5

Generation and Conduction of Action Potentials

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. How is a nerve membrane's response to small-amplitude stimuli like a passive electric circuit comprising batteries, resistors, and capacitors?
2. What factors determine the time and length constants of a nerve membrane? How do these constants shape the electric responses of the nerve membrane?
3. How does an action potential differ from the subthreshold responses of a membrane (i.e., the passive and local responses)?
4. What is the sequence of conductances that underlies the action potential?
5. How are the responses of Na^+ and K^+ channels to membrane depolarization similar? How does the presence of the Na^+ channel inactivation gate cause the responses to differ?
6. How do the gating properties of Na^+ and K^+ channels relate to the absolute and relative refractory periods of the action potential?
7. How is the action potential propagated without decrement? What are the factors that determine its propagation velocity?
8. What are the structural properties of myelin that underlie its ability to increase conduction velocity?
9. Given the all-or-none nature of action potentials, how are the characteristics of different stimuli distinguished by the central nervous system?

An **action potential** is a rapid, all-or-none change in the membrane potential, followed by a return to the resting membrane potential. This chapter describes how action potentials are generated by voltage-dependent ion channels in the plasma membrane and propagated with the same shape and size along the length of an axon. The influences of axon geometry, ion channel distribution, and myelin on action potentials are discussed and explained. The ways in which information is encoded by the frequency and pattern of action potentials in individual cells and in groups of nerve cells are also described. Finally, because the nervous system provides important information about the external world through specific sensory receptors, general principles of sensory transduction and coding are introduced. More detailed information about these sensory mechanisms and systems is provided in other chapters.

Membrane Potentials

Observations on Membrane Potentials

When a sharp microelectrode (tip diameter, <0.5 μm) is inserted through the plasma membrane of a neuron, a difference in potential is observed between the tip of the microelectrode inside the cell and an electrode placed outside the cell. The internal electrode is approximately 70 mV negative with regard to the external electrode, and this difference is referred to as the **resting membrane potential** or, simply, the *resting potential* (see Chapter 1 for details on the basis of the resting potential). (By convention, membrane potentials are expressed as the intracellular potential minus the extracellular potential.) Neurons have a resting potential that typically is around –70 mV.

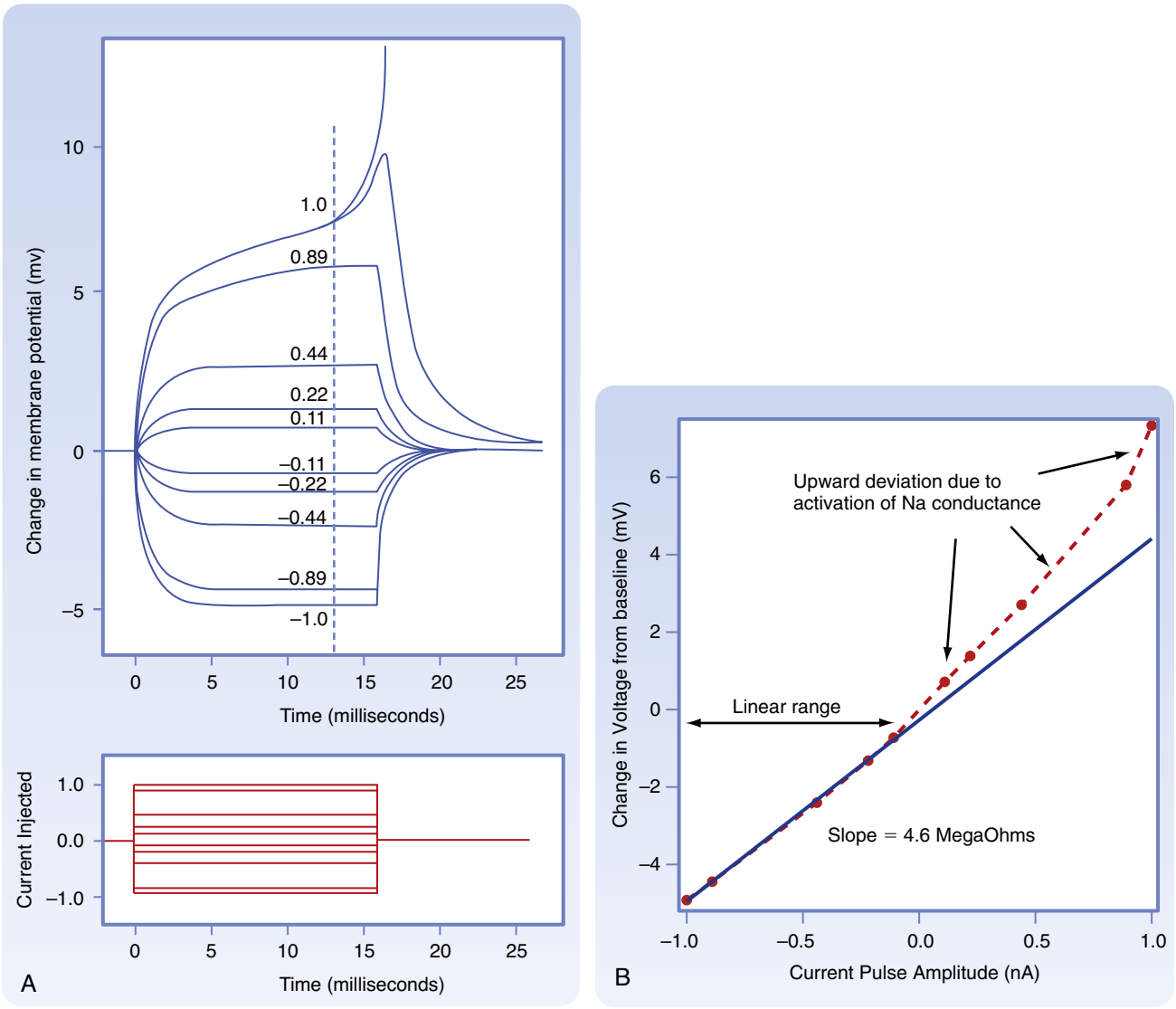
One of the signature features of neurons is their ability to change their membrane potential rapidly from rest in response to an appropriate stimulus. Two such classes of responses are action potentials and synaptic potentials, which are described in this chapter and the next, respectively. Current knowledge about the ionic mechanisms of action potentials comes from experiments with many species. One of the most studied is the squid because the large diameter (up to 0.5 mm) of the squid giant axon makes it an excellent model for electrophysiological research with intracellular electrodes.

The Passive Response

To understand how an action potential is generated and why it is needed, it is necessary to understand the passive electrical properties of the nerve cell membrane. The term *passive properties* refers to the fact that components of the cell membrane behave very similarly to some of the passive elements of electric circuits, including batteries, resistors, and capacitors. This is very useful because the properties of these elements are well understood. In particular, a piece of membrane containing ion channels responds to changes

in voltage across it much as a circuit containing a resistor and capacitor in parallel (parallel RC circuit) would: The ion channels correspond to the resistor, and the lipid bilayer acts as a capacitor. When a battery is *first* connected across the two terminals of a parallel RC circuit, all of the current flows through the branch of the circuit with the capacitor, causing the voltage across it to begin changing (recall that for a capacitor, $I \tilde{\alpha}\ dV/dt$). Over time, however, the current flow through the capacitor decreases, whereas that through the resistor increases. As this happens, the rate of voltage change across the capacitor (and resistor) slows, and the voltage approaches a steady-state value. This change in voltage has an exponential time course whose specific characteristics depend on the resistance (R) and capacitance (C) of the resistor and capacitor. Moreover, a time constant, τ, for this circuit can be defined by the equation $\tau = R \times C$, and it equals the time it takes for the voltage to rise (or fall) exponentially by approximately 63% of the difference between its initial and final values.

With regard to how an axon actually responds to electrical stimulation, Fig. 5.1 illustrates the results of an experiment in which the membrane potential of an axon is altered by passing rectangular pulses of **depolarizing** (upward-going pulses) or **hyperpolarizing** (downward-going pulses) current across its cell membrane. The injection of positive charge is depolarizing because it makes the cell less negative



• **Fig. 5.1** **A,** Voltage responses of an axon to rectangular pulses of hyperpolarizing current (*negative numbers*) or depolarizing current (*positive numbers*) as injected and recorded from an intracellular electrode. The changes in transmembrane potential are mirror images of the small-amplitude pulses. At the threshold level (current = 1.0), there is a 50:50 chance of returning to resting potential or of generating an action potential. For clarity, only the rising phase of the action potential is shown. **B,** Current-voltage (I-V) plot derived from data in **A**. Current pulse amplitude is plotted on the x-axis, and voltage response (measured at *dotted line*) is plotted on the y-axis. Note the deviation from linearity with large depolarizations, which is due to activation of voltage-gated conductances. (Redrawn from Hodgkin AL, Rushton WAH. The electrical constants of a crustacean nerve fibre. *Proc R Soc Lond B Biol Sci* 1946;133:444-479.)

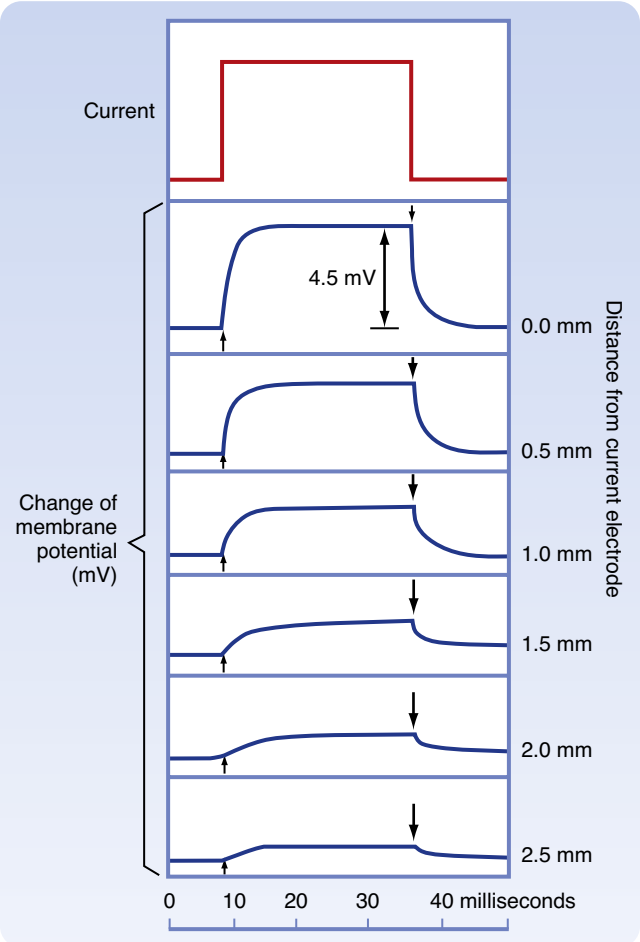
(i.e., decreases the potential difference across the cell membrane). Conversely, the injection of negative charge makes the membrane potential more negative, and this change in potential is called *hyperpolarization.* The larger the current that is injected, the greater the change in the membrane potential will be. The responses to hyperpolarizing and small-amplitude depolarizing current pulses (see Fig. 5.1*A*) all have the same fundamental shape because of the passive properties of the membrane. In contrast, the shapes of the responses to the larger depolarizing stimulus pulses differ from those to hyperpolarizing and small-amplitude depolarizing current pulses because the larger stimuli activate nonpassive elements in the membrane.

For the responses to hyperpolarizing current pulses, once a long enough time has elapsed from the start of the current pulse to allow the membrane voltage to plateau (essentially several times τ), virtually all of the injected current is flowing through the membrane resistance. If the difference between the initial and steady-state voltages is plotted against the amplitude of the current pulse (see Fig. 5.1*B*), a linear relationship is observed for the hyperpolarizing pulses, which is exactly what is expected from Ohm's law ($V = I \times R$) for current flowing through a resistor. The slope of this line ($\Delta V/\Delta I$) is referred to as the **input resistance** of the cell **(R_{in})** and is determined experimentally, exactly as just described. R_{in} is related to the **membrane resistance (r_m)** of the cell, but the exact relationship depends on the geometry of the cell and is complex in most cases.

