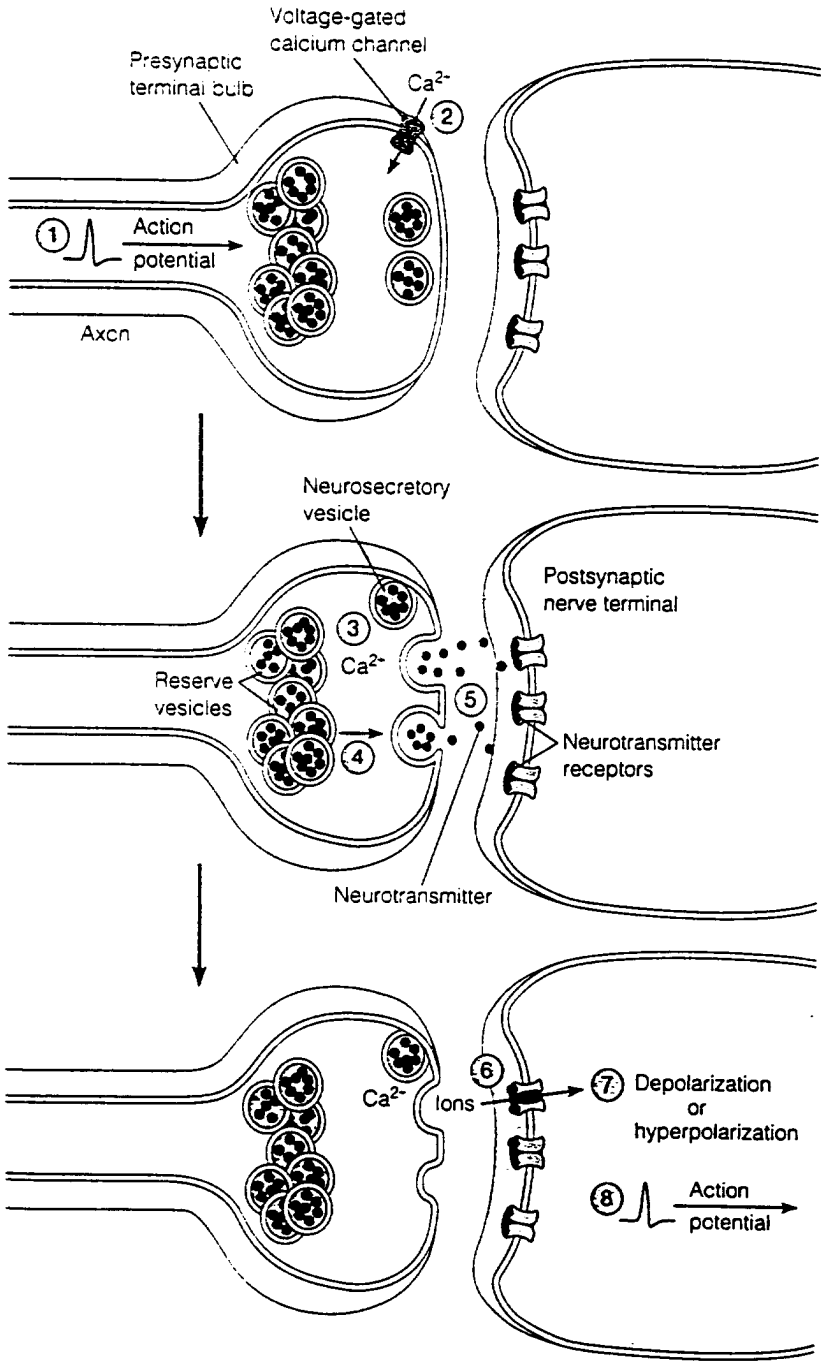


Figure 22-28 The Transmission of a Signal Across a Synapse. ① An action potential arrives at the terminal bulb, resulting in a transient depolarization. ② Depolarization opens voltage-gated calcium channels, allowing calcium ions to rush into the terminal. ③ This increase in the calcium concentration in the terminal bulb induces the secretion of a fraction of the neurosecretory vesicles. ④ Calcium also causes reserve vesicles to be released from the actin cytoskeleton so that they are ready for secretion. ⑤ Secreted neurotransmitter molecules diffuse across the synaptic cleft to receptors on the postsynaptic cell. ⑥ Binding of neurotransmitter to the receptor alters the receptor properties. ⑦ For receptors that are ligand-gated channels, the channel opens, letting ions flow into the postsynaptic cell. Depending on the ion, channel opening leads to either depolarization or hyperpolarization of the postsynaptic cell membrane. ⑧ If depolarization results, a sufficient amount of excitatory neurotransmitter will result in an action potential in the postsynaptic cell.

tion potential arrives, the depolarization causes the calcium concentration in the terminal bulb to increase temporarily due to the opening of voltage-gated calcium channels in the terminal bulbs. Normally, the cell is relatively impermeable to calcium ions, so that the cytosolic calcium concentration remains low (about 10^{-4} m*M*). However, there is a very large concentration gradient of calcium across the membrane because the calcium concentration outside the cell is about 10,000 times higher than that of the cytosol. As a result, calcium ions will rush into the cell when the calcium channels open.

