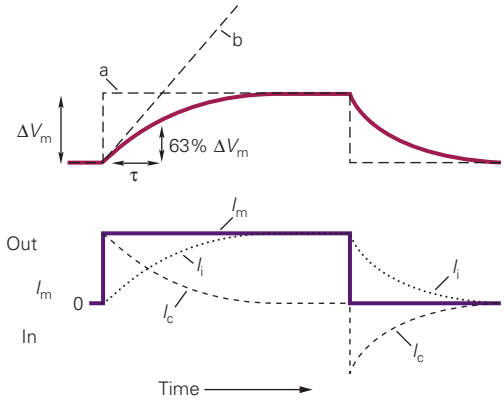

Figure 9–10 **The rate of change in the membrane potential is slowed by the membrane capacitance.** The **upper** plot shows the response of the membrane potential (ΔV_m) to a step current pulse (I_m). The shape of the actual voltage response (**red line**) combines the properties of a purely resistive element (**dashed line a**) and a purely capacitive element (**dashed line b**). The time taken to reach 63% of the final voltage defines the membrane time constant, τ. The **lower** plot shows the two elements of the total membrane current (I_m) during the current pulse: the ionic current (I_i) across the resistive elements of the membrane (ion channels) and the capacitive current (I_c).

does not. A true resistor responds to a step change in current with a similar step change in voltage, but the neuron's membrane potential rises and decays more slowly than the step change in current because of its *capacitance* (Figure 9–10).

To understand how the capacitance slows down the voltage response, recall that the voltage across a capacitor is proportional to the charge stored on the capacitor. To alter the voltage, charge Q must be added to or removed from the capacitor C:

$$\Delta V = \Delta Q/C.$$

To change the charge across the capacitor (the membrane lipid bilayer), there must be current across the capacitor (I_c). Since current is the flow of charge per unit time ($I_c = \Delta Q/\Delta t$), the change in voltage across a capacitor is a function of the magnitude and duration of the current:

$$\Delta V = I_c \cdot \Delta t/C.$$

Thus, the magnitude of the change in voltage across a capacitor in response to a current pulse depends on the duration of the current, because time is required to deposit and remove charge from the capacitor.

If the membrane had only resistive properties, a step pulse of outward current would change the membrane potential instantaneously. Conversely, if the membrane had only capacitive properties, the membrane potential would change linearly with time in response to the same step of current. Because the membrane has both capacitive and resistive properties in parallel, the actual change in membrane potential combines features of the two pure responses. The initial slope of the change reflects a purely capacitive element, whereas the final slope and amplitude reflect a purely resistive element (Figure 9–10, upper plot).

In the simple case of the spherical cell body of a neuron, the time course of the potential change is described by the following equation:

$$\Delta V_m\,(t) = I_m R_m (1 - e^{-t/\tau}),$$

where e is the base of the system of natural logarithms with a value of approximately 2.72, and τ is the *membrane time constant*, given by the product of the membrane resistance and capacitance ($R_m C_m$). The time constant can be measured experimentally as the time it takes the membrane potential to rise to $1 - 1/e$, or approximately 63% of its steady-state value (Figure 9–10, upper plot). Typical values of τ for neurons range from 20 to 50 ms. We shall return to the time constant in Chapter 13 where we consider the temporal summation of synaptic inputs in a cell.

Membrane and Cytoplasmic Resistance Affect the Efficiency of Signal Conduction

So far, we have considered the effects of the passive properties of neurons on signaling only within the cell body. Distance is not a factor in the propagation of a signal in the neuron's soma because the cell body can be approximated as a sphere whose membrane voltage is uniform. However, a subthreshold voltage signal traveling along extended structures (dendrites, axons, and muscle fibers) decreases in amplitude with distance from the site of initiation because some charge leaks out of the resting membrane conductance as it flows along the dendrite or axon. To show how this attenuation occurs, we will consider how the geometry of a neuron influences the distribution of current.