Next, note that although the current is injected as rectangular pulses, with vertical rising and falling edges, the shape of the membrane voltage responses just after the starts and ends of the pulses has slower rises and falls. Moreover, with regard to only the responses to hyperpolarizing and small-amplitude depolarizing current pulses (see Fig. 5.1*A*), the fall and rise in the membrane voltage have exponential shapes. This shows that the membrane is responding to these current pulses as a parallel RC circuit would; that is, the stimulus causes no change in membrane resistance or **capacitance (c_m),** and thus the time course of the rise and fall in voltage is the same in all cases because it is governed by the same membrane time constant (τ).

The relationships between voltage and current just described show that within a certain range of stimulation, the cell membrane in one region of the axon can be modeled by a passive RC circuit. However, this model circuit, with only a single resistor and capacitor, takes no account of the fact that axons are spatially extended structures and that because of this, the resistance of the intracellular space is a significant factor in how electrical events in one region affect other regions. That is, if axons had no intracellular resistance, their intracellular space would be isoelectric, and voltage changes, like those just described, across one part of the axonal membrane would occur across all regions instantaneously. In this case, there would be no need for a special mechanism (i.e., the action potential) to propagate signals actively down the axon. In actuality, axons (and neurons in general) are spatially extended structures with significant resistance to current flow between different regions (this is one reason the relationship of R_{in} and r_m is complicated). Therefore, it is important to understand how current injected at one point along the axon affects the membrane potential at other points because this both helps explain why action potentials are needed and helps explain some of their characteristics.

When current pulses that elicit only passive responses are passed across the plasma membrane, the size of the change in potential recorded depends on the distance of the recording electrode from the point of passage of the current (Fig. 5.2). The closer the recording electrode is to the site of current passage, the larger and steeper the change in potential is. The magnitude of the change in potential decreases exponentially with distance from the site of passage of the current, and the change in potential is said to reflect **passive** or **electrotonic conduction.** Such passively conducted changes in potential do not spread very far along the membrane before they become insignificant. As shown



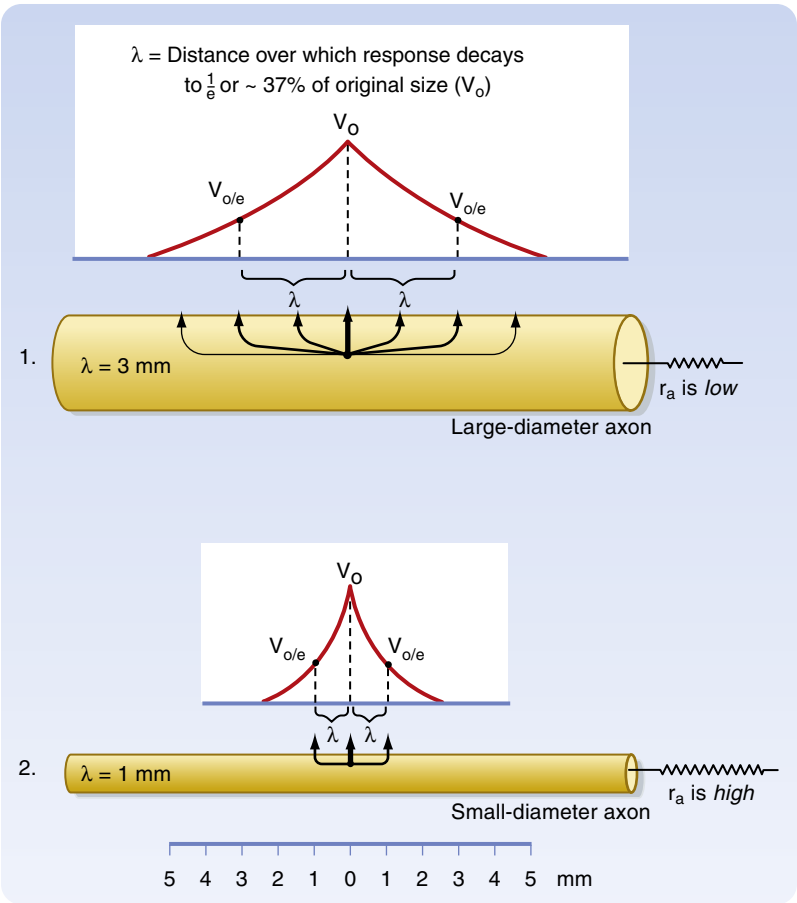
• **Fig. 5.2** Responses of an axon of a shore crab to a subthreshold rectangular current pulse by an extracellular electrode applied closely to its surface and located at different distances from the current-passing electrode. As the recording electrode is moved farther from the point of stimulation, the response of the membrane potential is slower and smaller. (Redrawn from Hodgkin AL, Rushton WAH. The electrical constants of a crustacean nerve fibre. *Proc R Soc Lond B Biol Sci* 1946;133:444-479.)

in Fig. 5.2, an electrotonically conducted signal dies away over a distance of a few millimeters. The distance over which the change in potential decreases to 1/e (37%) of its maximal value is called the **length constant** or **space constant** (where e is the base of natural logarithms and is equal to 2.7182). A length constant of 1 to 3 mm is typical for mammalian axons, which can be more than a meter long, which makes obvious the need for a mechanism to propagate information about electrical events generated at the soma to the far end of the axon.

The length constant can be related to the electrical properties of the axon according to cable theory because nerve fibers have many of the properties of an electrical cable. In a perfect cable, the insulation surrounding the core conductor prevents all loss of current to the surrounding medium, so that a signal is transmitted along the cable with undiminished strength. If an unmyelinated nerve fiber (discussed later) is compared to an electrical cable, the plasma membrane equates to the insulation and the cytoplasm as the core conductor, but the plasma membrane is not a perfect insulator. Thus the spread of signals depends on the ratio of the membrane resistance to the **axial resistance of the axonal cytoplasm (r_a)**. When the ratio of r_m to r_a is high, less current is lost across the plasma membrane per unit of axonal length, the axon can function better as a cable, and the distance that a signal can be conveyed electrotonically without significant decrement is longer. A useful analogy is to think of the axon as a garden hose with holes poked in it. The more holes there are in the hose, the more water leaks out along its length (analogous to more loss of current when r_m is low) and the less water is delivered to its nozzle.

According to cable theory, the length constant can be related to axonal resistance and is equal to $\sqrt{r_m / r_a}$. This relationship can be used to determine how changes in axonal diameter affect the length constant and, hence, how the decay of electrotonic potentials varies. An increase in the diameter of the axon reduces both r_a and r_m. However, r_m is inversely proportional to diameter (because it is related to the circumference of the axon), whereas r_a varies inversely to the diameter squared (because it is related to the cross-sectional area of the axon). Therefore, r_a decreases more rapidly than r_m does as axonal diameter increases, and the length constant increases (Fig. 5.3).

In sum, in the passive domain, the membrane response to electrical stimuli is essentially identical to that of a circuit composed of passive electrical elements, and it can thus be characterized by the length and time constants of the membrane, which will determine how far and how



• **Fig. 5.3** Comparison of the length constant to axon diameter. Note that the increase in diameter is associated with a decrease in axial resistance of the axonal cytoplasm *(r_a)* and an increase in the length constant *(λ)*. (Redrawn from Blankenship J. *Neurophysiology.* Philadelphia: Mosby; 2002.)

rapidly electrical signals at one point in the cell spread to other parts.

The Local Response

With regard to the experiment shown in Fig. 5.1, if larger depolarizing current pulses are injected, the voltage response of the membrane no longer resembles that of a passive RC circuit. This is most easily observed with pulses that elicit depolarizations either just below or to the **threshold membrane potential** for an action potential but fail to evoke an action potential (tracings 0.89 and 1.0; the threshold membrane potential can be defined as the voltage at which the probability of evoking an action potential is 50%). In these cases, the voltage response shape is altered from that of the passive responses because the stimulus has changed the membrane potential sufficiently to cause the opening of significant numbers of voltage-sensitive Na^+ channels (described later).

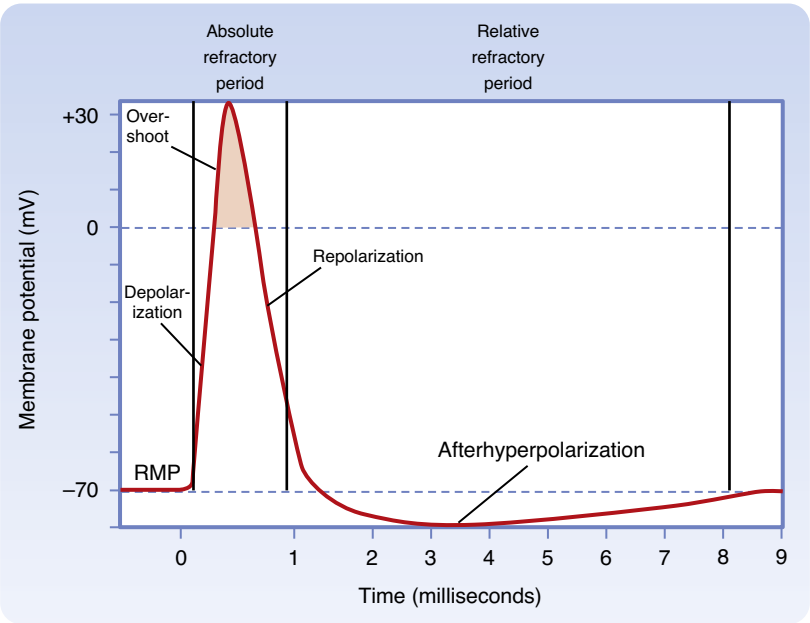
Also, note the upward deviation from linearity for the corresponding points in the I-V curve (see Fig. 5.1*B*). Opening of these voltage-sensitive channels changes the membrane's resistance and allows Na^+ to enter more easily, driven by its electrochemical gradient. This entry of positive charge (Na^+ current) enhances the depolarization by adding to the current pulse delivered by the electrode. The resulting depolarization is called a **local response.** The local response results from active changes in membrane properties (specifically, its Na^+ conductance), whereas in a passive electrotonic response, the conductance to various ions remains constant. Nevertheless, the local response is not self-regenerating but, again, decreases in amplitude with distance. The change in membrane properties is insufficient for what is needed to generate an action potential.

Suprathreshold Response: The Action Potential

Local responses will increase in size as the amplitude of the depolarizing current pulse is increased, until the threshold membrane potential is reached, at which point a different sort of response, the **action potential** (or **spike**), can occur. The threshold value is typically near −55 mV. Normally, when the membrane potential exceeds this value, an action potential is always triggered.

Fig. 5.4 shows the typical shape of an action potential. When the membrane is depolarized past threshold, the depolarization becomes explosive and overshoots in such a way that the membrane potential reverses from negative to positive and approaches, but does not reach, the Nernst equilibrium potential for Na^+ (E_{Na}; see Chapter 2). The membrane potential then returns toward the resting membrane potential **(repolarizes)** almost as rapidly as it was depolarized, and in general, it hyperpolarizes beyond its resting potential (the **afterhyperpolarization**). The main phase of the action potential (from the onset to the return to the resting potential) typically has a duration of 1 to 2 milliseconds, but for the afterhyperpolarization, it can persist from a few to 100 milliseconds, depending on the particular type of neuron.

The action potential differs from the subthreshold and passive responses in three important ways: (1) It is a response of much larger amplitude, in which the polarity



• **Fig. 5.4** Components of the action potential with regard to time and Voltage. *Markers* indicate the absolute and relative refractory periods. Note that the time scale for the first few milliseconds has been expanded for clarity. *RMP*, Resting membrane potential. (Redrawn from Blankenship J. *Neurophysiology.* Philadelphia: Mosby; 2002.)

of the membrane potential actually overshoots 0 mV (the cell interior becomes positive in relation to the exterior). (2) The action potential is generally propagated down the entire length of the axon without decrement (i.e., it maintains its size and shape because it is regenerated as it travels along the axon). (3) It is an **all-or-none response,** which means that a stimulus normally either produces a full-sized action potential or fails to produce one. This all-or-none nature is in contrast both to the graded nature of the passive and local responses described previously and to synaptic responses (see Chapter 6).