The details of how calcium stimulates secretion are only beginning to be unraveled. For any given action potential, only a tiny fraction of the total number of vesicles stored in the terminal is secreted. Furthermore, only a relatively small fraction of the total number of vesicles are even available for secretion, the rest being held in reserve. Thus, in the terminal bulb there are at least two pools of vesicles, those that are available for secretion and those held in reserve. Calcium appears to act on these two kinds of neurosecretory vesicles in different ways. Calcium ions appear to trigger the conversion of vesicles from reserve status to those that are ready for secretion. In addition, for those vesicles that are ready, calcium also triggers the actual secretory event.

Neurons hold vesicles in reserve by linking them to actin microfilaments so that they cannot move close to the synaptic membrane for secretion. For the vesicles to become available for secretion, they must become disengaged from the actin meshwork. The key event controlling this transition is the phosphorylation of a protein called *synapsin* by a calcium-calmodulin-regulated kinase called *CAM kinase II*. Synapsin is an integral membrane protein found in the membrane of neurosecretory vesicles. In its unphosphorylated form, synapsin binds to actin filaments and also stimulates the polymerization of G-actin. In doing so, it anchors vesicles to actin filaments and prevents their secretion. When phosphorylated, synapsin no longer binds to actin, freeing the vesicles from the actin cytoskeleton.

Calcium ions also act directly at the secretory step to induce secretion. The key event in secretion is the fusion of the neurosecretory vesicle with the plasma membrane. When this occurs, the contents of the neurosecretory vesicle are discharged into the synaptic cleft. The fusion of neurosecretory vesicles with the plasma membrane appears to be mediated by a complex of proteins that functions as a "secretion machine." The process of vesicle-membrane fusion requires ATP and proceeds through several steps (see Figure 22-28). In the case of neurotransmitter secretion, one of these steps is calcium-dependent.

The calcium dependence of neurotransmitter secretion may be due to a protein called *synaptotagmin*, which is present on the membranes of neurosecretory vesicles. In the absence of calcium, synaptotagmin blocks one of the steps of secretion. When an action potential arrives at an axon terminal and triggers the opening of voltage-gated calcium channels, calcium enters the terminal bulb and binds to synaptotagmin. Once calcium is bound to it, synaptotagmin is no longer inhibitory and secretion proceeds.

Terminating Synaptic Transmission

For neurons to transmit signals effectively, it is just as important to turn off the stimulus as it is to turn it on. Whether excitatory or inhibitory, once the neurotransmitter has been secreted, it must be rapidly removed from the synaptic cleft or neurotransmission becomes effectively paralyzed. In fact, the persistence of an excitatory neurotransmitter such as acetylcholine renders muscles unable to relax, ultimately leading to death.

Neurotransmitters are removed from the synaptic cleft by two specific mechanisms. One is to degrade them into inactive molecules, and the other is to resorb them back into the presynaptic terminals. In the case of acetylcholine, an enzyme called *acetylcholinesterase* hydrolyzes acetylcholine into acetic acid (or acetate ion) and choline. Neither of these products can stimulate the acetylcholine receptor. A much more common method of terminating synaptic transmission is through resorption. This mechanism involves specific transporter proteins in the membrane of the presynaptic terminals that pump the neurotransmitter back into the presynaptic axon terminals.

Integration and Processing of Nerve Signals

Sending a signal across a synapse does not automatically generate an action potential in the postsynaptic cell. If we consider a cholinergic synapse, for example, there is not necessarily a one-to-one relationship between an action potential arriving at the presynaptic neuron and one initiated in the postsynaptic neuron. A single action potential causes the secretion of enough acetylcholine to produce a detectable depolarization in the postsynaptic neuron, but usually not enough to cause the firing of an action potential. These small incremental changes in potential due to the binding of neurotransmitter are referred to as *postsynaptic potentials (PSPs)*. If a neurotransmitter is excitatory, it will cause a small amount of depolarization known as an **excitatory postsynaptic potential (EPSP)** (Figure 22-29a). Likewise, if the neurotransmitter is inhibitory, it will hyperpolarize the postsynaptic neuron by a small amount; this is called an **inhibitory postsynaptic potential (IPSP)**.