If current is injected into a dendrite at one point, how will the membrane potential change along its length? For simplicity, consider how membrane potential varies with distance after a constant-amplitude current pulse has been on for some time ($t >> \tau$). Under these conditions, the membrane capacitance is fully charged, so membrane potential reaches a steady value. The variation of the potential with distance depends on the fraction of charge that leaks out of the dendrite compared to the fraction that flows inside the dendrite towards the soma. Since charge flows along the path of least resistance, this depends on the relative values of the *membrane resistance* in a unit length of dendrite r_m

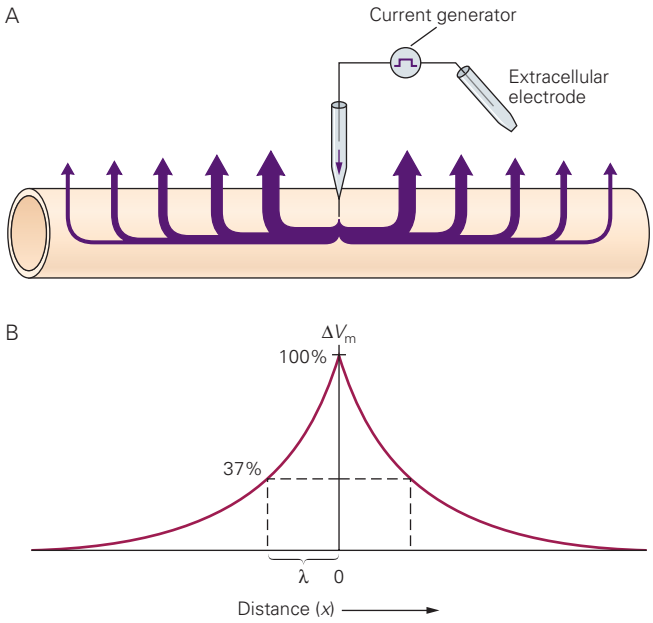

Figure 9–11 The change in membrane potential along a neuronal process during electrotonic conduction decreases with distance.

A. Current injected into a neuronal process by a microelectrode follows the path of least resistance to the return electrode in the extracellular fluid. (The thickness of the arrows represents the magnitude of membrane current.)

B. The change in V_m decays exponentially with distance from the site of current injection. The distance at which ΔV_m has decayed to 37% of its value at the point of current injection defines the length constant, λ.

(units of Ω · cm) and the *axial resistance* per unit length of dendrite r_a (units of Ω/cm). The change in membrane potential along the dendrite becomes smaller with distance from the current electrode (Figure 9–11A). This decay with distance is exponential and expressed by

$$\Delta V(x) = \Delta V_0 \, e^{-x/\lambda},$$

where λ is the membrane *length constant*, x is the distance from the site of current injection, and ΔV_0 is the change in membrane potential produced by the current at the site of injection ($x = 0$). The length constant is the distance along the dendrite to the site where ΔV_m has decayed to $1/e$, or 37% of its initial value (Figure 9–11B). It is a measure of the efficiency of electrotonic conduction—the passive spread of voltage changes along the neuron—and is determined by the values of membrane and axial resistance as follows:

$$\lambda = \sqrt{(r_m / r_a)}.$$

The better the insulation of the membrane (that is, the greater r_m) and the better the conducting properties of the inner core (the lower r_a), the greater the length constant of the dendrite. That is because current is able to spread farther along the inner conductive core of the dendrite before leaking across the membrane at some point x to alter the local membrane potential:

$$\Delta V(x) = i(x) \cdot r_m.$$

The length constant is also a function of the diameter of the neuronal process. Neuronal processes vary greatly in diameter, from as much as 1 mm for the squid giant axon to 1 μm for fine dendritic branches in the mammalian brain. For neuronal processes with similar ion channel surface densities (number of channels per unit membrane area) and cytoplasmic composition, thicker axons and dendrites have longer length constants than do narrower processes and hence can transmit passive electrical signals for greater distances. Typical values for neuronal length constants for unmyelinated axons range from about 0.5 to 1.0 mm. Myelinated axons have longer length constants—up to about 1.5 mm—because the insulating properties of myelin lead to an increase in the effective r_m of the axon.