Ionic Basis of Action Potentials

Recall that the resting membrane potential is determined primarily by the weighted average of the Nernst potentials for Na^+ (E_{Na}) and K^+ (E_K), as defined by the chord conductance equation (see Chapter 2). The weighting factors are the conductance (g = 1/resistance) to each ion. At rest the conductance to K^+ (g_K) is high in relation to that for Na^+ (g_{Na}), and so the resting membrane potential (V_r) is closer to E_K ($V_r \cong -70$ mV). If, however, the relative conductances to these ions were to change, this would cause a corresponding change in the membrane potential. For example, an increase in g_K would hyperpolarize the membrane, whereas a decrease in g_K would depolarize the membrane because E_K is approximately −100 mV. Conversely, an increase in g_{Na} would depolarize the membrane and, if of sufficient magnitude, even lead to reversal in membrane polarity because E_{Na} is approximately +65 mV.

An axonic action potential is, in fact, the result of a rapid sequence of transient changes in g_{Na} or g_K, or both. In all axons there is a brief rise in g_{Na}, followed by a decline back to baseline levels. In some axons, this change in g_{Na} occurs against a fixed resting g_K (because of leak channels, which are not voltage-gated; discussed later). In many other cases, however, both g_{Na} and g_K change. Thus as with the resting membrane potential, the action potential depends on the opposing tendencies of (1) the Na^+ gradient to bring the resting membrane potential toward the Nernst potential for Na^+ and (2) the K^+ gradient to bring the resting membrane potential toward the Nernst potential for K^+; but in contrast to when the neuron is at rest, the g_K/g_{Na} ratio is not constant but is changing continuously. One additional difference is that because the membrane potential is changing, a capacitative current also exists, and this must also be taken into account to describe the membrane potential quantitatively during an action potential (as a corollary, note that the chord conductance equation is valid only when the membrane potential is constant because then there is no capacitative current).

The early phase of the action potential (the positive deflection of the membrane potential toward E_{Na}) is a result of a rapid increase in g_{Na} and thus of the Na^+ current (I_{Na}). These changes cause the membrane potential to move toward the equilibrium potential for Na^+. The peak of the action potential does not reach E_{Na} because the rise in g_{Na} is not infinite (i.e., the g_K/g_{Na} ratio does not fall to zero).

Because of the nature of the underlying Na^+ channels (described later), the rise in g_{Na} with depolarization is transient. Moreover, in many cases, the depolarization leads to a rise in g_K. These two factors cause the g_K/g_{Na} ratio to stop falling and start increasing; as a result, the membrane potential is driven back toward E_K and thus repolarizes toward its resting value. In cases in which the repolarization involves a rise in g_K, the membrane potential hyperpolarizes temporarily beyond its normal rest value (if g_K does not change, the drop in g_{Na} causes the membrane simply to return to its resting potential). This afterhyperpolarization occurs because g_K remains elevated for a period of time after the action potential. As g_K returns to its baseline level, the membrane potential returns to its rest value.

These changes in conductance can be explained by the properties of Na^+ and K^+ ion channels, which are described next.

Ion Channels and Gates

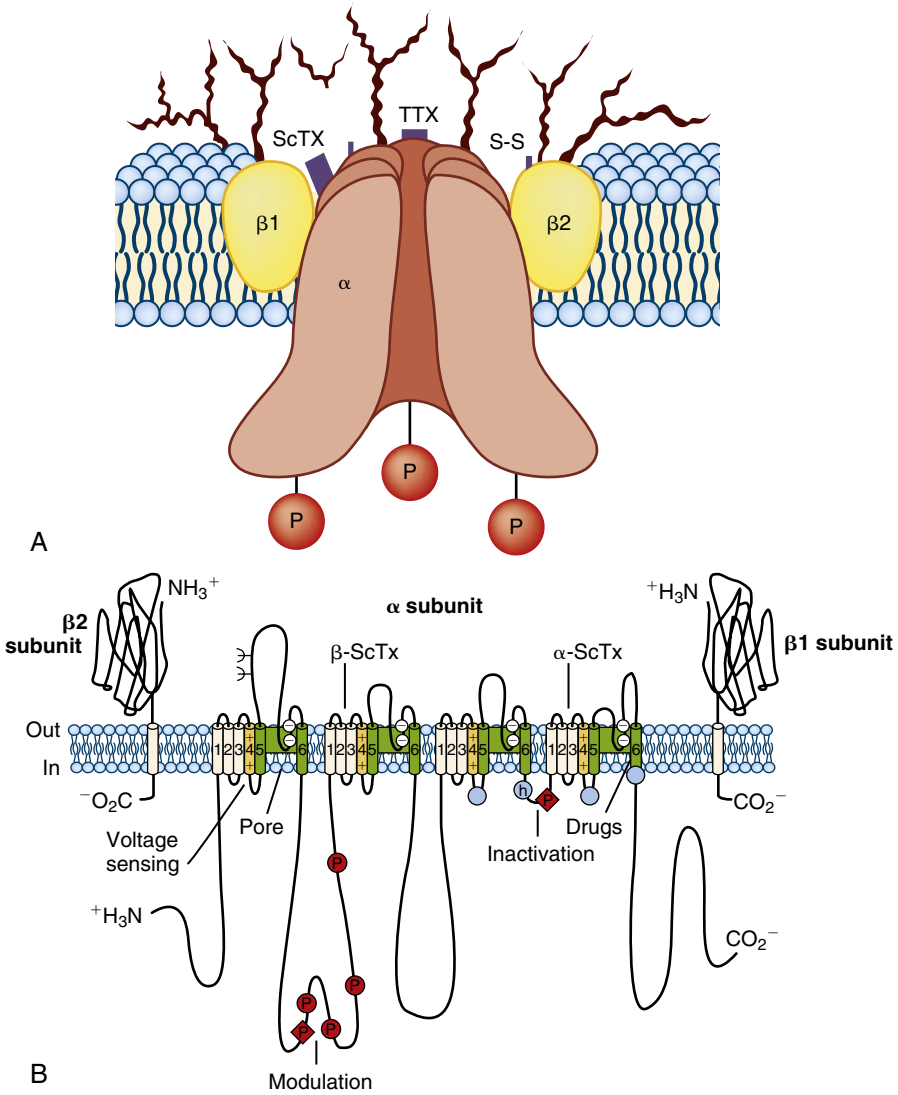
Early studies of the mechanism underlying action potentials indicated that ion currents pass through separate Na^+ and K^+ channels, each with distinct characteristics, in the cell membrane. Subsequent research has supported this interpretation. The amino acid sequences of the channel proteins and many of the functional and structural characteristics of the channels are now known in detail.

The structure of a voltage-gated Na^+ channel (Fig. 5.5) consists of four α subunits and two β subunits. The α subunit has four repeated motifs each of six transmembrane helices that surround a central ion pore. The pore walls are partly formed by the six helices in each motif. Most voltage-gated K^+ channels are composed of four separate subunits, each consisting of a polypeptide with six membrane-spanning segments, similar to the motifs that make up the α subunit of the Na^+ channel.

An important characteristic of some channels, such as those that underlie the action potential, is that they are gated by the membrane voltage. These voltage-gated channels sense changes in the potential across the membrane, and then respond by opening or closing the pore/gate, depending on the membrane voltage. The gates are formed by groups of charged amino acid residues, and the voltage dependence of the Na^+ and K^+ channel gates can account for the complex changes in g_{Na} and g_K that occur during an action potential.

The Characteristics of the Na^+ and K^+ Channels Explain the Conductance Changes During the Action Potential

Use of standard intracellular recording along with voltage-clamp techniques enabled investigators to characterize the underlying ionic currents and conductance changes associated with the action potential. Detailed statistical analyses of these recordings also allowed remarkable inferences to be made about the nature of the channels that passed these

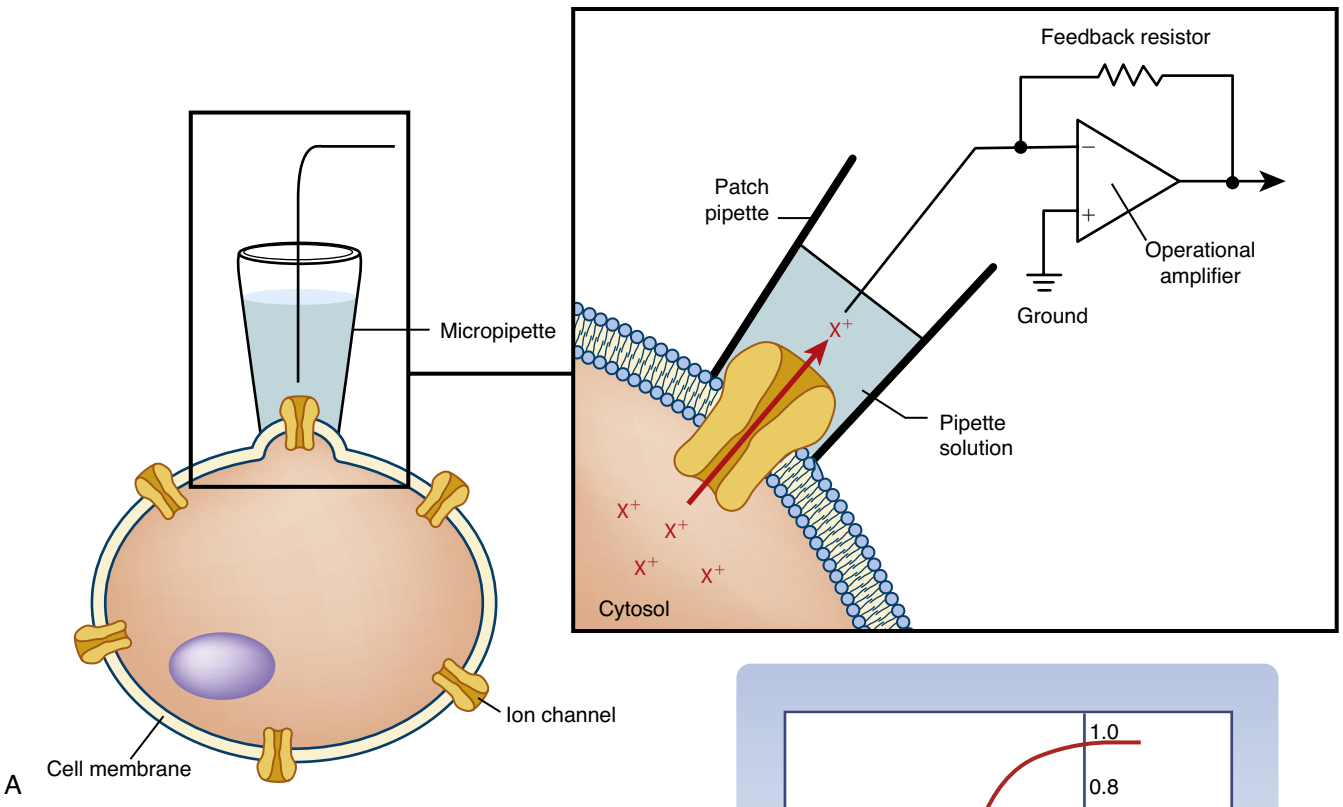


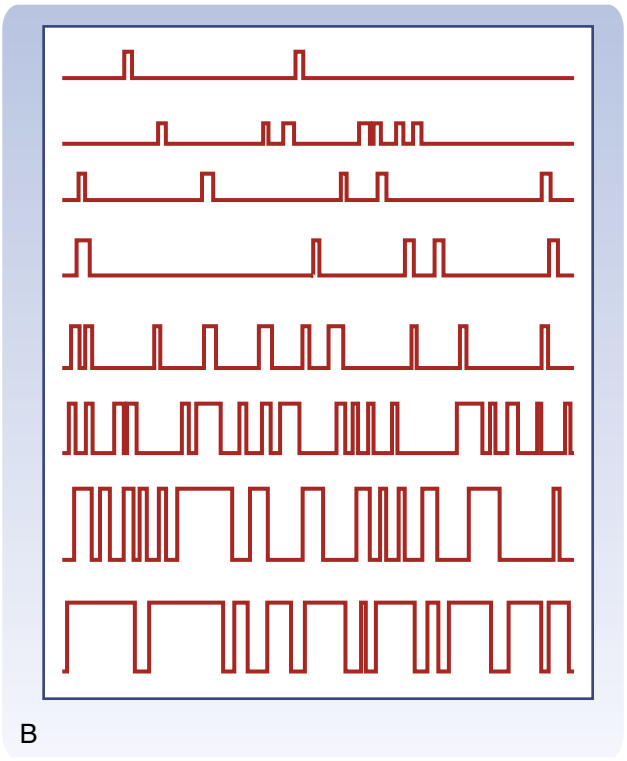
• **Fig. 5.5** A model of the voltage-gated Na^+ channel. **A,** The *large red elements* represent the four α subunits and the *two yellow elements* are β subunits with the receptor sites for α scorpion toxin *(ScTX)* and tetrodotoxin *(TTX)* indicated. **B,** β1 and β2 subunits flanking an α subunit are shown with their transmembrane helices. (Redrawn from Catterall WA. Structure and function of voltage-gated sodium channels at atomic resolution. *Exp Physiol* 2014;99:35-51.)