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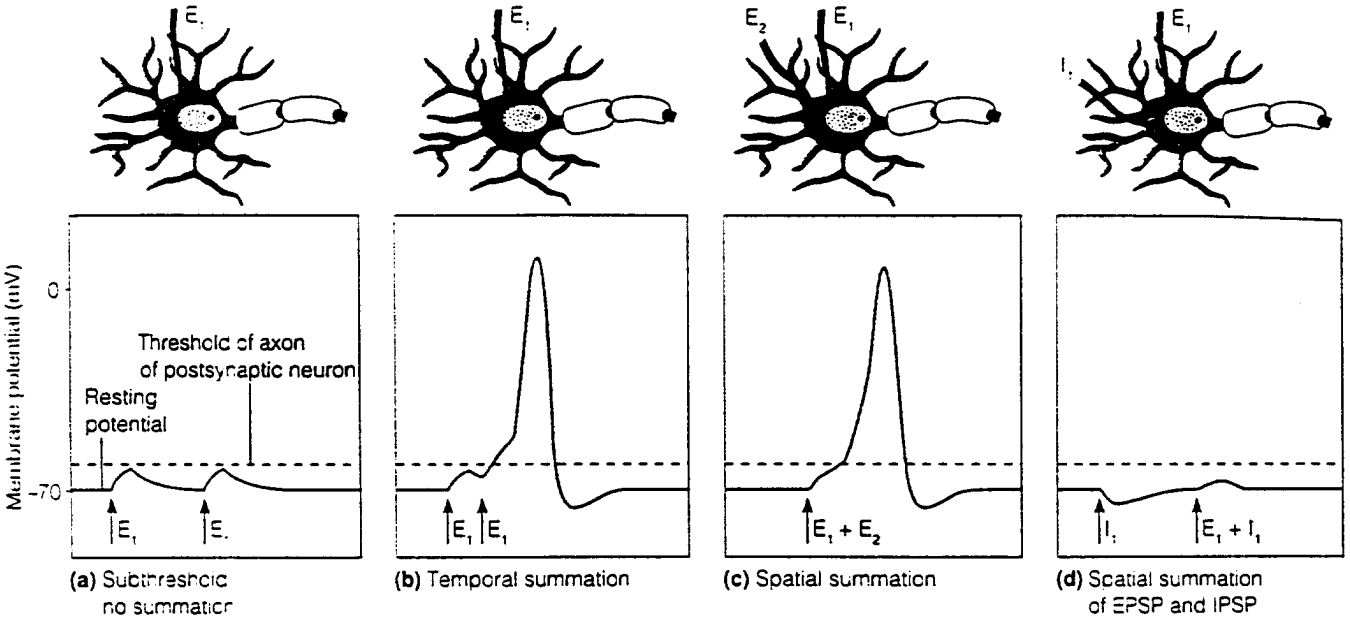

Figure 22-29 Summation of EPSPs and IPSPs. Neurons detect the strength of incoming signals and the strength of excitatory versus inhibitory inputs. **(a)** A single presynaptic action potential does not cause the release of enough neurotransmitter to produce an action potential in the postsynaptic neuron. **(b)** In temporal summation, the response of the postsynaptic neuron is determined by the rate of action potentials arriving at the presynaptic terminal bulb. The strength of a nerve signal is often encoded by varying the frequency of action potentials such that a weak stimulus produces infrequent action potentials and a strong stimulus produces frequent action potentials. When two action potentials arrive at close intervals, the effects of the two overlap and summate to produce an action potential in the postsynaptic cell. **(c)** In spatial summation, even infrequent action potentials can cause an action potential in the postsynaptic cell. This is because many neurons can form synapses with a single postsynaptic cell. If two or more neurons send an action potential at the same time, these action potentials summate. **(d)** One neuron can receive many synaptic inputs, either excitatory or inhibitory. The stimulation of inhibitory inputs makes it more difficult for excitatory transmissions to cause an action potential in the postsynaptic cell.

For a cholinergic presynaptic neuron to stimulate the formation of an action potential in the postsynaptic neuron, the EPSP must build up to a point at which the postsynaptic membrane reaches its threshold for firing an action potential. EPSPs can do so in two different ways, known as temporal and spatial summation. We will examine both means here.

Temporal Summation

As mentioned earlier, an action potential is an all-or-none event, so that neurons do not produce larger or smaller action potentials. Yet sensory neurons, for example, can detect whether the stimulus is weak or strong, and this information must be encoded in the form of action potentials. To encode the strength of a stimulus, neurons fire action potentials at different rates. If a neuron is maintained in a strongly depolarized state, it will fire a train of action potentials in rapid succession.

An individual action potential will only produce a temporary EPSP. However, if two action potentials fire in rapid succession at the presynaptic neuron, the postsynaptic neuron will not have time to recover from the first EPSP before experiencing a second EPSP. The result is that the postsynaptic neuron will be more depolarized. A rapid sequence of action potentials effectively sums EPSPs over time and brings the postsynaptic neuron to its threshold. This is called **temporal summation** (Figure 22-29b).

Spatial Summation

It was noted earlier that neurons can receive literally thousands of synaptic inputs from other neurons, and that the amount of neurotransmitter released at a single synapse during an action potential is usually not sufficient to produce an action potential in the postsynaptic cell. However, when many action potentials occur, causing the release of neurotransmitter, their effects combine, resulting in a large depolarization of the postsynaptic cell. This is known as **spatial summation** because the postsynaptic neuron integrates the numerous small depolarizations that occur over its surface into one large depolarization (Figure 22-29c).