To understand how the diameter of a process affects the length constant, we must consider how the diameter (or radius) affects r_m and r_a. Both r_m and r_a are measures of resistance for a unit length of a neuronal process of a given radius. The axial resistance r_a of the process depends inversely on the number of charge carriers (ions) in a cross section of the process. Therefore, given a fixed cytoplasmic ion concentration, r_a depends inversely on the cross-sectional area of the process $1/(\pi \cdot \text{radius}^2)$. The resistance of a unit length of membrane r_m depends inversely on the total number of channels in a unit length of the neuronal process.

Channel density, the number of channels per μm^2 of membrane, is often similar among different-sized processes. As a result, the number of channels per unit length of a neuronal process increases in direct proportion to increases in membrane area, which depends on the circumference of the process times its length; therefore, r_m varies as $1/(2 \cdot \pi \cdot \text{radius})$. Because r_m/r_a varies in direct proportion to the radius of the process, the length constant is proportional to the square root of the radius. In this analysis, we have assumed that dendrites have only passive electrical properties. As discussed in Chapter 13, however, voltage-gated ion channels endow most dendrites with active properties that modify their purely passive length constants.

The efficiency of electrotonic conduction has two important effects on neuronal function. First, it influences spatial summation, the process by which synaptic potentials generated in different regions of the

neuron are added together at the trigger zone of the axon (Chapter 13). Second, electrotonic conduction is a factor in the propagation of the action potential. Once the membrane at any point along an axon has been depolarized beyond threshold, an action potential is generated in that region. This local depolarization spreads passively down the axon, causing successive adjacent regions of the membrane to reach the threshold for generating an action potential (Figure 9–12). Thus, the depolarization spreads along the length of the axon by local current driven by the difference in potential between the active and resting regions of the axon membrane. In axons with longer length constants, local current spreads a greater distance down the axon, and therefore, the action potential propagates more rapidly.

Large Axons Are More Easily Excited Than Small Axons

The influence of axonal geometry on action potential conduction plays an important role in a common neurological exam. In the examination of a patient for diseases of peripheral nerves, the nerve often is stimulated by passing current between a pair of external cutaneous electrodes placed over the nerve, and the population of resulting action potentials (the *compound action potential*) is recorded farther along the nerve by a second pair of cutaneous voltage-recording electrodes. In this situation, the total number of axons that generate action potentials varies with the amplitude of the current pulse (Chapter 57).

To drive a cell to threshold, a stimulating current from the positive electrode must pass through the cell membrane into the axon. There it travels along the axoplasmic core, eventually exiting the axon into the extracellular fluid through the membrane to reach the second (negative) electrode. However, most of the stimulating current does not even enter the axon, moving instead through neighboring axons or through the low-resistance pathway of the extracellular fluid. Thus, the axons into which current enters most easily are the ones most excitable.

In general, axons with the largest diameter have the lowest threshold for such excitation. The greater the