Na^+ and K^+ currents. The development of the **patch recording,** however, enabled direct observation of the behavior of individual channels. In this technique, a specially shaped microelectrode (tip diameter, 1 to 3 μm) is placed against the surface of a cell, and suction is applied to the microelectrode. As a result, a high-resistance seal is formed between the membrane and the tip of the microelectrode (Fig. 5.6*A*), which allows recording of the activity of whatever channels happen to be in the patch of membrane that is inside the seal. Under ideal conditions only one or a few ion channels of a single type are present in the membrane patch.

Patch recordings show that many ion channels flip spontaneously between open and closed conductance states as if they have gates that open and close the entrance to their pore. In the case of voltage-gated channels, the gate is sensitive to the voltage across the membrane, and thus the time a gate spends in each state is a probabilistic function of the membrane potential. A patch recording of a K^+ channel demonstrates this probabilistic behavior (see Fig. 5.6*B*). As the membrane potential is clamped to more depolarized levels, the channel spends more time in its open state, which reflects the voltage dependence of the probability that the channel will open (see Fig. 5.6*C*). Also, the amplitude of the current in the open state increases with the level of depolarization; this is because the driving force for K^+ is greater at more depolarized levels (i.e., the membrane potential is farther from the K^+ Nernst potential).

The behavior of a Na^+ channel is more complex than that of the K^+ channel. Like the K^+ channel, it has a voltage-sensitive gate (activation gate) whose probability of being open


Micropipette
Ion channel
Cell membrane
A
Feedback resistor
Patch pipette
Operational amplifier
Ground
Pipette solution
X+
Cytosol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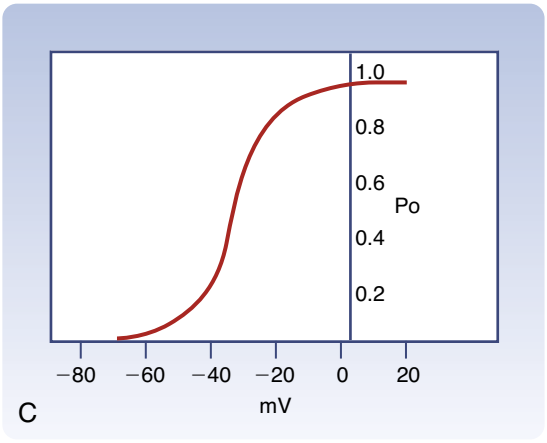
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0.8
0.6
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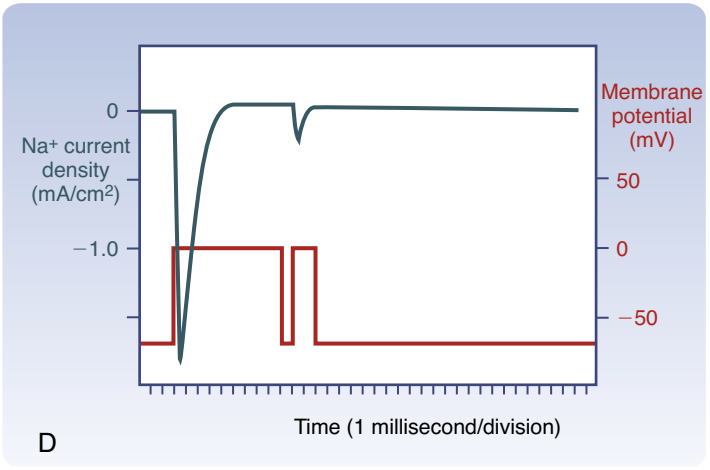
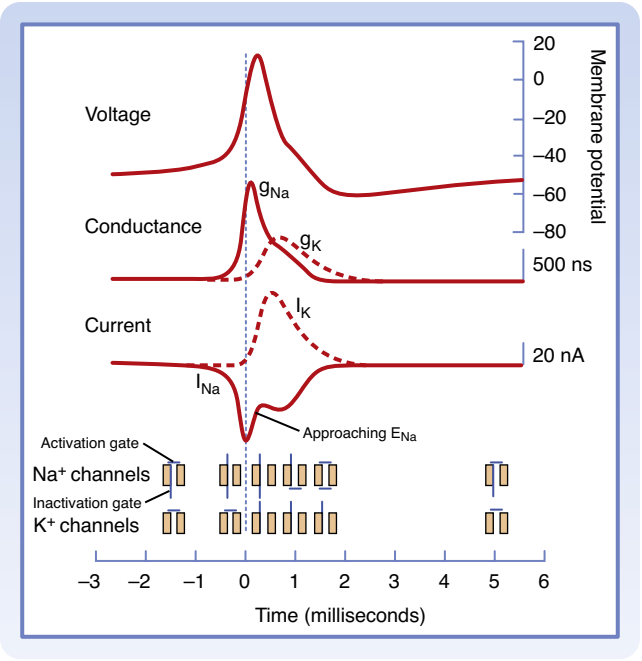

0
Na+ current density (mA/cm2)
−1.0
Membrane potential (mV)
50
0
−50
Time (1 millisecond/division)
D

• **Fig. 5.6** **A,** A micropipette is applied to the cell membrane and sufficient suction is applied to electrically isolate a single channel at the tip. An amplifier records the current that passes through the channel. **B,** Each line shows the current passed through a K^+ channel as it opens spontaneously. Note that as the transmembrane voltage is progressively depolarized (from top to bottom), both the probability that the channel will open and the amplitude of the current are increased. **C,** A graph of the probability that the channel will open versus membrane depolarization. **D,** A graph of transmembrane voltage (lower tracing, right-sided scale) and the current density from a population of Na^+ channels (upper tracing, left-sided scale) isolated in a patch similar to that in **A** (except that it contains several Na^+ channels). Initially, at resting potential, there is no current flow. With depolarization to 0 mV, there is an inward Na^+ current that is curtailed even while the depolarization continues. This is due to the closing of the channels' inactivation gates. After a brief return to resting potential, another depolarization to 0 mV evokes inward current flow, but it is smaller and briefer because there has not been enough time for most of the slow inactivation gates to reopen. (**B, C,** and **D** are redrawn from http://www.physiologymodels.info/electrophysiology.)

increases with depolarization. However, unlike K^+ channels, with maintained depolarization, Na^+ channels open only at the onset of the depolarization and then remain closed. This suggests that Na^+ channels have a second gate (*inactivation gate*) whose probability of being open decreases as the membrane is depolarized. Thus any Na^+ current conducted by these channels will be transient (see Fig. 5.6*D*), because the same stimulus (depolarization) increases both the probabilities that the activation gate will open and that the inactivation gate will close. Note that the Na^+ channel has two closed states, one in which the activation gate is closed, and the channel is said to be "closed," and the other in which the inactivation gate is closed, and the channel is referred to as "inactivated." The reason the channel is called "inactivated" when the second gate closes is that once this gate closes, it will remain so until the membrane is repolarized. The activation gate, in contrast, can open and close at all membrane potentials, just with differing probabilities.

With the knowledge of the Na^+ and K^+ channel gating behavior just discussed, we can understand how the action potential is generated by the interaction of these channels (in the following, we assume that both g_{Na} and g_K change during the action potential). As stated previously, the action potential starts with a rapid increase in Na^+ conductance (g_{Na}; Fig. 5.7). This increase in Na^+ conductance reflects the opening of many Na^+ channels in response to the depolarization. The open channels allow the influx of Na^+ ions, and the effect of this current is to depolarize the membrane further. Note that this is a positive feedback loop, which accounts for the explosive nature of the action potential: the Na^+ current depolarizes the membrane, which causes more Na^+ channels to open, which in turn increases the Na^+ current. In sum, the voltage-dependent opening of Na^+ channels and the depolarizing action of the Na^+ current account for the rising phase of the action potential.

The end of the rising phase and the subsequent falling (repolarization) phase of the action potential is the result of two processes: a reduction in g_{Na} and an increase in g_K. The rise in g_K is simply a consequence of membrane depolarization, which increases the probability that the K^+ channel will be open. The decrease in g_{Na} results from two factors. First, Na^+ channels are inactivated as a result of the closing of the inactivation gate with depolarization. Unlike the activation gate, which can flip between states even when the membrane is depolarized, the inactivation gate, once closed, remains closed until significant repolarization occurs. Second, as the g_K/g_{Na} ratio increases (as a result of both inactivation of Na^+ channels and opening of K^+ channels), the membrane begins to repolarize, and this repolarization acts to shut the activation gate of the Na^+ channel. The closure of both voltage-gated Na^+ and K^+ channels during the falling phase brings the membrane back to its resting state. If only Na^+ channels had opened during the action potential (as is the case for some axons), the membrane would simply return to its rest potential. If voltage-gated K^+ channels also



• **Fig. 5.7** The action potential and the conductance and currents that underlie the action potential with regard to time. Note that the increased conductance for Na^+ (g_{Na}), as well as its inward flow, is associated with the rising phase of the action potential, whereas the slower increase in conductance for K^+ (g_K), as well as its outward flow, is associated with repolarization of the membrane and with afterhyperpolarization. The reduction in the Na^+ current (I_{Na}) before the peak of the action potential (even though g_{Na} is still high) is due to inactivation of the Na^+ channels. (Redrawn from Squires LR, Berg D, Bloom F, et al. *Fundamental Neuroscience.* 2nd ed. San Diego, CA: Academic Press; 2002.)

had opened during the action potential, an afterhyperpolarization would be present because these K^+ channels close slowly in response to hyperpolarization.

AT THE CELLULAR LEVEL

Knowledge of the molecular structure of channels has increased the understanding of the basis of their properties. For example, most channels are highly selective for a particular ion. First, if the channel walls are lined with either positive or negative charges, then either cations or anions can be excluded; however, most channels are also differentially permeable by different ions of the same charge. This further selectivity appears to be the result of requiring ions to become dehydrated as they pass through the narrowest part of a channel, known as the **selectivity filter.** Ions in solution are hydrated (are surrounded by a shell of H_2O molecules), and the radius of this hydration shell is different for each type of ion. In Na^+ and K^+ channels, to make dehydration energetically possible, the pore of the channel is lined with negatively polarized amino acid substituents of a particular geometry, and these substituents substitute for the water molecules. Such substitution, however, requires close matching of the filter's size to the ion's hydration shell. Because each ion has a different-sized shell, a particular channel will best allow passage of one particular ionic species.