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BOX

22A

Clinical Applications

POISONED ARROWS, SNAKEBITES, AND NERVE GASES

Because the coherent functioning of the human body depends so critically on its nervous system, anything that disrupts the transmission of nerve impulses is likely to be very harmful. And because of the importance of acetylcholine as a neurotransmitter, any substance that interferes with its function is almost certain to be lethal. Various toxins are known that disrupt nerve and muscle function by specific effects on cholinergic synapses. We will consider several of these substances, not only to underscore the serious threat they pose to human health, but also to illustrate how clearly their modes of action can be explained once the physiology of synaptic transmission is understood. We will also see how useful such compounds can be as research tools in studying the very phenomenon they disrupt so effectively.

Once acetylcholine has been released into the synaptic cleft and depolarization of the postsynaptic membrane has occurred, excess acetylcholine must be rapidly hydrolyzed. If it is not, the membrane cannot be restored to its polarized state, and further transmission will not be possible. The enzyme acetylcholinesterase is therefore essential, and substances that inhibit its activity are usually very toxic.

One such family of acetylcholinesterase inhibitors consists of *carbamoyl esters*. These compounds inhibit acetylcholinesterase by covalently blocking the active site of the enzyme, effectively preventing the breakdown of acetylcholine. An example of such an inhibitor is *physostigmine* (sometimes also called *eserine*), a naturally occurring alkaloid produced by the Calabar bean. Once used as a poison, physostigmine now finds use as an acetylcholinesterase inhibitor in studies of cholinergic transmission. Figure 22A-1 shows the structure of physostigmine and illustrates how it inhibits the enzyme by forming a stable carbamoyl-enzyme complex at the active site.

Many synthetic organic phosphates form even more stable covalent complexes with the active site of acetylcholinesterase and are therefore still more potent inhibitors. Included in this class of compounds are the widely used insecticides *parathion* and *malathion*, as well as nerve gases such as *tabun* and *sarin*. The structures of several such poisons are shown in Figure 22A-2. The primary effect of these compounds is muscle paralysis, caused by an inability of the postsynaptic membrane to regain its polarized state.

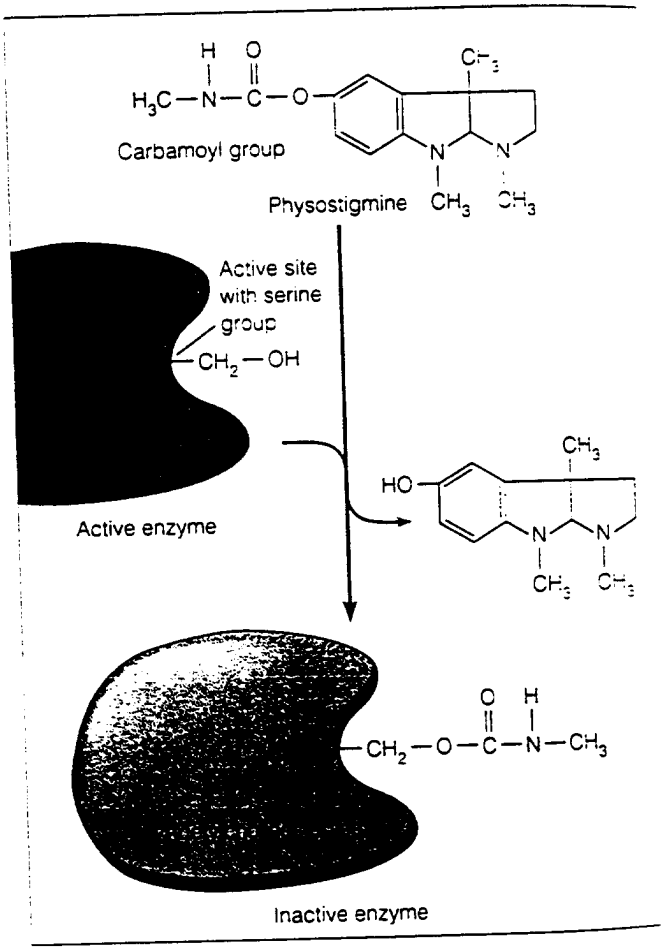
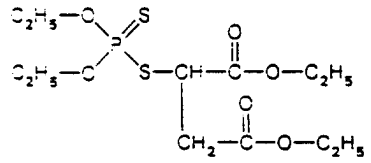
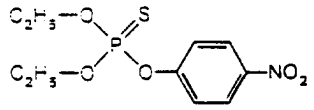


Figure 22A-1 Inactivation of Acetylcholinesterase by Physostigmine. Physostigmine is a carbamoyl ester that inactivates acetylcholinesterase by carbamoylating the serine group at the active site of the enzyme.

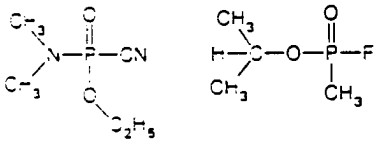
Nerve transmission at cholinergic synapses can be blocked not only by inhibitors of acetylcholinesterase, but



Malathion



Parathion



Tabun Sarin

Figure 22A-2 Structures of Several Organophosphate Inhibitors of Acetylcholinesterase.

also by substances that compete with acetylcholine for binding to its receptor on the postsynaptic membrane. A particularly notorious example of such a poison is *curare*, a plant extract once used by Native South Americans to poison arrows. One of the active factors in curare is *d-tubocurarine* (Figure 22A-3). Snake venoms act in the same way. Both α-bungarotoxin (from snakes of the genus *Bungarus*) and *cobratoxin* (from cobra snakes) are small, basic proteins that bind noncovalently to the acetylcholine receptor, thereby blocking depolarization of the postsynaptic membrane.

