PROPAGATION OF THE ACTION POTENTIAL

the action potential as though it occurs at one spot on the membrane. However, an action potential elicited at any one point on an excitable membrane usually excites adjacent portions of the membrane, resulting in propagation of the action potential along the membrane.

Figure 6-A shows a normal resting nerve fiber and Figure 6-B shows a nerve fiber that has been excited in its midportion, which suddenly develops increased permeability to sodium. The arrows show a local circuit of current flow from the depolarized areas of the membrane to the adjacent resting membrane areas. That is, positive electrical charges are carried by the inward-diffusing sodium ions through the depolarized membrane and then for several millimeters in both directions along the core of the axon. These positive charges increase the voltage for a distance of 1 to 3 millimeters inside the large myelinated fiber to above the threshold voltage value for initiating an action potential.

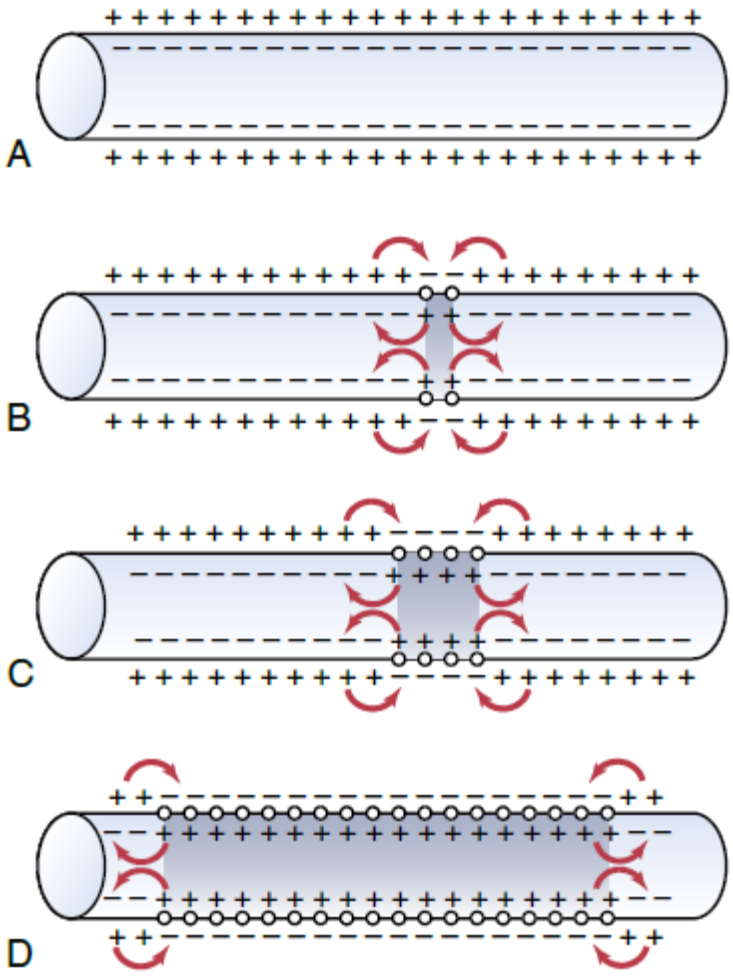

Figure 6

The sodium channels in these new areas immediately open, as shown in Figure 6-C and D, and the explosive action potential spreads. These newly depolarized areas produce still more local circuits of current flow farther along the membrane, causing progressively more and more depolarization. Thus, the depolarization process travels along the entire length of the fiber. This transmission of the depolarization process along a nerve or muscle fiber is called a nerve or muscle impulse.

Direction of Propagation. an excitable membrane has no single direction of propagation, but the action potential travels in all directions away from the stimulus—even along all branches of a nerve fiber—until the entire membrane has become depolarized.

All-or- Nothing Principle. Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, but it does not travel at all if conditions are not right. This principle is called the all-or- nothing principle, and it applies to all normal excitable tissues. Occasionally, the action potential reaches a point on the membrane at which it does not generate sufficient voltage to stimulate the next area of the membrane. When this situation occurs, the spread of depolarization stops.

Therefore, for continued propagation of an impulse to occur, the ratio of action potential to threshold for excitation must at all times be greater than 1. This “greater than 1” requirement is called the safety factor for propagation.