AT THE CELLULAR LEVEL

Tetrodotoxin (TTX), one of the most potent poisons known, specifically blocks the Na^+ channel. TTX binds to the extracellular side of the sodium channel (see Fig. 5.5A). **Tetraethylammonium (TEA^+),** another poison, blocks K^+ channels. TEA^+ enters the K^+ channel from the cytoplasmic side and blocks the channel because TEA^+ is unable to pass through it. The ovaries of certain species of puffer fish, also known as blowfish, contain TTX. Raw puffer fish is a highly prized delicacy in Japan. Connoisseurs of puffer fish enjoy the tingling numbness of the lips caused by the minuscule quantities of TTX present in the flesh. Sushi chefs who are trained to remove the ovaries safely are licensed by the government to prepare puffer fish. Despite these precautions, several people die each year as a result of eating improperly prepared puffer fish.

Saxitoxin is another blocker of Na^+ channels that is produced by the reddish dinoflagellates that are responsible for so-called red tides. Shellfish eat the dinoflagellates and concentrate saxitoxin in their tissues. A person who eats these shellfish may experience life-threatening paralysis within 30 minutes after the meal.

Accommodation

When a nerve is depolarized very slowly, the normal threshold may be passed without the firing of an action potential; this phenomenon is called **accommodation.** Both Na^+ and K^+ channels are involved in accommodation. In response to membrane depolarization, g_{Na} first increases and then, a short time later, decreases. This is due to the opening of the activation gates and closing of the inactivation gates of the Na^+ channels. Normally, membrane depolarization to threshold or beyond triggers an action potential; however, the explosive depolarization of the action potential can occur only if a critical number of Na^+ channels are recruited. Thus if a cell is slowly depolarized, then Na^+ channels can become inactivated without the occurrence of an action potential, and the pool of available noninactivated Na^+ channels (i.e., channels in the closed state) can be reduced to the point at which a stimulus may not be able to recruit a sufficient number of Na^+ channels to generate an action potential. An additional factor in causing accommodation is that K^+ channels open slowly in response to the depolarization. The increased g_K tends to oppose depolarization of the membrane, which makes it even less likely to fire an action potential.

Refractory Periods

When a cell is refractory, it is either completely unable to fire an action potential or it requires a much stronger stimulation than usual. During much of the action potential, the cell is completely refractory because it will not fire another action potential no matter how strongly it is stimulated. This **absolute refractory period** (see Fig. 5.4) occurs when a large fraction of the Na^+ channels are inactivated and therefore cannot be reopened until the membrane is repolarized. During this period, the critical number of Na^+ channels required to produce an action potential cannot be recruited.

IN THE CLINIC

In an inherited disorder called **primary periodic hyperkalemic paralysis,** patients have episodes of painful spontaneous muscle contractions followed by periods of paralysis of the affected muscles. These symptoms are accompanied by elevated $[K^+]$ in plasma and extracellular fluid. Some patients with this disorder have mutations of voltage-gated Na^+ channels that result in a decreased rate of voltage inactivation. This results in longer-lasting action potentials in skeletal muscle cells and increased efflux of K^+ during each action potential, which can raise extracellular $[K^+]$.

The elevation in extracellular $[K^+]$ causes depolarization of skeletal muscle cells. Initially, the depolarization brings muscle cells closer to threshold, and so spontaneous action potentials and contractions are more likely to occur. As depolarization of the cells becomes more marked, the cells become refractory because increasing numbers of Na^+ channels become inactivated. Consequently, the cells become unable to fire action potentials and are not able to contract in response to action potentials in their motor axons.

During the latter part of the action potential, and during the afterhyperpolarization period, the cell is able to fire a second action potential, but a stimulus stronger than normal is required. This period is called the **relative refractory period.** Early in the relative refractory period, before the membrane potential has returned to the resting potential level, some Na^+ channels are still voltage inactivated, but there are enough in the closed state (and therefore have the potential to open when the membrane is depolarized) to support the generation of an action potential if they are stimulated to open. However, a stimulus stronger than normal

is necessary to recruit the critical number of Na^+ channels needed to trigger an action potential (i.e., the reduction in the total number of available Na^+ channels is countered by increasing the probability of opening). Throughout the relative refractory period, conductance to K^+ is elevated, which opposes depolarization of the membrane. This increase in K^+ conductance continues throughout the afterhyperpolarization and accounts for most of the duration of the relative refractory period.

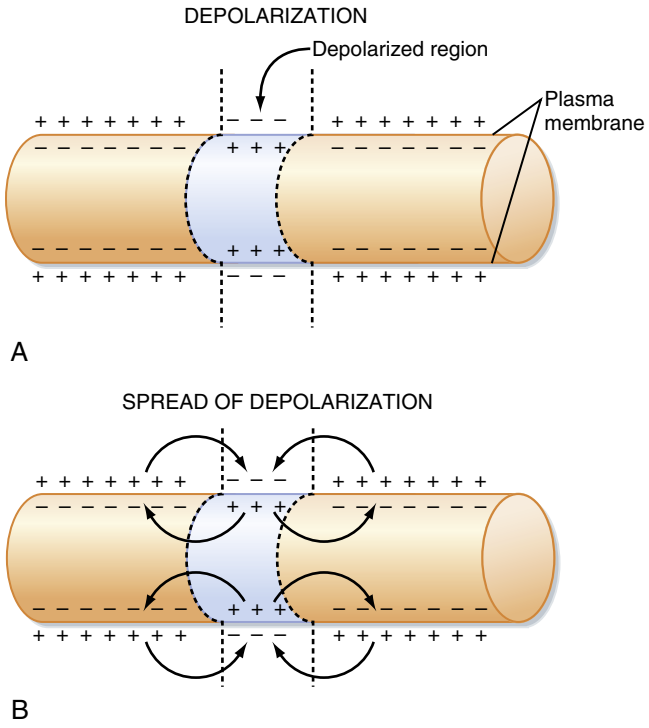
Conduction of Action Potentials

Fundamental to nervous system function is the transmission of information along neuronal pathways. To accomplish this, neurons generate action potentials that propagate down the length of their axon without decrement in size in order to trigger neurotransmitter release from the presynaptic terminals. How action potentials propagate down an axon and how the characteristics of the axon affect this propagation are discussed in this section. How they trigger transmitter release is covered in Chapter 6.

Action Potential Propagation

Passive conduction will not transport a signal from one end of an axon to the other unless the axon is very short (i.e., on the order of its length constant) because passively conducted signals decrease in size rapidly with distance from their origin. Neurons with such short axons exist; for example, in the retina of the eye, the distance from one neuron to the next is so small that electrotonic (passive) conduction is sufficient. However, in most cases, axons are many times longer than their length constant. In fact, they can be up to 1 m or more in length (e.g., those of motor neurons) and thus hundreds of times their length constant. Nonetheless, if researchers were to record from points along a typical axon, they would find that as the action potential arrives at successive points traveling along the axon, its shape and size remain constant. This is because the action potential regenerates itself as it is conducted along the fiber and thus is said to be actively **propagated.**

Fig. 5.8 shows how in a local response the current that flows in through one part of the membrane acts to depolarize the neighboring membrane. The same thing happens when the Na^+ channels are opened by an action potential at one site along the axon, except that in this case the current will be large enough to depolarize the areas on either side past threshold and thus generate action potentials in these neighboring areas. The inward Na^+ current in these areas can then provide the current to depolarize their neighbors past threshold so that they in turn generate action potentials, and so on. In short, action potential propagation along an axon involves recurring cycles of depolarization to provide sufficient local current flow for generation of an action potential in an adjacent region of the cell membrane. Thus the action potential is said to be propagated down the axon, with "new" action potentials being generated along its length. In this way, the action potential can propagate down



• **Fig. 5.8** Mechanism of electrotonic spread of depolarization. **A,** The reversal of membrane polarity that occurs with local depolarization. **B,** The local currents that flow to depolarize adjacent areas of the membrane and allow conduction of the depolarization.

the entire length of the axon while retaining the same size and shape.

Normally, action potentials are first generated at the axon's initial segment (i.e., where the axon is attached to the neuron cell body or proximal dendrite) and then conducted to the terminal end. The reason for this is that the initial segment has a very high density of voltage-gated Na^+ channels, and thus it has a lower threshold for spiking than does the soma or dendrites. However, axons are not inherently unidirectional conductors. For example, as implied by the local circuits shown in Fig. 5.8, an action potential generated by a depolarization in the middle of an axon is conducted in both directions from its initiation site simultaneously.

Why does a spike that starts at the initial segment not propagate in both directions? In fact, it does. In addition to propagating down the axon, the current flowing from the initial segment back to the soma can cause a spike to be generated in the soma, and in some neuron types (pyramidal, medium spiny, and more; not Purkinje), continue to backpropagate into dendrites, because the soma and dendrites also have voltage-gated Na^+ channels. Action potentials backpropagating into dendrites provide a retrograde signal of neuronal output to the dendritic tree. Dendritic action potentials also have been shown to open voltage-gated Ca^{++} channels in dendrites that can contribute to changes in the strength of synaptic transmission (see Chapter 6).

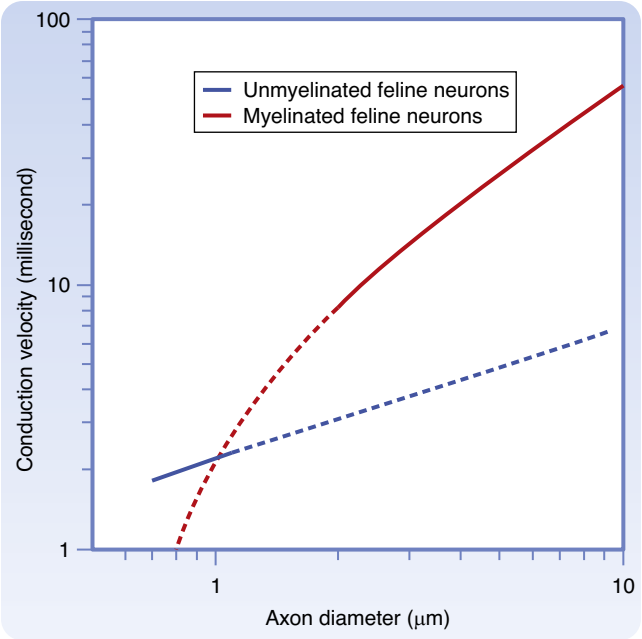
Additional "backpropagating" spikes from the axon do not occur, however, nor do the somatic and dendritic spikes cause the initial segment of the axon to fire a second time (and thereby send another spike down the axon and start a

repeating cycle). This does not happen because the refractory period of the membrane makes any area that has already spiked unable to fire a second spike for a short time. Thus for a spike that started at the initial segment and has begun traveling down the axon, current flowing in at the site of the spike depolarizes the membrane on both sides of that site. However, the side closer to the cell body, which has recently fired a spike, cannot respond to this depolarization because its Na^+ channels are still inactivated. By the time Na^+ channels are de-inactivated (have returned to their closed state and would be able to open) the depolarization of membrane at that site has ended (because the action potential lasts only for ≈1 millisecond). Thus the inactivation gate of the Na^+ channel not only helps determine the duration of the action potential, but it also is responsible for its singular and unidirectional propagation from its origin at the initial segment.

Action Potential Conduction Velocity Is Correlated With Axon Diameter

The speed of conduction in a nerve fiber is determined by the electrical properties of the cytoplasm and the plasma membrane that surrounds the fiber, as well as by its geometry. In nonmyelinated fibers, conduction velocity is proportional to the square root of the cross-sectional diameter (Fig. 5.9). This effect is related to the changes in r_a and r_m with diameter. As the diameter of a fiber increases, r_a decreases with the square of the diameter, and r_m increases only linearly with diameter; as a result, resistance to current flow down the axon decreases more than it does to current flow across the membrane. This increases the length constant (see Fig. 5.3), which means that a greater amount of the current entering at one site is delivered to neighboring regions of the axon, which brings those regions to threshold more quickly, and thus the action potential is conducted faster along fibers with large diameters.

However, increasing the diameter also increases the surface area of the plasma membrane over which inner negative and outer positive charges are held to each other. Discharging this increased capacitance tends to slow conduction and mitigate the increase in conduction velocity gained by increasing diameter.