Substances that function in this way are referred to as *antagonists* of cholinergic systems. Other compounds, called *agonists*, have just the opposite effect. Agonists also bind to the acetylcholine receptor, but in so doing they mimic acetylcholine, causing depolarization of the postsynaptic membrane. Unlike acetylcholine, however, they cannot be rapidly inactivated, so the membrane does not regain its polarized state.

As these effects imply, agonists effectively lock the acetylcholine receptor in its "open" state, whereas antagonists essentially lock it in its "closed" state. These substances have therefore proved inordinately valuable in studying the receptor and especially the effects of its open and closed states on membrane permeability. In addition, several of these toxins have been useful in purification of the receptor protein because of their great specificity for this single protein.

An analogue of acetylcholine called *succinylcholine* is an agonist that is medically useful as a muscle relaxant (Figure 22A-4). Compared with acetylcholine, succinylcholine is hydrolyzed more slowly in vivo, resulting in a persistent depolarization of the postsynaptic membrane. The muscle relaxation that this depolarization produces at neuromuscular junctions is especially useful in surgical procedures.

Though of disparate origins and uses, poisoned arrows, snake venom, nerve gases, and surgical muscle relaxants all turn out to have some features in common. Each interferes in some way with the normal functioning of acetylcholine, and each is therefore a neurotoxin because it disrupts the transmission of nerve impulses, usually with lethal consequences. Each one has turned out to be useful as an investigative tool, illustrating again the strange but powerful arsenal of exotic tools upon which biologists and biochemists are able to draw in their continued probings into the intricacies of cellular function.

Why do you suppose that inhibition is so important for nervous function? A useful analogy is to imagine driving a car with a gas pedal only: In the absence of brakes (inhibition), it would be difficult to control the car's response. You could speed up or slow down but would have trouble making fine adjustments (not to mention stopping entirely). In the same way, most physiological functions, including nervous function, have regulatory processes that include both excitatory and inhibitory controls to "fine-tune" the response.

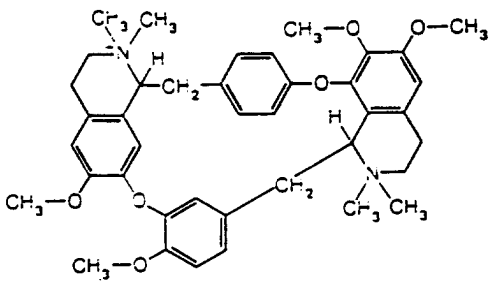


Figure 22A-3 The Structure of d-Tubocurarine.

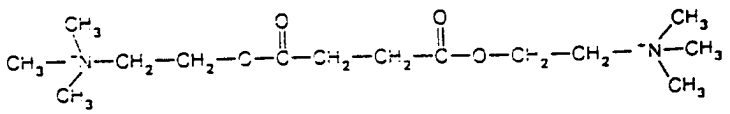


Figure 22A-4 The Structure of Succinylcholine.

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A clear example of the importance of inhibition is the effect of *strychnine*, a plant toxin, on motor control. Strychnine blocks the glycine receptors of the spinal cord, so that their normal inhibitory function is lost. As a result, excitatory motor neurons take over, producing uncontrolled convulsions that often lead to death. Another interesting example of an inhibitory response is the effect of *benzodiazepines* on the brain. The benzodiazepines are a family of pharmacologically active compounds that include the drugs Valium and Librium. GABA receptors have highly specific binding sites for benzodiazepines, which produce an enhancement of the hyperpolarizing chloride ion flux that inhibits the excitability of cells with GABA receptors (see Figure 22-27). ■

Summation of Excitatory and Inhibitory Signals

We have seen the two ways that neurons can assess the strength and significance of an incoming signal. Signal strength can be evaluated in terms of how rapidly a single neuron is firing or by how many neurons are firing all at once. Yet there is a third component to the processing of nerve signals, in which a postsynaptic neuron must respond to signals arriving from different kinds of synaptic inputs.

A postsynaptic neuron can receive synaptic inputs from different kinds of neurons, and these synapses do not necessarily all use the same neurotransmitter. A particular presynaptic neuron is capable of secreting only one type of neurotransmitter, and therefore can send only one kind of chemical stimulus to the postsynaptic cell. However, a postsynaptic neuron can receive synapses from both excitatory and inhibitory neurons (Figure 22-29d). When these different neurons fire at the same time, the postsynaptic neuron has to integrate the two kinds of signals in terms of their combined effect on the membrane potential. Thus, an individual neuron can become a "decision-making center" by virtue of its ability to determine which incoming signal (excitatory or inhibitory) is more significant.