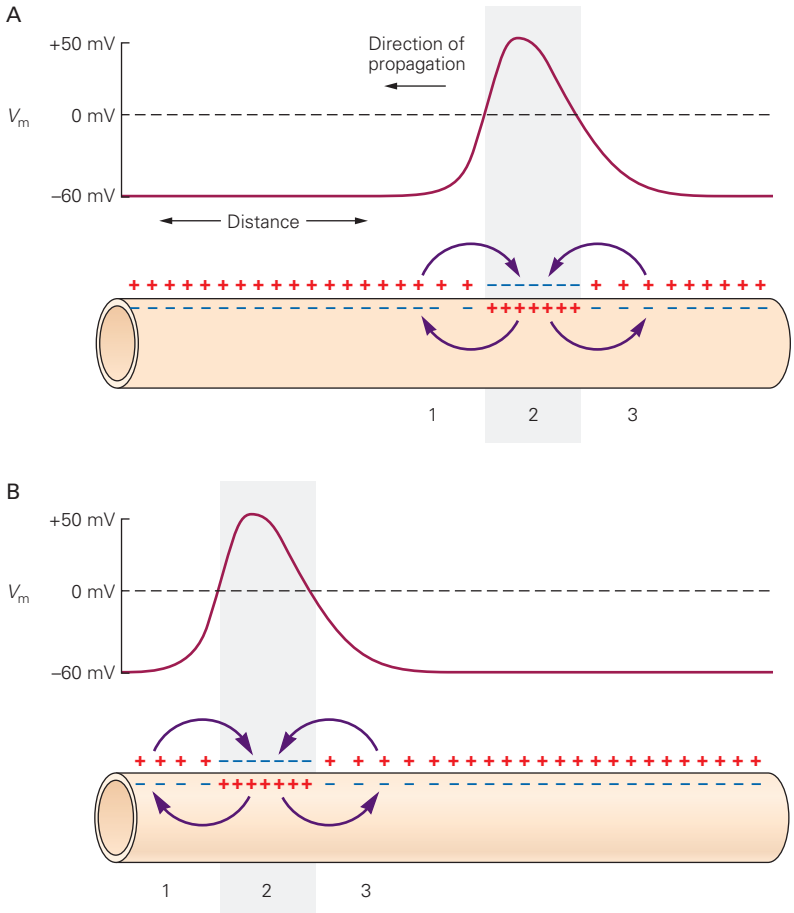

Figure 9–12 Electrotonic conduction contributes to propagation of the action potential.

A. An action potential propagating from right to left causes a difference in membrane potential between two adjacent regions of the axon. The difference creates a local-circuit current that causes the depolarization to spread passively. Current spreads from the more positive active region (**2**) to the less positive resting region *ahead* of the action potential (**1**), as well as to the less positive area *behind* the action potential (**3**). However, because there is also an increase in membrane K^+ conductance in the wake of the action potential (Chapter 10), the buildup of positive charge along the inner side of the membrane in area 3 is more than balanced by the local efflux of K^+, allowing this region of membrane to repolarize.

B. A short time later, the action potential has traveled down the axon and the process is repeated.

diameter of the axon, the lower is the axial resistance to the flow of current down the axon because the number of charge carriers (ions) per unit length of the axon is greater. Because more current enters the larger axon, the axon is depolarized more efficiently than a smaller axon. For these reasons, larger axons are recruited at low values of current; axons with smaller diameter are recruited only at relatively greater current strengths.

The fact that larger axons conduct more rapidly and have a lower current threshold for excitation aids in the interpretation of clinical nerve-stimulation tests. Neurons that convey different types of information (eg, motor versus sensory) often differ in axon diameter and thus conduction velocity (Chapter 18). In addition, a specific disease may preferentially affect certain functional classes of axons. Thus, using conduction velocity as a criterion to determine which classes of axons have defective conduction properties can help one infer the neuronal basis for the neurological deficit.

Passive Membrane Properties and Axon Diameter Affect the Velocity of Action Potential Propagation

The passive spread of depolarization during conduction of the action potential is not instantaneous. In fact, electrotonic conduction is a rate-limiting factor in the propagation of the action potential. We can understand this limitation by considering a simplified equivalent circuit of two adjacent segments of axon membrane connected by a segment of axoplasm.

An action potential generated in one segment of membrane supplies depolarizing current to the adjacent membrane, causing it to depolarize gradually toward threshold (Figure 9–12). According to Ohm's law, the larger the axoplasmic resistance, the smaller is the current between adjacent membrane segments ($I = V/R$) and thus the longer it takes to change the charge on the membrane capacitance of the adjacent segment.

Recall that, since $\Delta V = \Delta Q/C$, the membrane potential changes slowly if the current is small because ΔQ, equal to the magnitude of the current multiplied by time, changes slowly. Similarly, the larger the membrane capacitance, the more charge must be deposited on the membrane to change the potential across the membrane, so the current requires a longer time to produce a given depolarization. Therefore, the time it takes for depolarization to spread along the axon is determined by both the axial resistance r_a and the capacitance per unit length of the axon c_m (units F/cm). The rate of passive spread of charge varies inversely with the product $r_a c_m$. If this product is reduced, the rate of passive spread increases and the action potential propagates faster.