• **Fig. 5.9** Conduction velocities of unmyelinated *(blue)* and myelinated *(red)* feline axons as functions of axon diameter. *Solid lines* represent measured data. *Dotted lines* represent extrapolations that show the advantage of myelination over simply increasing axon diameter as a mechanism for increased conduction velocity. (From Schmidt-Nielsen K. *Animal Physiology: Adaptation and Environment.* 5th ed. Cambridge: Cambridge University Press; 1997.)

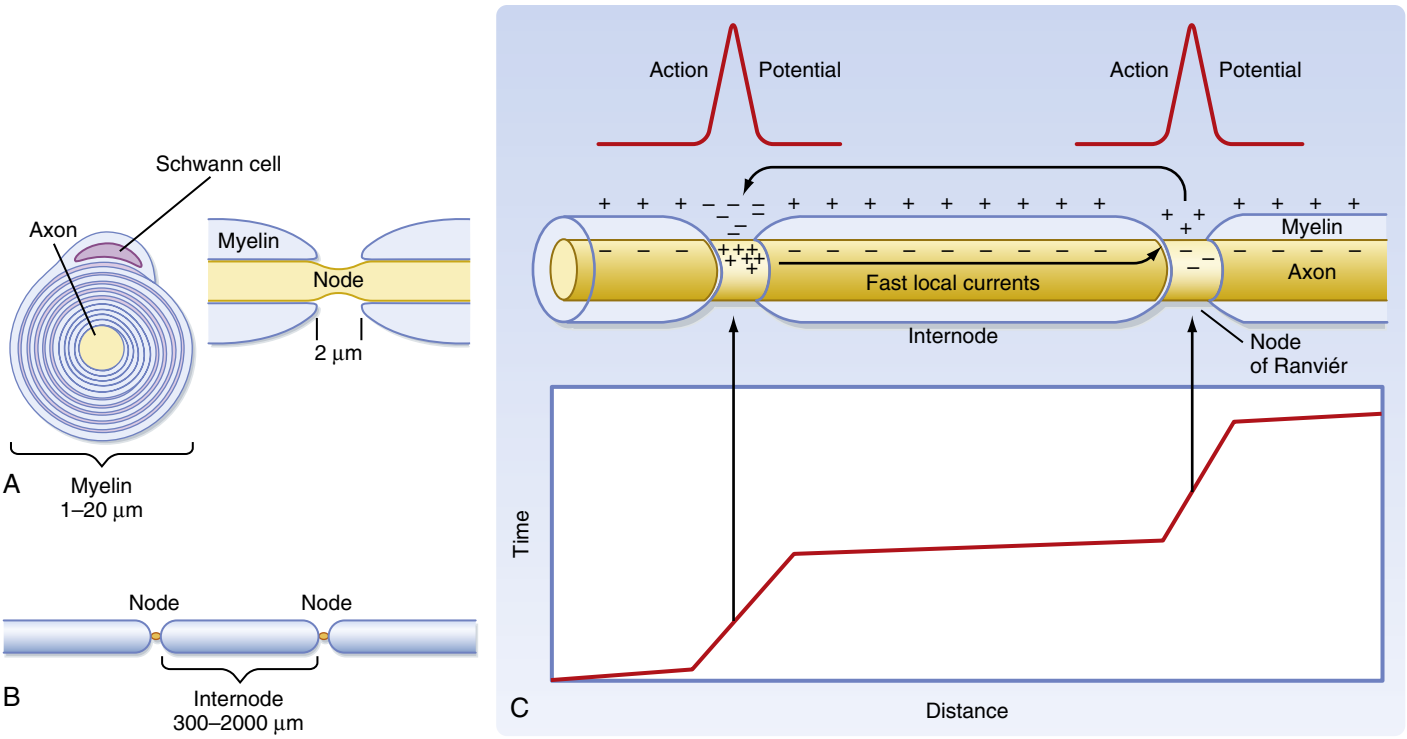
Myelination Greatly Increases Conduction Velocity

In vertebrates, many nerve fibers are coated with **myelin,** and such fibers are said to be *myelinated.* Myelin consists of the plasma membranes of **Schwann cells** (in the peripheral nervous system) or **oligodendroglia** (in the central nervous system [CNS]), which wrap around and insulate the nerve fiber (Fig. 5.10*A*,*B*). The myelin sheath consists of several to more than 100 layers of glial cell plasma membrane. Gaps about 1 to 2 μm wide, known as **nodes of Ranvier,** separate the contribution of one Schwann cell (or oligodendrocyte) from that of another. For all but the axons of smallest diameter, a myelinated axon has much greater conduction velocity than does an unmyelinated fiber of the same caliber because the myelin sheath increases the effective membrane resistance of the axon, decreases the capacitance of the axon membrane, and limits the generation of action potentials to the nodes of Ranvier. In short, myelination greatly alters the electrical properties of the axon.

Because the many wrappings of membrane around the axon increase the effective membrane resistance r_m/r_a and the length constant are much greater. The increased membrane resistance means that less current is lost through the membrane per length of axon, and thus the amplitude of a conducted signal decreases less with distance along the axon and needs to be regenerated (by opening of Na^+ channels) less often.

In addition, the thicker myelin-wrapped membrane results in a much larger separation of charges across it than exists across the bare membrane of an axon, so that the charges across it are much less tightly bound to each other. This is analogous to when the plates of a capacitor are moved apart and reduce its capacitance. Because the effect of membrane capacitance is to slow the rate at which the membrane potential can be changed, the reduced capacitance of myelinated axons means that the depolarization occurs more rapidly. For all these reasons, conduction velocity is greatly increased by myelination, and the current generated at one node of Ranvier is conducted at great speed to the next (see Fig. 5.10).

In myelinated axons, the Na^+ channels that bring about generation of an action potential are highly concentrated at



• **Fig. 5.10** **A,** Schematic illustrations, in cross section and longitudinal section through a node of Ranvier, of a Schwann cell wrapped around an axon to form myelin. Note that the axon is exposed to the extracellular space only at the node of Ranvier. **B,** View of two nodes and the intervening internode of myelin. **C,** Saltatory conduction in a myelinated axon with a plot of the action potential location along the axon (x-axis) versus time (y-axis). Note the short time taken for the action potential to traverse the large distance between nodes (*shallow sloped lines* on the plot) because of the high resistance and low capacitance of the internodal region. In contrast, the action potential slows as it crosses each node *(steep sloped line segments).* (**B,** Redrawn from Squires LR, Berg D, Bloom F, et al. *Fundamental Neuroscience.* 2nd ed. San Diego, CA: Academic Press; 2002. **C,** Redrawn from Blankenship J. *Neurophysiology.* Philadelphia: Mosby; 2002.)

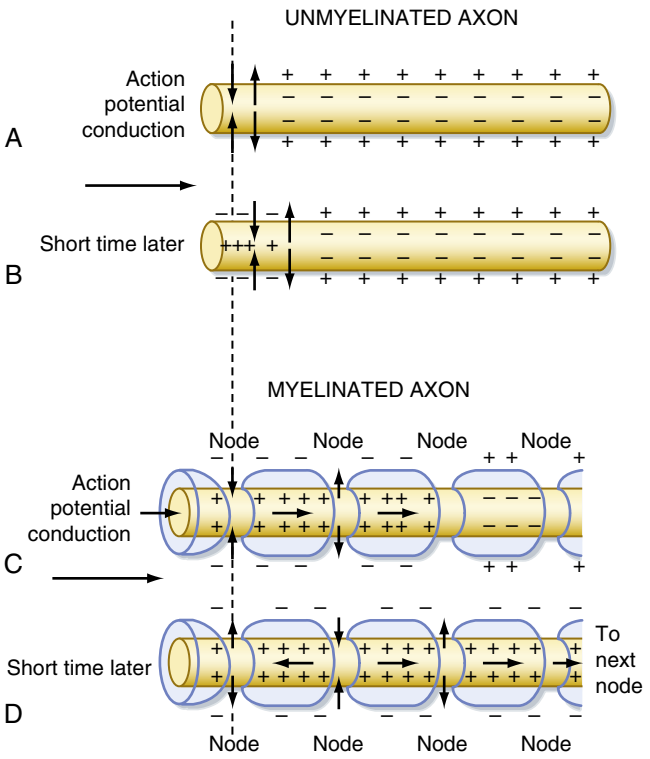
the nodes of Ranvier and are not found between them. Thus the action potential is regenerated only at the nodes of Ranvier (0.3–2 mm apart) rather than being regenerated continuously along the fiber, as is the case in an unmyelinated fiber. Resistance to the flow of ions across the many layers that make up the myelin sheath is so high that transmembrane currents are largely restricted to the short stretches of naked plasma membrane that are present at the nodes of Ranvier (see Fig. 5.10*C*). Therefore, the action potential is regenerated at each successive node. The local currents entering the node are almost entirely conducted from one node to the next node, bringing each node to threshold in about 20 µsec. Thus the action potential appears to "jump" from one node of Ranvier to the next, and the process is called **saltatory** (from the Latin word *saltare,* "to leap") **conduction** (Fig. 5.11).

Functional Consequences of Myelination

The functional consequences of myelination can be highlighted by a comparison of squid and mammalian axons. Although human nerve fibers are much smaller in diameter than squid giant axons, human axons conduct at comparable or even faster speeds because of myelination. The unmyelinated squid giant axon has a 500-µm diameter and a conduction velocity of about 20 m/second. In mammals, axon diameters range from about 0.2 to 20 µm, and all fibers with diameters larger than 1 to 2 µm are myelinated. An unmyelinated mammalian nerve fiber, which has a diameter of less than 1 to 2 µm, has a conduction velocity of less than 2 m/second (see Fig. 5.9), as expected because of its smaller diameter in comparison to the squid giant axon. In contrast, a 10-µm myelinated mammalian fiber has a conduction velocity in the range of 50 m/second, more than twice that of the 500-µm squid giant axon, despite being 1/50 of its diameter. Therefore, the high conduction velocity with far narrower axons achieved by myelination allows a tremendous increase in neuronal connectivity without enormously expanding the volume of the CNS. This is certainly one factor that enabled the evolution of mammalian nervous systems with their huge numbers of neurons that are able to generate everything from fast reflexes to efficient and complex mental processing.

Sensory Transduction

To receive information about the world, the CNS contains a wide variety of sensory receptors, each of which is specialized to detect a particular type of energy **(stimulus).** When



• **Fig. 5.11** Comparison of action potential conduction in an unmyelinated axon and in a myelinated axon. At the initial time (**A** and **C**), an action potential is being generated at the left side of each axon. Note that the inward current in the unmyelinated axon **(A)** is depolarizing an adjacent portion, whereas the inward current in the myelinated axon **(C)** is depolarizing all of the membrane to the next node. At the second instant in time (**B** and **D**), the action potential in the unmyelinated axon **(B)** has been generated in the adjacent portion, whereas the action potential in the myelinated axon **(D)** has been generated at subsequent nodes and is already depolarizing the last node to the right. (Redrawn from Castro A, Neafsey E, Wurster R, Merchut M. *Neuroscience: An Outline Approach.* Philadelphia: Mosby; 2002.)

IN THE CLINIC

In some diseases known as **demyelinating disorders,** the myelin sheath deteriorates. In **multiple sclerosis,** scattered progressive demyelination of axons in the CNS results in loss of motor control and sensory deficits. The neuropathy common in severe cases of diabetes mellitus is caused by the demyelination of peripheral axons. When myelin is lost, the length constant becomes much shorter. Hence, the action potential loses amplitude as it is electrotonically conducted from one node of Ranvier to the next. If demyelination is sufficiently severe, the action potential may arrive at the next node of Ranvier with insufficient strength to fire an action potential at that node, leading to propagation failure.