Facilitation: Making Synaptic Transmission Stronger

We can see that synapses give neurons flexibility in how incoming signals are processed. The strength of an incoming signal can be weighed in terms of the number of action potentials received in a unit of time, whether from a few neurons firing in rapid succession or many neurons firing at the same time. When we consider that some incoming signals may be inhibitory and others excitatory, we find another level of complexity. Yet this is only part of the story.

Neurons have yet another level of complexity, referred to as **facilitation**, in which the repeated use of a synapse leads to changes that make synaptic transmission stronger. These changes can affect both the presynaptic and the postsynaptic cells. In principle, facilitation can be achieved by increasing the number of synapses formed between the presynaptic cell and the postsynaptic cell, increasing the pool of neurotransmitter vesicles that are available for secretion, or increasing the responsiveness of the postsynaptic cell. In fact, all of these methods may be involved.

Many neuroscientists believe that facilitation is closely related to learning. If so, this would also suggest that learning relates to connections between neurons. Thus, when we think of a specific memory, we might imagine that a neuron can store that memory. However, studies have shown that memory in a rat that has learned to traverse a maze cannot be localized even to a particular section of the brain. Indeed, large portions of the cerebral cortex can be removed without drastically affecting the memory. This suggests a model of learning and memory involving large numbers of neurons, a model in which memory is somehow due to active neuronal connections distributed over a vast number of neurons.

PERSPECTIVE

All cells maintain an electrical potential across their membranes, but neurons have specialized to use membrane potentials as a means of transmitting signals from one part of an organism to another. For this function they possess slender processes (dendrites and axons) that either receive transmitted impulses or conduct them to the next cell. The membrane of an axon may or may not be encased in a myelin sheath.

Cells develop a membrane potential due to the separation of positive and negative charges across the plasma membrane. This potential develops as each ion to which the membrane is permeable moves down its concentration gradient. The maximum membrane potential that an ion gradient can produce is the equilibrium potential for that ion—a theoretical condition that is not met in cells because it requires that the membrane be permeable only to that ion. However, it can be useful to calculate equilibrium potentials for specific ions using the Nernst equation. To calculate the resting membrane potential of a cell, the Goldman equation is used. This equation gives the algebraic sum of the equilibrium potentials for sodium, potassium, and chloride ions, each weighted for the relative permeability of the unstimulated membrane for that ion. The resting potential for the plasma membrane of most animal cells is usually in the range −60 to −75 mV. These values are quite near the equilibrium potential for potassium ion (usually about −75 mV), but very far from that for sodium ion (about +55 mV), reflecting the greater permeability of the resting membrane for potassium.

The action potential of a neuron represents a transient depolarization and repolarization of its membrane, due to the sequential opening and closing of sodium and potassium ion channels. These channels have been characterized structurally by molecular techniques and functionally by patch clamping. They are voltage-gated ion channels whose probability of opening, and consequently their conductance, depends on the membrane potential and the state of activation.

An action potential is initiated when the membrane is depolarized to its threshold, a point at which the rate of sodium influx exceeds the maximum rate of potassium efflux under resting conditions (usually about +20 mV). The entry of sodium ions drives the membrane potential to approximately +40 mV before voltage-gated sodium channels inactivate. Depolarization also stimulates the opening of slower voltage-gated potassium channels, which leads to repolarization of the membrane, including a short period of hyperpolarization. This sequence of channel opening and closing takes place within a few milliseconds.

The depolarization of the membrane due to an action potential spreads to adjacent regions of the membrane by passive conductance. When an adjacent region is depolarized to its threshold potential, it also undergoes an action potential. This action potential is then propagated along the membrane, eventually reaching a synapse, or junction, between a nerve cell and another cell with which it communicates. Such synapses may be either electrical or chemical. In a chemical synapse, the electrical impulse increases the permeability of the membrane to calcium. As calcium ions cross the presynaptic membrane, they cause synaptic vesicles to fuse with the membrane. The synaptic vesicles contain neurotransmitter molecules, which are released into the synaptic cleft by the fusion event. Neurotransmitter molecules migrate across the cleft to the postsynaptic membrane, where they bind to specific receptors, often ligand-gated ion channels.

The best-understood receptor is the nicotinic acetylcholine receptor of the neuromuscular junction. Binding of acetylcholine stimulates this receptor channel to open, permitting sodium to enter. The resulting sodium influx produces a local depolarization of the postsynaptic membrane, which in turn can initiate an action potential in the postsynaptic cell. Following depolarization, the enzyme acetylcholinesterase hydrolyzes the acetylcholine, thereby returning the synapse to its resting state. An example of an inhibitory receptor is the GABA (γ-aminobutyric acid) receptor, which is a voltage-gated chloride channel. Upon binding GABA, this receptor allow increased chloride influx, leading to hyperpolarization of the postsynaptic membrane and reduced neuronal excitability.

Thirty or more specific neurotransmitters have been identified in the central nervous system that can produce either excitatory or inhibitory postsynaptic potentials. Therefore, transmission of an action potential from one neuron to another requires that the cell body of the postsynaptic neuron integrate the excitatory and inhibitory activity of thousands of synaptic inputs. Because the nerve cell body has a relatively low density of sodium channels, it is less excitable than the axon hillock. Through temporal or spatial summation, however, incoming signals can depolarize the nerve cell body sufficiently to initiate a new action potential at the axon hillock.