Rapid propagation of the action potential is functionally important, and two adaptations have evolved to increase it. One is an increase in the diameter of the axon core. Because r_a decreases in proportion to the square of axon diameter, whereas c_m increases in direct proportion to diameter, the net effect of an increase in diameter is a decrease in $r_a c_m$. This adaptation has been carried to an extreme in the giant axon of the squid, which can reach a diameter of 1 mm. No larger axons have evolved, presumably because of the competing need to keep neuronal size small so that many cells can be packed into a limited space.

The second adaptation that increases conduction velocity is the wrapping of a myelin sheath around an axon (Chapter 7). This process is functionally equivalent to increasing the thickness of the axonal membrane by as much as 100-fold. Because the capacitance of a parallel-plate capacitor such as the membrane is inversely proportional to the thickness of the insulation, myelination decreases c_m and thus $r_a c_m$. Each layer of myelin is extremely thin—only 80 Å. Therefore, myelination results in a proportionately much greater decrease in $r_a c_m$ than does the same increase in the diameter of a bare axon core, because the many layers of membrane in the myelin sheath produce a large decrease in c_m with a relatively small increase in overall axon diameter. For this reason, conduction in myelinated axons is faster than in nonmyelinated axons of the same diameter.

In a neuron with a myelinated axon, the action potential is triggered at the nonmyelinated initial segment of the axon. The inward current through this region of membrane is available to discharge the capacitance of the myelinated axon ahead. Even though the capacitance of the axon is quite small (because of the myelin insulation), the amount of current down the core of the axon from the trigger zone is not enough to discharge the capacitance along the entire length of the myelinated axon.

To prevent the action potential from dying out, the myelin sheath is interrupted every 1 to 2 mm by the nodes of Ranvier, bare patches of axon membrane approximately 1 µm in length (Chapter 7). Although the area of membrane at each node is quite small, the nodal membrane is rich in voltage-gated Na^+ channels and thus can generate an intense depolarizing inward Na^+ current in response to the passive spread of depolarization down the axon. These regularly distributed nodes thus periodically boost the amplitude of the action potential, preventing it from decaying with distance.

The action potential, which spreads quite rapidly along the internodal region because of the low capacitance of the myelin sheath, slows down as it crosses the high-capacitance region of each bare node. Consequently, as the action potential moves down the axon, it jumps quickly from node to node (Figure 9–13A). For this