AT THE CELLULAR LEVEL

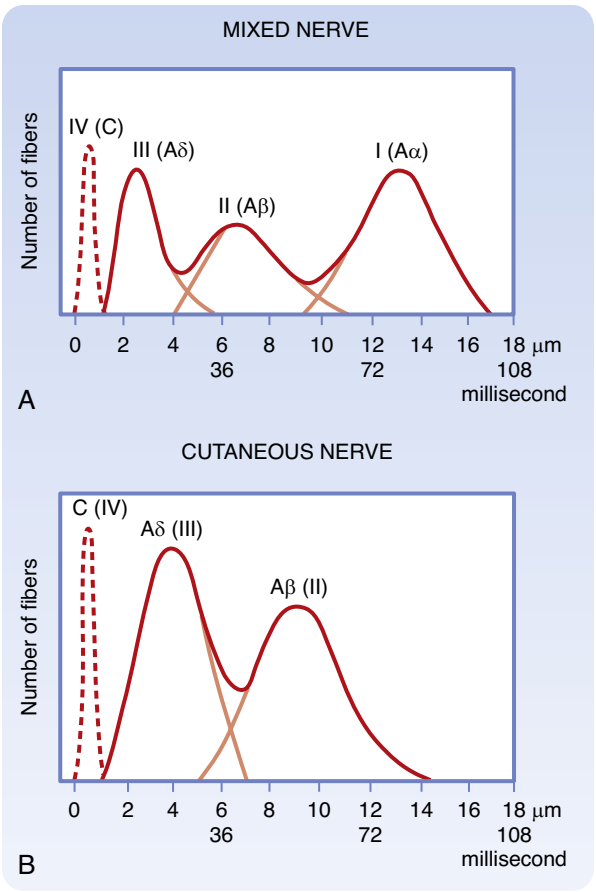
The action potentials of myelinated axons may not have a hyperpolarizing afterpotential or an extended relative refractory period because their K^+ channels are displaced from the nodes into the partly exposed flanking paranodes. That increases the rate at which these fast-conducting axons can fire. Myelinated axons are also more metabolically efficient than unmyelinated axons. Na^+,K^+-ATPase extrudes the Na^+ that enters the cell and causes the K^+ that leaves the cell to reaccumulate during action potentials. In myelinated axons, ionic currents are restricted to the small fraction of the membrane surface at the nodes of Ranvier. For this reason, far fewer ions traverse a unit length of fiber membrane, and much less ion pumping—and energy expenditure—is necessary to maintain the gradients.

IN THE CLINIC

Investigators can record an action potential with a microelectrode without penetrating the axon by placing two spaced electrodes on its surface and comparing the electrical charge at each point. An electrode located where there is an action potential would yield a somewhat negative signal in comparison to an electrode where there is no action potential. As the action potential is conducted to the second electrode, the polarity of the recording reverses. This technique is used clinically to assess nerve function. Peripheral nerves and many central pathways consist of a population of axons of various diameters (Fig. 5.12); some of the axons are myelinated, and some are not. Consequently, action potentials travel at different velocities in the individual axons. As a result, a recording from such a nerve with external electrodes does not show a single synchronous peak but a series of peaks that vary in time (which reflects the conduction velocity of groups of axons) and in magnitude (which reflects the number of axons in each velocity group). This is called a **compound action potential.** The clinical value of such a recording is its ability, in certain disease states, to reveal the dysfunction of a particular group of axons associated with specific functions, as well as the noninvasive nature of the technique because it can be performed with skin surface electrodes (Table 5.1).

a stimulus activates a sensory receptor, it initiates a process called **sensory transduction** by which information about the stimulus (e.g., its intensity and duration) is converted into local electrical signals. These local signals are called **receptor** or **generator potentials**. The receptor potentials can then be transformed into patterns of action potentials that are conducted over one or more axons into the CNS. In order for this to happen, the stimulus must produce receptor potentials that are large enough to change the spiking levels of one or more primary afferent fibers that are connected to the receptor. Weaker intensities of stimulation can produce subthreshold receptor potentials, but such stimuli do not change the activity of central sensory neurons and thus are not detected. S**timulus threshold** is defined as the weakest stimulus that can be reliably detected.

Environmental events that evoke sensory transduction can be mechanical, thermal, chemical, or other forms of energy. However, the types of information used by a particular organism depend on its set of sensory receptors. For example, humans cannot sense electrical or magnetic fields, but other animals can sense such stimuli. In particular, many fish have electroreceptors, and various fish and birds



• **Fig. 5.12** The distribution of axons, by size and conduction velocity, in a mixed (muscle) nerve **(A)** and a cutaneous nerve **(B).** Note the increased number of small-diameter fibers and the absence of Aα fibers in the cutaneous nerve. (From Haines DE. *Fundamental Neuroscience for Basic and Clinical Applications.* 3rd ed. Philadelphia: Churchill Livingstone; 2006.)

use the earth's magnetic field to orient themselves during migration.

The transduction process varies with the type of environmental stimulus being detected. Fig. 5.13 shows three examples of how stimuli can alter the membrane properties of the specific sensory receptors that transduce such stimuli (further details for each of these examples are given in other chapters). Fig. 5.13*A* illustrates how a **chemoreceptor,** such as that used for taste and smell, might respond when a chemical stimulant reacts with receptor molecules on the plasma membrane of the sensory receptor. Binding of the chemical stimulant to the receptor molecule opens an ion channel, which enables the influx of an ionic current that depolarizes the sensory receptor cell. (This is similar to what is described for ligand-gated channels in Chapter 6.) In Fig. 5.13*B,* the ion channel of a **mechanoreceptor,** such as those in the skin, opens in response to the application of a mechanical force along the membrane, and this allows an influx of current to depolarize the sensory receptor. In Fig. 5.13*C,* the ion channel of a retinal **photoreceptor** cell (so-called because it responds to light) is open in the dark and closed when a photon is absorbed by pigment on an internal disk membrane. In this case, an influx of current occurs in the dark; the current ceases when light is applied. When the current stops, the photoreceptor hyperpolarizes. (Because capture of the photon is distant from the ion channel that it influences, this process must involve an intracellular "second messenger" mechanism.)

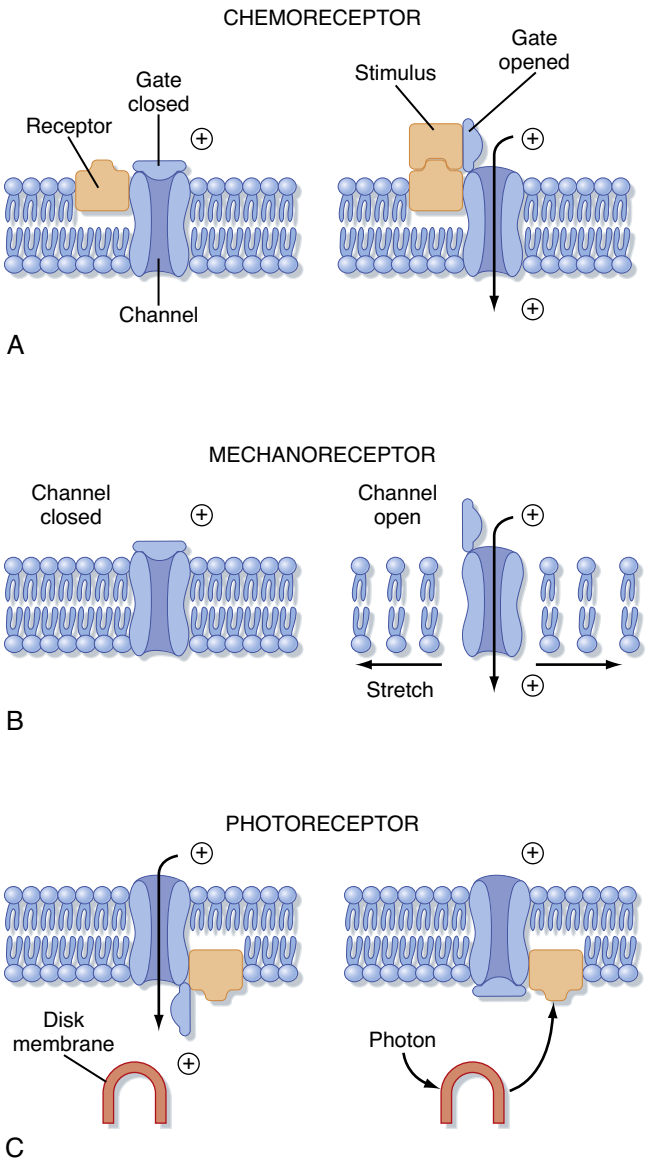
The nature of the receptor also can vary. In the simplest situation, a receptor is just a specialized portion of an axon, in which case the transduction of a stimulus into receptor potential and the translation of this potential into a spike train all take place in the same cell. For example, a

TABLE 5.1 Correlation of Axon Groups, as Revealed by Compound Action Potential Recordings, With Their Functional Properties

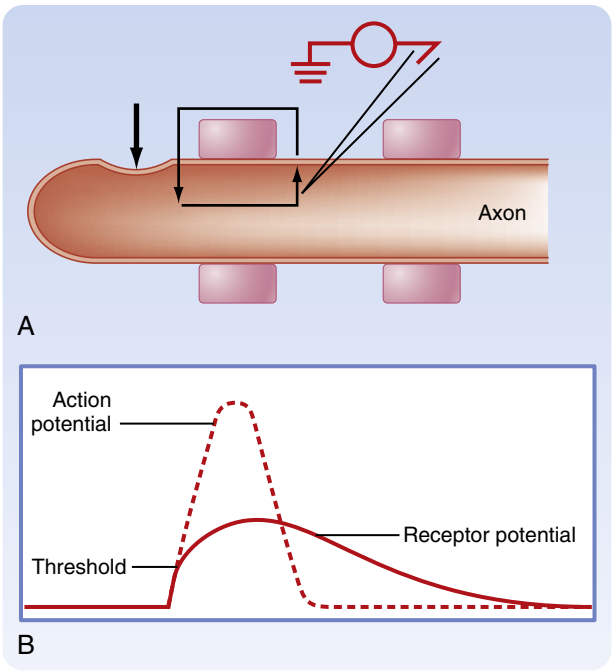
Electrophysiological Classification of Peripheral Nerves	Classification of Only Afferent Fibers (Class/Group)	Fiber Diameter (μm)	Conduction Velocity (m/second)	Receptor Supplied
Sensory Fiber Type				
Aα	Ia	13–20	80–120	Primary muscle spindles
Aβ	Ib and II	6–12	35–75	Golgi tendon organ, secondary muscle spindles, skin mechanoreceptors
Aδ	III	1–5	5–30	Skin mechanoreceptors, thermal receptors, nociceptors
C	IV	0.2–1.5	0.5–2	Skin mechanoreceptors, thermal receptors, nociceptors
Motor Fiber Type				
Aα	N/A	8–13	44–78	Extrafusal skeletal muscle fibers
Aγ	N/A	2–8	12–48	Intrafusal muscle fibers
B	N/A	1–3	6–18	Preganglionic autonomic fibers
C	N/A	0.2–2	0.5–2	Postganglionic autonomic fibers

N+A, Not applicable.

From Haines DE. *Fundamental Neuroscience for Basic and Clinical Applications*. 3rd ed. Philadelphia: Churchill Livingstone; 2006.



• **Fig. 5.13** Models of transducer mechanisms in three types of receptors. **A,** Chemoreceptor. **B,** Mechanoreceptor. **C,** Photoreceptor.



• **Fig. 5.14 A,** Current flow *(thin arrows)* produced by stimulation *(thick arrow)* of a mechanoreceptor at the tip of an axon. An intracellular recording electrode is placed at the first node of Ranvier. **B,** The receptor potential produced by the current and an action potential that would be superimposed on the receptor potential if it were to exceed threshold at the first node of Ranvier.

mechanical stimulus, such as pressure on the skin of a finger, can distort the membrane of an axon that forms part of a mechanoreceptor, as shown in Fig. 5.14*A*. This distortion causes inward current flow at the end of the axon and longitudinal and outward current flow along the neighboring parts of the axon. The outward current produces a depolarization (the receptor potential) that might exceed the threshold for an action potential (see Fig. 5.14*B*). If so, one or more action potentials are evoked and then travel along this primary afferent fiber to the CNS and thereby convey information about the mechanical stimulus.