KEY TERMS FOR SELF-TESTING

The Nervous System

nervous system (p. 714)
central nervous system (CNS) (p. 714)
peripheral nervous system (PNS) (p. 714)
somatic nervous system (p. 714)
autonomic nervous system (p. 714)
neuron (p. 714)
sensory neuron (p. 714)
motor neuron (p. 714)
interneuron (p. 714)
glial cell (p. 714)
cell body (p. 716)
process (p. 716)
dendrite (p. 716)
axon (p. 716)
axoplasm (p. 716)
nerve (p. 716)
terminal bulb (p. 717)
synapse (p. 717)
myelin sheath (p. 717)
oligodendrocyte (p. 717)
Schwann cell (p. 717)
node of Ranvier (p. 717)

Electrical Properties of Neurons

membrane potential (p. 717)
resting membrane potential (V_m) (p. 717)
electrical excitability (p. 717)

Understanding Membrane Potentials

potential (voltage) (p. 719)
electrochemical equilibrium (p. 720)
equilibrium membrane potential (p. 720)
Nernst equation (p. 720)
Donnan equilibrium (p. 720)
sodium-potassium pump (p. 722)
depolarization (p. 722)
steady-state ion movement (p. 723)
Goldman equation (p. 723)

Electrical Excitability

ion channel (p. 724)
voltage-gated ion channel (p. 724)
ligand-gated ion channel (p. 724)
channel inactivation (p. 725)
patch clamping (p. 726)
gating current (p. 727)

The Action Potential

threshold potential (p. 729)
action potential (p. 729)
propagation (p. 729)
subthreshold depolarization (p. 731)
hyperpolarization (undershoot) (p. 731)
absolute refractory period (p. 731)
relative refractory period (p. 731)

The Propagation of an Action Potential

passive spread of depolarization (p. 733)
axon hillock (p. 733)
nerve impulse (p. 733)
resistance (p. 734)
capacitance (p. 734)

Synaptic Transmission

electrical synapse (p. 736)
presynaptic neuron (p. 736)
postsynaptic neuron (p. 736)
chemical synapse (p. 736)
synaptic cleft (p. 736)
neurotransmitter (p. 736)
acetylcholine (p. 738)
cholinergic synapse (p. 738)
catecholamine (p. 738)
adrenergic synapse (p. 738)
neuropeptide (p. 739)
neurosecretory vesicle (p. 740)

Integration and Processing of Nerve Signals

excitatory postsynaptic potential (EPSP) (p. 742)
inhibitory postsynaptic potential (IPSP) (p. 742)
temporal summation (p. 743)
spatial summation (p. 743)
facilitation (p. 746)

PROBLEM SET

22-1. The Truth About Nerve Cells. For each of the following statements, indicate whether it is true of all nerve cells (A), of some nerve cells (S), or of no nerve cells (N).

(a) The axonal endings make contact with muscle or gland cells.

(b) An electrical potential is maintained across the axonal membrane.

(c) The axon is surrounded by a discontinuous sheath of myelin.

(d) The resting potential of the membrane is much closer to the equilibrium potential for potassium ions than to that for sodium ions because the sodium-potassium pump maintains a much larger transmembrane gradient for potassium than for sodium.

(e) Excitation of the membrane results in a permanent increase in its permeability to sodium ions.

(f) The electrical potential across the membrane of the axon can be easily measured using electrodes.

(g) Both the sodium and potassium concentration gradients completely "collapse" every time a nerve impulse is transmitted along the axon.

(h) Upon arrival at a synapse, a nerve impulse causes the secretion of acetylcholine into the synaptic cleft.

22-2. The Resting Membrane Potential. The Goldman equation is used to calculate V_m, the resting potential of a biological membrane. As presented in the chapter, it contains terms for sodium, potassium, and chloride ions only.

(a) Why do only these three ions appear in the Goldman equation as it applies to nerve impulse transmission?

(b) Suggest a more general formulation for the Goldman equation that would be applicable to membranes that might be selectively permeable to other monovalent ions as well.

(c) Would the version of the Goldman equation you suggested in part b be adequate for calculating the resting potential of the membrane of the sarcoplasmic reticulum in muscle cells? Explain.

(d) How much would the resting potential of the membrane change if the relative permeability for sodium ions were 1.0 instead of 0.01?

(e) Would you expect a plot of V_m versus the relative permeability of the membrane to sodium to be linear? Why or why not?

22-3. Equilibrium Potentials Versus Resting Potentials. Based on the Nernst equation, the equilibrium membrane potential for potassium (E_K) is about −15 mV more negative than the measured resting potential of the cell. For mammalian neurons, the measured resting potential is −75 mV and E_K is −90 mV. However, the equilibrium membrane potential for sodium (E_{Na}) is about +55 mV, far different from the resting membrane potential. Explain why the mammalian resting membrane potential is closer to E_K than to E_{Na}.