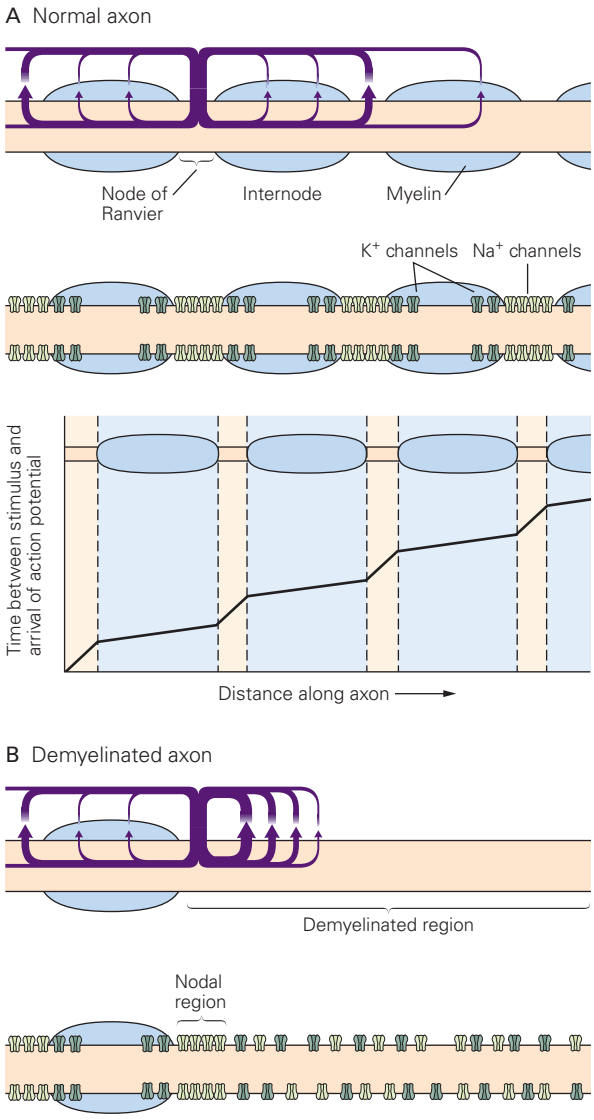

Figure 9–13 Action potentials in myelinated nerves are regenerated at the nodes of Ranvier.

A. The densities of capacitive and ionic membrane currents (membrane current per unit area of membrane) are much higher at the nodes of Ranvier than in the myelin-insulated internodal regions. (The density of membrane current at any point along the axon is represented by the thickness of the arrows.) Because of the higher capacitance of the axon membrane at the nodes, the action potential slows down as it approaches each node and thus appears to skip rapidly from node to node as it propagates from left to right.

B. In regions of the axon that have lost their myelin, the spread of the action potential is slowed down or blocked. The local-circuit currents must discharge a larger membrane capacitance, and because of the shorter length constant (caused by the low membrane resistance in demyelinated stretches of axon), they do not spread as well down the axon. In response to demyelination, additional voltage-gated Na^+ and K^+ ion channels are inserted into the membrane that is normally myelinated.

reason, the action potential in a myelinated axon is said to move by *saltatory conduction* (from the Latin *saltare*, to jump). Because ions flow across the membrane only at the nodes in myelinated fibers, saltatory conduction is also favorable from a metabolic standpoint. Less energy must be expended by the Na^+-K^+ pump to restore the Na^+ and K^+ concentration gradients, which tend to run down as the action potential is propagated.

The distribution of conduction velocities varies widely among neurons and even between different branches of an axon, depending on axon diameter and degree of myelination. Additional geometric features of myelinated axons, such as internodal length and nodal diameter, can also affect velocity. Evolution has adapted conduction velocities to optimize the behavioral functions of each neuron. In general, axons that are involved in rapid sensory and motor computations generally have high rates of conduction. More specifically, in certain neural circuits in the auditory system, an optimal behavioral response depends on the precise temporal relationship of presynaptic action potentials in two pathways that converge on the same postsynaptic neuron (Chapter 28). In such cases, values of the geometrical parameters of myelinated axons in the two input pathways can result in different conduction velocities that compensate for the differences in the input path lengths.

Various diseases of the nervous system are caused by demyelination, such as multiple sclerosis and Guillain-Barré syndrome. As an action potential goes from a myelinated region to a bare stretch of demyelinated axon, it encounters a region of relatively high c_m and low r_m. The inward current generated at the node just before the demyelinated segment may be too small to provide the capacitive current required to depolarize the segment of demyelinated membrane to threshold. In addition, this local-circuit current does not spread as far as it normally would because it encounters a segment of axon that has a relatively short length constant resulting from its low r_m (Figure 9–13B). These two factors can combine to slow, and in some cases actually block, the conduction of action potentials, causing devastating effects on behavior (Chapter 57).

Highlights

1. When the cell is at rest, passive fluxes of ions into and out of the cell through ion channels are balanced, such that the charge separation across the membrane remains constant and the membrane potential is maintained at its resting value.