RE-ESTABLISHING SODIUM AND POTASSIUM IONIC GRADIENTS AFTER ACTION POTENTIALS ARE COMPLETED—IMPORTANCE OF ENERGY METABOLISM

Transmission of each action potential along a nerve fiber slightly reduces the concentration differences of sodium and potassium inside and outside the membrane because sodium ions diffuse to the inside during depolarization, and potassium ions diffuse to the outside during repolarization. For a single action potential, this effect is so minute that it cannot be measured. Indeed, 100,000 to 50 million impulses can be transmitted by large nerve fibers before the concentration differences reach the point that action potential conduction ceases. With time, however, it becomes necessary to re-establish the sodium and potassium membrane concentration differences, which is achieved by action of the Na+-K+ pump in the same way as described previously for the original establishment of the resting potential. That is, sodium ions that have diffused to the interior of the cell during the action potentials and potassium ions that have diffused to the exterior must be returned to their original state by the Na+-K+ pump. Because this pump requires energy for operation, this “recharging” of the nerve fiber is an active metabolic process, using energy derived from the adenosine triphosphate (ATP) energy system

of the cell. Figure 7 shows that the nerve fiber produces increased heat during recharging, which is a measure of energy expenditure when the nerve impulse frequency increases.

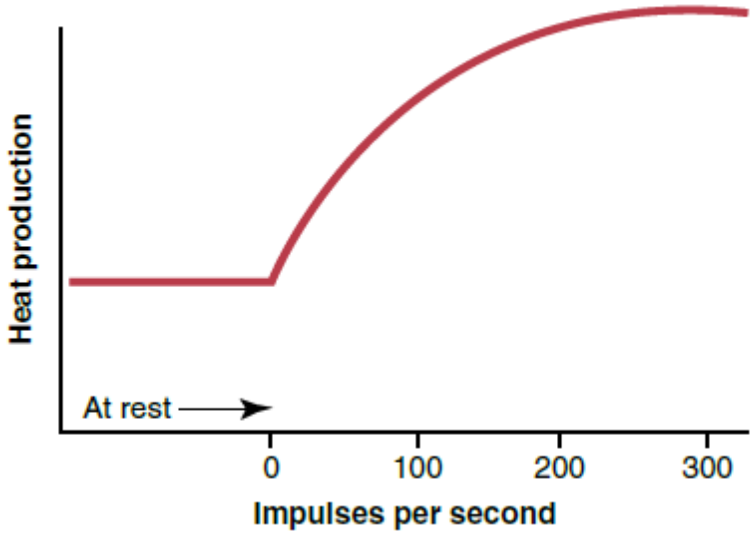

Figure 6

A special feature of the Na+-K+ ATP pump is thatits degree of activity is strongly stimulated when excess sodium ions accumulate inside the cell membrane. In fact, the pumping activity increases approximately in proportion to the third power of this intracellular sodium concentration.

As the internal sodium concentration rises from 10 to 20 mEq/L, the activity of the pump does not merely double but increases about eightfold. Therefore, it is easy to understand how the recharging process of the nerve fiber can be set rapidly into motion whenever the concentration differences of sodium and potassium ions across the membrane begin to run down.

PLATEAU IN SOME ACTION POTENTIALS

In some cases, the excited membrane does not repolarize immediately after depolarization; instead, the potential remains on a plateau near the peak of the spike potential for many milliseconds before repolarization begin. Such a plateau is shown in Figure 7; one can readily see that the plateau greatly prolongs the period of depolarization.

This type of action potential occurs in heart muscle fibers, where the plateau lasts for as long as 0.2 to 0.3 second and causes contraction of heart muscle to last for this same long period.

The cause of the plateau is a combination of several factors. First, in heart muscle, two types of channels contribute to the depolarization process: (1) the usual voltage-activated sodium

channels, called fast channels; and (2) voltage-activated calcium-sodium channels (L-type calcium channels), which are slow to open and therefore are called slow channels. Opening of fast channels causes the spike portion of the action potential, whereas the prolonged opening of the slow calcium-sodium channels mainly allows calcium ions to enter the fiber, which is largely responsible for the plateau portion of the action potential.