22-4. Patch Clamping. Patch-clamp instruments enable researchers to measure the opening and closing of a single channel in a membrane. A typical acetylcholine receptor channel passes about 5 pA of ionic current (1 picoampere = 10^{-12} ampere) at −60 mV over a period of about 5 msec.

(a) Given that an electrical current of 1 A is about 6.2×10^{18} electrical charges per second, how many ions (potassium or sodium) pass through the channel during the time it is open?

(b) Do you think the opening of a single receptor channel would be sufficient to depolarize a postsynaptic membrane? Why or why not?

22-5. The Equilibrium Membrane Potential. Answer each of the following questions with respect to E_{Cl}, the equilibrium membrane potential for chloride ions. The chloride ion concentration inside the squid giant axon can vary from 50 to 150 m*M*.

(a) Before doing any calculations, predict whether E_{Cl} will be positive or negative. Explain.

(b) Now calculate E_{Cl}, assuming an internal chloride concentration of 50 m*M*.

(c) How much difference would it make in the value of E_{Cl} if the internal chloride concentration were 150 m*M* instead?

(d) Why do you suppose the chloride concentration inside the axon is so variable?

22-6. Heart Throbs. An understanding of muscle cell stimulation involves some of the same principles as nerve cell stimulation, except that calcium ions play an important role in the former. The following ion concentrations are typical of those in human heart muscle and in the serum that bathes the muscles:

$[K^+]$: 130 m*M* in cell, 4.6 m*M* in serum
$[Na^+]$: 10 m*M* in cell, 145 m*M* in serum
$[Ca^{2+}]$: 0.001 m*M* in cell, 6 m*M* in serum

Figure 22-30 depicts the change in membrane potential with time upon stimulation of a cardiac muscle cell.

(a) Calculate the equilibrium membrane potential for each of the three ions, given the concentrations listed.

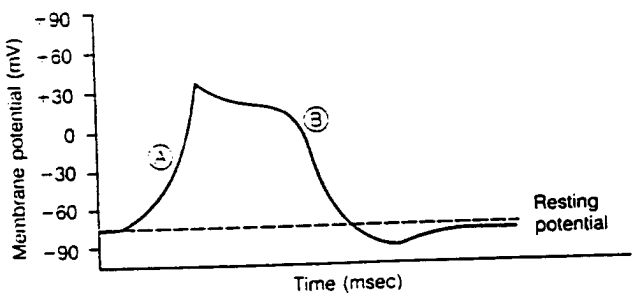

Figure 22-30 The Action Potential of a Muscle Cell of the Human Heart.

(b) Why is the resting membrane potential significantly more negative than that of the squid axon (−75 mV versus −60 mV)?

(c) The increase in membrane potential in the region of the graph marked ① could in theory be due to the movement across the membrane of one or both of two cations. Which cations are they, and in what direction would you expect each to move across the membrane?

(d) How might you distinguish between the possibilities suggested in part c?

(e) The rapid decrease in membrane potential that is occurring in the region marked ③ is caused by the outward movement of potassium ions. What are the driving forces that cause potassium to leave the cell at this point? Why aren't the same forces operative in the region of the curve marked ②?

(f) People with heart disease often take drugs that can double or triple their serum potassium levels to about 10 m*M* without altering intracellular potassium levels. What effect should this increase have on the rate of potassium ion movement across the heart cell membrane during muscle stimulation? What effect should it have on the resting potential of the muscle?

22-7. The All-or-None Response of Membrane Excitation. A nerve cell membrane exhibits an all-or-none response to excitation; that is, the magnitude of the response is independent of the magnitude of the stimulus, once a threshold value is exceeded.

(a) Explain in your own words why this is so.

(b) Why is it necessary that the stimulus exceed a threshold value?

(c) If every neuron exhibits an all-or-none response, how do you suppose the nervous system of an animal can distinguish different intensities of stimulation? How do you think your own nervous system can tell the difference between a warm iron and a hot iron, or between a chamber orchestra and a rock band?

22-8. Excitability of Dendrites and Axons. The dendrites and cell body of a typical motor neuron have a much lower density of sodium channels than does the axon hillock or the nodes of Ranvier. Would the threshold potential be the same in the dendrites, the axon hillock, and the nodes of Ranvier? Why or why not?

22-9. One-Way Propagation. Why does the action potential move in only one direction down the axon?

22-10. Inhibitory Neurotransmitters. Some inhibitory neurotransmitters cause chloride channels to open, while others stimulate the opening of potassium channels. Explain why increasing the permeability of the neuronal membrane to either chloride or potassium would make it more difficult to stimulate an action potential. What generalization can you make about inhibitory neurotransmitters?

22-11. Trouble at the Synapse. Transmission of a nerve impulse across a cholinergic synapse is subject to inhibition by a variety of neurotoxins. Indicate, as specifically as possible, what effect each of the following poisons or drugs has on synaptic transmission and what effect each has on the polarization of the postsynaptic membrane.

(a) The snake poison α-bungarotoxin

(b) The insecticide malathion

(c) Succinylcholine

(d) The carbamoyl ester neostigmine

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