2. The permeability of the cell membrane for an ion species is proportional to the number of open channels that allow passage of that ion. According to the Goldman equation, the value of the resting membrane potential in nerve cells is determined by resting channels that conduct K^+, Cl^-, and Na^+; the membrane potential is closest to the equilibrium (Nernst) potential of the ion or ions with the greatest membrane permeability.
3. Changes in membrane potential that generate neuronal electrical signals (action potentials, synaptic potentials, and receptor potentials) are caused by changes in the membrane's relative permeabilities to these three ions and to Ca^{2+} ions.
4. Although the changes in permeability caused by the opening of gated ion channels change the net charge separation across the membrane, they typically produce only negligible changes in the bulk concentrations of ions.
5. The functional properties of a neuron can be described by an electrical equivalent circuit, which includes the membrane capacitance, the ionic conductances, the EMF–generating properties of ion channels, and cytoplasmic resistance. In this model, membrane potential is determined by the ion or ions with the greatest membrane conductances.
6. Ion pumps prevent the ionic batteries from running down due to passive fluxes through the ion channels. The Na^+-K^+ pump uses the chemical energy of one molecule of ATP to exchange three intracellular Na^+ ions for two extracellular K^+ ions, an example of primary active transport. Secondary active transport by cotransporters is powered by coupling the downhill ionic gradients of one or two types of ions to drive the uphill transport of another ion. The coupling may take the form of symtransport (in the same direction) or antitransport (opposite directions).
7. The Na^+-Ca^{2+} antitransporter exchanges internal Ca^{2+} ion for external Na^+ ions. There are two types of Cl^- cotransporters in the cell membrane. The Cl^--K^+ symtransporter, which transports Cl^- and K^+ out of the cell, maintains E_{Cl} at a relatively negative potential, and is the most common variant of Cl^- transporter found in mature neurons. The Cl^--Na^+-K^+ symtransporter, which transports Cl^-, Na^+, and K^+ into the cell, generates an E_{Cl} that is relatively positive. It is expressed in immature neurons and in certain adult neurons.
8. The details of the molecular transitions during primary and secondary active transport are an area of active investigation.
9. The nerve cell membrane has a relatively high capacitance per unit of membrane area. As a result, when a channel opens and ions begin to flow, the membrane potential changes more slowly than the membrane current.
10. The currents that change the charge on the membrane capacitance along the length of an axon or dendrite pass through a relatively poor conductor—a thin column of cytoplasm. These two factors combine to slow down the conduction of voltage signals. Moreover, the various ion channels that are open at rest and that give rise to the resting potential also degrade the signaling function of the neuron, as they make the cell leaky and limit how far a signal can travel passively.
11. To overcome the physical constraints on long-distance signaling, neurons use sequential transient opening of voltage-gated Na^+ and K^+ channels to generate action potentials. The action potential is continually regenerated along the axon and thus conducted without attenuation.
12. For pathways in which rapid signaling is particularly important, conduction of the action potential is enhanced by myelination of the axon, an increase in axon diameter, or both. Conduction velocities can vary between or within axons in ways that optimize the timing of neuronal signals within a neuronal circuit.

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10

Propagated Signaling: The Action Potential

Nerve cells are able to carry electrical signals over long distances because the long-distance signal, the action potential, is continually regenerated and thus does not attenuate as it moves down the axon. In Chapter 9, we saw how an action potential arises from sequential changes in the membrane's permeability to Na^+ and K^+ ions and how the membrane's passive properties influence the speed at which the action potential is conducted. In this chapter, we describe in detail the voltage-gated ion channels that are critical for generating and propagating action potentials and consider how these channels are responsible for important features of a neuron's electrical excitability.

Action potentials have four properties important for neuronal signaling. First, they can be initiated only when the cell membrane voltage reaches a *threshold*. As we saw in Chapter 9, in many nerve cells, the membrane behaves as a simple resistor in response to small hyperpolarizing or depolarizing current steps. The membrane voltage changes in a graded manner as a function of the size of the current step according to Ohm's law, $\Delta V = \Delta I \cdot R$ (in terms of conductance, $\Delta V = \Delta I / G$). However, as the size of the depolarizing current increases, the membrane voltage will eventually reach a threshold, typically at around –50 mV, at which an action potential can be generated (see Figure 9–2C). Second, the action potential is an all-or-none event. The size and shape of an action potential initiated by a large depolarizing current is the same as that of an action potential evoked by a current that just surpasses the

threshold.[1] Third, the action potential is conducted without decrement. It has a self-regenerative feature that keeps the amplitude constant, even when it is conducted over great distances. Fourth, the action potential is followed by a *refractory period*. For a brief time after an action potential is generated, the neuron's ability to fire a second action potential is suppressed. The refractory period limits the frequency at which a nerve can fire action potentials, and thus limits the information-carrying capacity of the axon.