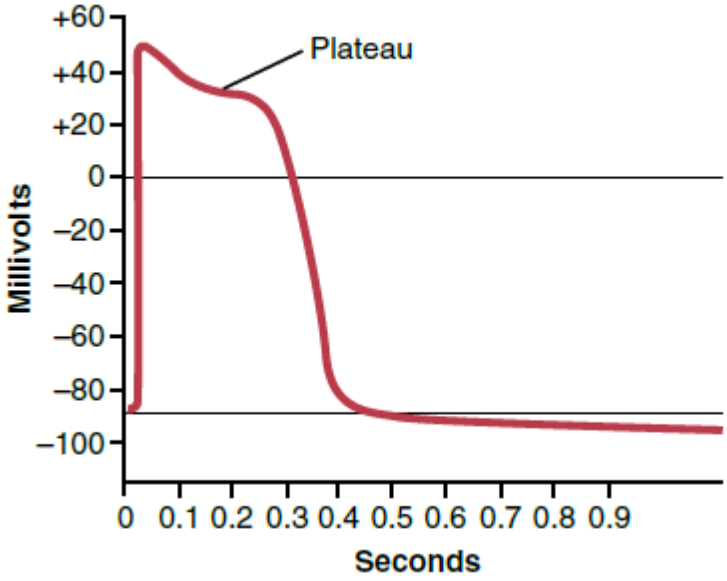

Figure 7

Another factor that may be partly responsible for the plateau is that the voltage-gated potassium channels are slower to open than usual, often not opening much until the end of the plateau. This factor delays the return of the membrane potential toward its normal negative value of −70 millivolts. The plateau ends when the calcium-sodium channels close, and permeability to potassium ions increases.

RHYTHMICITY OF SOME EXCITABLE TISSUES—REPETITIVE DISCHARGE

Repetitive self-induced discharges occur normally in the heart, in most smooth muscle, and in many of the neurons of the central nervous system. These rhythmical discharges cause the following: (1) rhythmical beat of the heart; (2) rhythmical peristalsis of the intestines; and (3) neuronal events such as the rhythmical control of breathing.

In addition, almost all other excitable tissues can discharge repetitively if the threshold for stimulation of the tissue cells is reduced to a low enough level. For example, even large nerve fibers and skeletal muscle fibers, which normally are highly stable, discharge repetitively when they are placed in a solution that contains the drug veratridine, which activates sodium ion

channels, or when the calcium ion concentration decreases below a critical value, which increases the sodium permeability of the membrane.

Re-Excitation Process Necessary for Spontaneous Rhythmicity. For spontaneous rhythmicity to occur, the membrane—even in its natural state—must be permeable enough to sodium ions (or to calcium and sodium ions through the slow calcium-sodium channels) to allow automatic membrane depolarization. Thus, Figure 8 shows that the resting membrane potential in the rhythmical control center of the heart is only −60 to −70 millivolts, which is not enough negative voltage to keep the sodium and calcium channels totally closed. Therefore, the following sequence occurs: (1) some sodium and calcium ions flow inward; (2) this activity increases the membrane voltage in the positive direction, which further increases membrane permeability; (3) still more ions flow inward; and (4) the permeability increases more, and so on, until an action potential is generated.

Then, at the end of the action potential, the membrane repolarizes. After another delay of milliseconds or seconds, spontaneous excitability causes depolarization again, and a new action potential occurs spontaneously. This cycle continues over and over and causes self-induced rhythmical excitation of the excitable tissue.

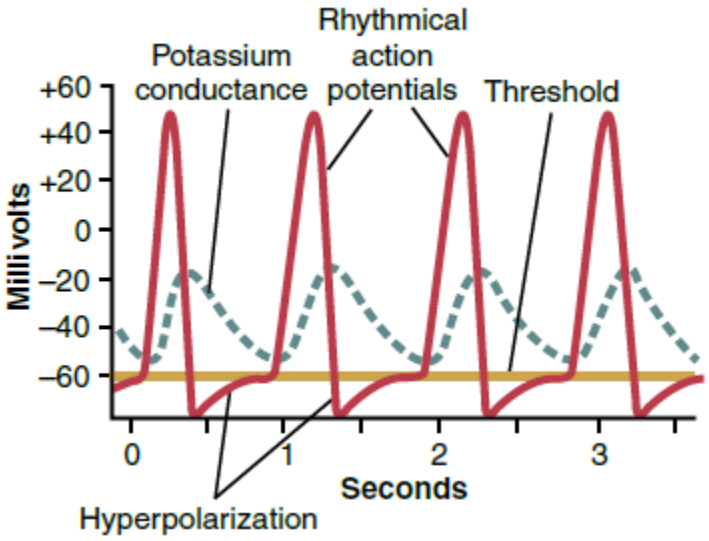

Figure 8

Why does the membrane of the heart control center not depolarize immediately after it has become repolarized, rather than delaying for nearly 1 second before the onset of the next action potential? The answer can be found by observing the curve labeled “potassium conductance” in Figure 8.