In many other cases, the receptor is composed of more than one cell. In this situation, transduction occurs in one cell, but spikes are generated in other cells that are synaptically connected to it (see Chapter 6). For example, in the **cochlea,** the primary afferent fibers get synaptic input from mechanoreceptive **hair cells.** Sensory transduction in such sense organs can be more complex in this arrangement. In photoreceptors, moreover, the receptor potential is hyperpolarizing, as mentioned earlier, and interruption of the dark current is the signal event. Information about each of these mechanisms is discussed in Chapter 8.

Although the mechanisms of sensory transduction vary between stimulus types, the end result is typically a receptor potential in either the receptor cell or the primary afferent neuron (i.e., the first neuron in a sensory pathway) that has a synapse with the receptor cell.

Receptive Fields

The relationship between the location of a stimulus and activation of particular sensory neurons is a major theme in the field of sensory physiology. The **receptive field** of a sensory neuron is the region that, when stimulated, affects the activity of that neuron. For example, a sensory receptor might be activated by indentation of only a small area of skin. That area is the **excitatory receptive field** of the sensory receptor. Moreover, a neuron in the CNS might have a receptive field several times as large as that of a sensory receptor because it may receive information from many sensory receptors, each with a slightly different receptive field. The receptive field of that CNS neuron is thus the sum of the receptive fields of the sensory receptors that influence it. The location of the receptive field is determined by the location of the sensory transduction apparatus responsible for signaling information about the stimulus to the sensory neuron.

In general, sensory receptive fields are excitatory. However, a central sensory neuron can have either an excitatory or an inhibitory receptive field or, indeed, a complex receptive field that includes areas that excite it and areas that inhibit it. Examples of such complex receptive fields are discussed in Chapters 7 and 8.

Coding of Information by Action Potentials

Central to CNS function is the transmission of information between neurons. This is accomplished primarily through action potentials, which propagate down the axon to the presynaptic terminals and cause neurotransmitter release, signaling the postsynaptic cells. As already explained, the regenerative nature of action potentials allows them to carry signals regardless of the length of the axon, whereas local signals, such as receptor or synaptic potentials (see Chapter 6), decay with distance and are therefore not suitable for this purpose. The trade-off, however, is that the all-or-none nature of action potentials means that their shape and size do not generally convey information in the way gradations of local potentials do. Instead, the variations in the rate or timing of action potentials appear to be used primarily as the "codes" for transmission of information between neurons.

Rate coding refers to information being coded in the firing rate of a neuron, where *firing rate* is defined as the number of spikes fired per unit time, usually expressed as spikes/second, also called hertz (Hz). For example, the force of a mechanical stimulus to the skin can be encoded in the firing rate of the primary afferent neuron that innervates the skin; the greater the force applied to the skin, the larger the resulting receptor potential in the primary afferent neuron will be and, as a consequence, the faster the rate of action potentials triggered by the receptor potential will be. Research has shown many neurons employ rate coding in the sense that the firing rate of a neuron shows a consistent relationship to particular parameters of sensory stimuli, upcoming movements, or other aspects of behavior.

The amount of information in such rate codes is constrained by several factors. One factor is a neuron's range of firing rates. The upper limit of this range is set by the maximal frequency that a neuron can fire action potentials, which is determined by the duration of the absolute and relative refractory periods (see Fig. 5.4) and rarely exceeds 1000 Hz. The lower limit of the firing range is, of course, 0 Hz, as neurons cannot fire at negative rates. To avoid this problem, many neurons have spontaneous activity levels. These can be quite high (e.g., some Purkinje cells fire spontaneously at 100 Hz) and let a cell either increase or decrease its activity over a similar range in response to inputs. A second constraining factor is the variability of neuron's firing rate, which determines the resolution of the neuron's information coding.

Timing, or **temporal coding,** refers to spike codes in which the specific timing of spikes rather than the overall firing rate encodes information. One often-studied version of temporal coding is the synchronization of spikes across neurons. Synchronization of neuronal spiking has been shown to occur in a number of brain regions and has been related to function in a number of instances. An advantage of temporal coding is that it can convey information more quickly than can rate coding, inasmuch as it does not require averaging, which takes time. Moreover, rate coding and temporal coding are not mutually exclusive, inasmuch as overall firing rates can be varied while synchronous events are superimposed. Such multiplexing of codes may increase the information transmission capacity of neuronal pathways.

Sensory Coding

Sensory neurons encode information about stimuli. In the process of sensory transduction, one or more aspects of the stimulus must be encoded in a way that can be interpreted by the CNS. The encoded information is an abstraction based on (1) which sensory receptors are activated, (2) the responses of sensory receptors to the stimulus, and (3) information processing in the sensory pathway. Some stimulus parameters that can be encoded include **sensory modality, location, intensity, frequency,** and **duration.** Other aspects of stimuli that are encoded are described in relation to particular sensory systems in later chapters.

A **sensory modality** is a class of sensation. For example, sustained mechanical stimuli applied to the skin result in sensations of touch or pressure, and transient mechanical stimuli may evoke sensations of flutter or vibration. Other cutaneous modalities include cold, warmth, and pain. Vision, audition, taste, and smell are examples of noncutaneous sensory modalities. The specific sensory receptors define the normal energy associated with the modality of a sensory pathway. For example, the visual pathway includes photoreceptors, neurons in the retina, the lateral geniculate nucleus of the thalamus, and the visual areas of the cerebral cortex (see Chapter 8). The normal means of activating the visual pathway is light striking the retina. However, mechanical stimulation (e.g., pressure on the eyeball) or electrical stimulation of neurons in the visual pathway also produce a visual sensation. Thus neurons of the visual system can be regarded as a **labeled line,** which, when activated by whatever means, results in a visual sensation.

The **location** of a stimulus is signaled by activation of the particular population of sensory neurons whose receptive fields are affected by the stimulus. The information may be encoded in the CNS as a neural map. For example, a **somatotopic map** is formed by arrays of neurons in the somatosensory cortex that receive information from corresponding locations on the body surface (see Chapter 7). In the visual system, points on the retina are represented by neuronal arrays that form **retinotopic maps** (see Chapter 8).

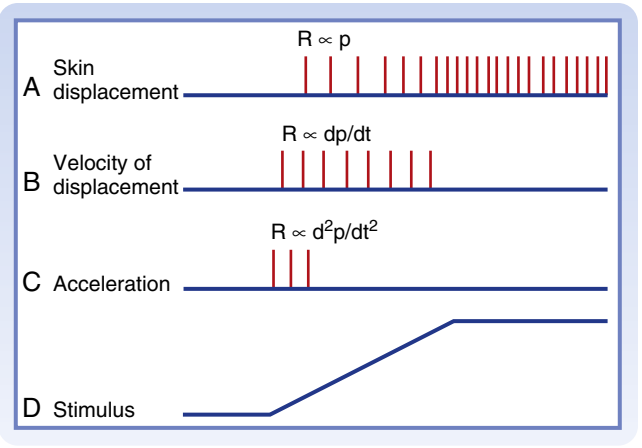
Intensity may be encoded in a number of ways. Because action potentials have a uniform magnitude, some sensory neurons encode intensity by their frequency of discharge

(rate coding). The relationship between stimulus intensity and response can be plotted as a stimulus-response function. For many sensory neurons, the stimulus-response function approximates an exponential curve with an exponent that can be less than, equal to, or greater than 1. Stimulus-response functions with fractional exponents characterize many **mechanoreceptors. Thermoreceptors,** which detect changes in temperature, have linear stimulus-response curves (exponent of 1). **Nociceptors,** which detect painful stimuli, may have linear or positively accelerating stimulus-response functions (i.e., the exponent for these curves is 1 or greater). The positively accelerating stimulus-response functions of nociceptors help explain the urgency that is experienced as the pain sensation increases.

Another way in which stimulus intensity is encoded is according to the number of sensory receptors that are activated. A stimulus at the threshold for perception may activate only one or only a few primary afferent neurons of an appropriate class, whereas a strong stimulus of the same type may recruit many similar receptors. Central sensory neurons that receive input from sensory receptors of this particular class would be more powerfully affected as more primary afferent neurons discharge. Greater activity in central sensory neurons may be perceived as a stronger stimulus.

Stimuli of different intensities may also activate different sets of sensory receptors. The limit of a neuron's firing rate of action potentials can also limit its range of response to a stimulus. However, mechanoreceptors with different thresholds can overcome this problem: Those with low thresholds can signal over a range of low input intensities, whereas others with higher thresholds can signal higher input intensities. Together they allow fine resolution over an extended range of intensities. In addition, still higher intensities might recruit nociceptors, and that will also change the perceived quality of the stimulus.

Stimulus **frequency** can sometimes be encoded by action potentials whose interspike intervals correspond exactly to the intervals between stimuli (e.g., at intervals corresponding to that of a low-frequency vibration). However, this mechanism is limited by the firing rate limits of neurons as discussed earlier. When higher frequencies need to be encoded (e.g., the auditory system, which in humans is capable of detecting frequencies up to 20,000 Hz; see Chapter 8), other strategies are needed. Other candidate codes depend on the spatiotemporal patterns of firing across populations of neurons.



• **Fig. 5.15** Responses of slowly and rapidly adapting mechanoreceptors to displacement of the skin. **A** to **C** are the discharges of primary afferent fibers during a ramp-and-hold stimulus shown in **D. A,** The response of a slowly adapting receptor that signals the magnitude and duration of displacement. **B,** The response of a rapidly adapting receptor whose output signals the velocity of displacement. **C,** The response of a different rapidly adapting receptor that responds to acceleration. *p*, Displacement; *R*, response; *t*, time.

The **duration** and the onset and offset of events are encoded by different populations of sensory neurons. For example, slowly adapting receptors in the skin produce a repetitive discharge throughout a prolonged stimulus. However, rapidly adapting receptors produce spikes at the onset (or offset) of the same stimulus. Fig. 5.15 shows the responses of three types of receptors to the slow deflection of the skin, which is depicted in the graph at the bottom of the figure. The functional implication is that different temporal features of a stimulus can be signaled by receptors with different adaptation rates.

Key Points

1. Ion channels are integral membrane proteins that have ion-selective pores. An ion channel typically has two states: high conductance (open) and zero conductance (closed). Different regions of an ion channel protein act as gates to open and close the channel. The channel flips spontaneously between the open and closed states.
2. For a voltage-dependent channel, the fraction of time that the channel spends in the open state is a function of the transmembrane potential difference.
3. The action potential is generated by the rapid opening and subsequent voltage inactivation of voltage-dependent Na^+ channels and by the delayed opening and closing of voltage-dependent K^+ channels.
4. The absolute and relative refractory periods result from voltage inactivation of Na^+ channels and the delayed closure of K^+ channels in response to membrane repolarization. These refractory periods limit the firing rate of action potentials.
5. Subthreshold signals and action potentials are conducted along the length of a cell by local circuit currents. Subthreshold signals are conducted only electrotonically, and thus decrease with distance.
6. The action potential is propagated rather than merely conducted; it is regenerated as it moves along the axon. In this way, an action potential retains the same size and shape as it travels along the axon.

7. A large-diameter axon has greater propagation velocity because increased axon diameter lowers axial resistance and allows greater amounts of current to flow farther down the axon.
8. Myelination dramatically increases the conduction velocity of a nerve axon because myelin increases membrane resistance and lowers membrane capacitance. Myelination allows an action potential to be conducted very rapidly from one node of Ranvier to the next. This makes the action potential appear to jump from node to node in a form of conduction called *saltatory conduction.*
9. A receptor responds preferentially to a particular form of stimulus energy. Its receptive field is that part of a sensory domain in which energy can affect the receptor.
10. Receptor potentials are the result of transduction of sensory stimuli. These potentials reflect the specific parameters of the stimulus and, if they exceed threshold, alter the action potential firing patterns of the afferent neurons.