These four properties of the action potential—initiation threshold, all-or-none amplitude, conduction without decrement, and refractory period—are unusual for biological processes, which typically respond in a graded fashion to changes in the environment. Biologists were puzzled by these properties for almost 100 years after the action potential was first recorded in the mid-1800s. Finally, in the late 1940s and early 1950s, studies of the membrane properties of the giant axon of the squid by Alan Hodgkin, Andrew Huxley, and Bernard Katz provided the first quantitative insight into the mechanisms underlying the action potential.

The Action Potential Is Generated by the Flow of Ions Through Voltage-Gated Channels

An important early insight into how action potentials are generated came from an experiment performed by Kenneth Cole and Howard Curtis that predated the studies by Hodgkin, Huxley, and Katz. While recording from the giant axon of the squid, they found that the conductance of the membrane increases dramatically during the action potential (Figure 10–1). This discovery provided evidence that the action potential results from a dramatic increase in the ion permeability of the cell membrane. It also raised two central questions: Which ions are responsible for the action potential, and how is the permeability of the membrane regulated?

Hodgkin and Katz provided a key insight into this problem by demonstrating that the amplitude of the action potential is reduced when the external Na^+ concentration is lowered, indicating that Na^+ influx is responsible for the rising phase of the action potential. They proposed that depolarization of the cell above the threshold for an action potential causes a brief increase in the cell membrane's Na^+ conductance, during which the Na^+ conductance overwhelms the K^+ conductance that predominates in the cell at rest, thereby driving the membrane potential towards E_{Na}. Their data also suggested that the falling phase of the action potential was caused by a later increase in K^+ permeability.

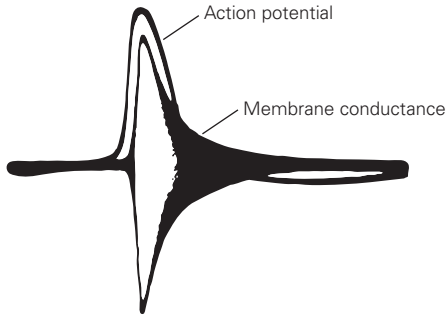

Figure 10–1 The action potential results from an increase in ion conductance of the axon membrane. This historic recording from an experiment conducted in 1939 by Kenneth Cole and Howard Curtis shows the oscilloscope record of an action potential superimposed on a simultaneous record of axonal membrane conductance.

Sodium and Potassium Currents Through Voltage-Gated Channels Are Recorded With the Voltage Clamp

This insight of Hodgkin and Katz raised a further question. What mechanism is responsible for regulating the changes in the Na^+ and K^+ permeabilities of the membrane? Hodgkin and Andrew Huxley reasoned that the Na^+ and K^+ permeabilities were regulated directly by the membrane voltage. To test this hypothesis, they systematically varied the membrane potential in the squid giant axon and measured the resulting changes in the conductance of voltage-gated Na^+ and K^+ channels. To do this, they made use of a new apparatus, the voltage clamp, developed by Kenneth Cole.

Prior to the availability of the voltage-clamp technique, attempts to measure Na^+ and K^+ conductance as a function of membrane potential had been limited by the strong interdependence of the membrane potential and the gating of Na^+ and K^+ channels. For example, if the membrane is depolarized sufficiently to open some voltage-gated Na^+ channels, the influx of Na^+ through these channels causes further depolarization. The additional depolarization causes still more

[1]The all-or-none property describes an action potential that is generated under a specific set of conditions. The size and shape of the action potential *can* be affected by changes in membrane properties, ion concentrations, temperature, and other variables, as discussed later in the chapter. The shape can also be affected slightly by the current that is used to evoke it, if measured near the point of stimulation.