This curve shows that toward the end of each action potential, and continuing for a short period

thereafter, the membrane becomes more permeable to potassium ions. The increased outflow of potassium ions carries tremendous numbers of positive charges to the outside of the membrane, leaving considerably more negativity inside the fiber than would otherwise occur. This continues for nearly 1 second after the preceding action potential is over, thus drawing the membrane potential nearer to the potassium Nernst potential. This state, called hyperpolarization, is also shown in Figure 8.

As long as this state exists, self–re-excitation will not occur. However, the increased potassium conductance (and the state of hyperpolarization) gradually disappears, as shown after each action potential is completed in the figure, thereby again allowing the membrane potential to increase up to the threshold for excitation. Then, suddenly, a new action potential results and the process occurs again and again.

SPECIAL CHARACTERISTICS OF SIGNAL TRANSMISSION IN NERVE TRUNKS

Myelinated and Unmyelinated Nerve Fibers. Figure 9 shows a cross section of a typical small nerve, revealing many large nerve fibers that constitute most of the cross-sectional area. However, a more careful look reveals many more small fibers lying between the large ones. The large fibers are myelinated, and the small ones are unmyelinated.

The average nerve trunk contains about twice as many unmyelinated fibers as myelinated fibers.

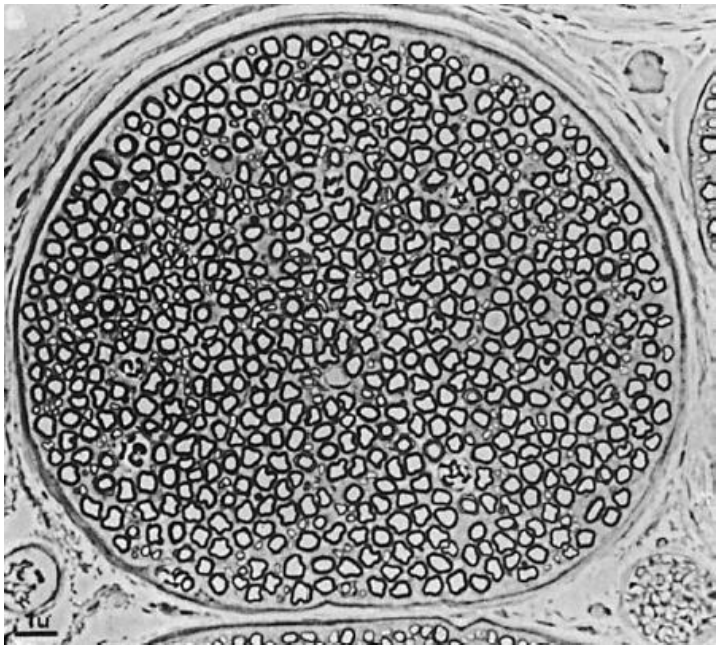

Figure 9

Figure 10 illustrates schematically the features of a typical myelinated fiber. The central core of the fiber is the axon, and the membrane of the axon is the membrane that actually conducts the action potential. The axon is filled in its center with axoplasm, which is a viscid intracellular fluid.

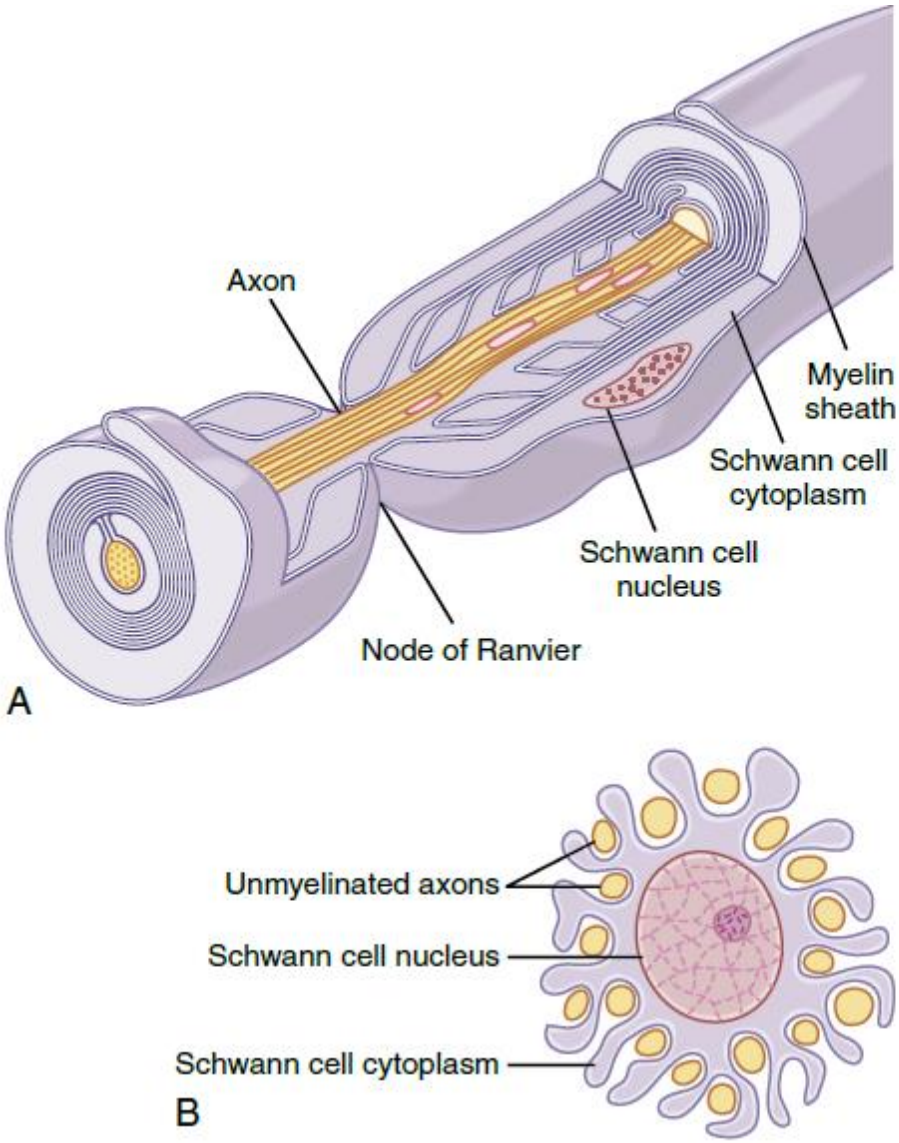

Figure 10

Surrounding the axon is a myelin sheath that is often much thicker than the axon itself. About once every 1 to 3 millimeters along the length of the myelin sheath is a node of Ranvier.

The myelin sheath is deposited around the axon by Schwann cells in the following manner. The membrane of a Schwann cell first envelops the axon. The Schwann cell then rotates around the axon many times, laying down multiple layers of Schwann cell membrane containing the lipid substance sphingomyelin.

This substance is an excellent electrical insulator that decreases ion flow through the membrane about 5000-fold.

At the juncture between each two successive Schwann cells along the axon, a small uninsulated area only 2 to 3 micrometers in length remains where ions still can flow with ease through the axon membrane between the extracellular fluid and intracellular fluid inside the axon. This area is called the node of Ranvier.

Saltatory Conduction in Myelinated Fibers from Node to Node. Even though almost no ions can flow through the thick myelin sheaths of myelinated nerves, they can flow with ease through the nodes of Ranvier. Therefore, action potentials occur only at the nodes. Yet, the action potentials are conducted from node to node by salutatory conduction, as shown in Figure 11.

That is, electrical current flows through the surrounding extracellular fluid outside the myelin sheath, as well as through the axoplasm inside the axon from node to node, exciting successive nodes one after another. Thus, the nerve impulse jumps along the fiber, which is the origin of the term saltatory.

Saltatory conduction is of value for two reasons:

1. First, by causing the depolarization process to jump long intervals along the axis of the nerve fiber, this mechanism increases the velocity of nerve transmission in myelinated fibers as much as 5-to 50-fold.

2. Second, saltatory conduction conserves energy for the axon because only the nodes depolarize, allowing perhaps 100 times less loss of ions than would otherwise be necessary, and therefore requiring much less energy expenditure for re-establishing the sodium and potassium concentration differences across the membrane after a series of nerve impulses.

The excellent insulation afforded by the myelin membrane and the 50-fold decrease in membrane capacitance also allow repolarization to occur with little transfer of ions.

Velocity of Conduction in Nerve Fibers. The velocity of action potential conduction in nerve fibers varies from as little as 0.25 m/sec in small unmyelinated fibers to as much as 100 m/sec—more than the length of a football field in 1 second—in large myelinated fibers.

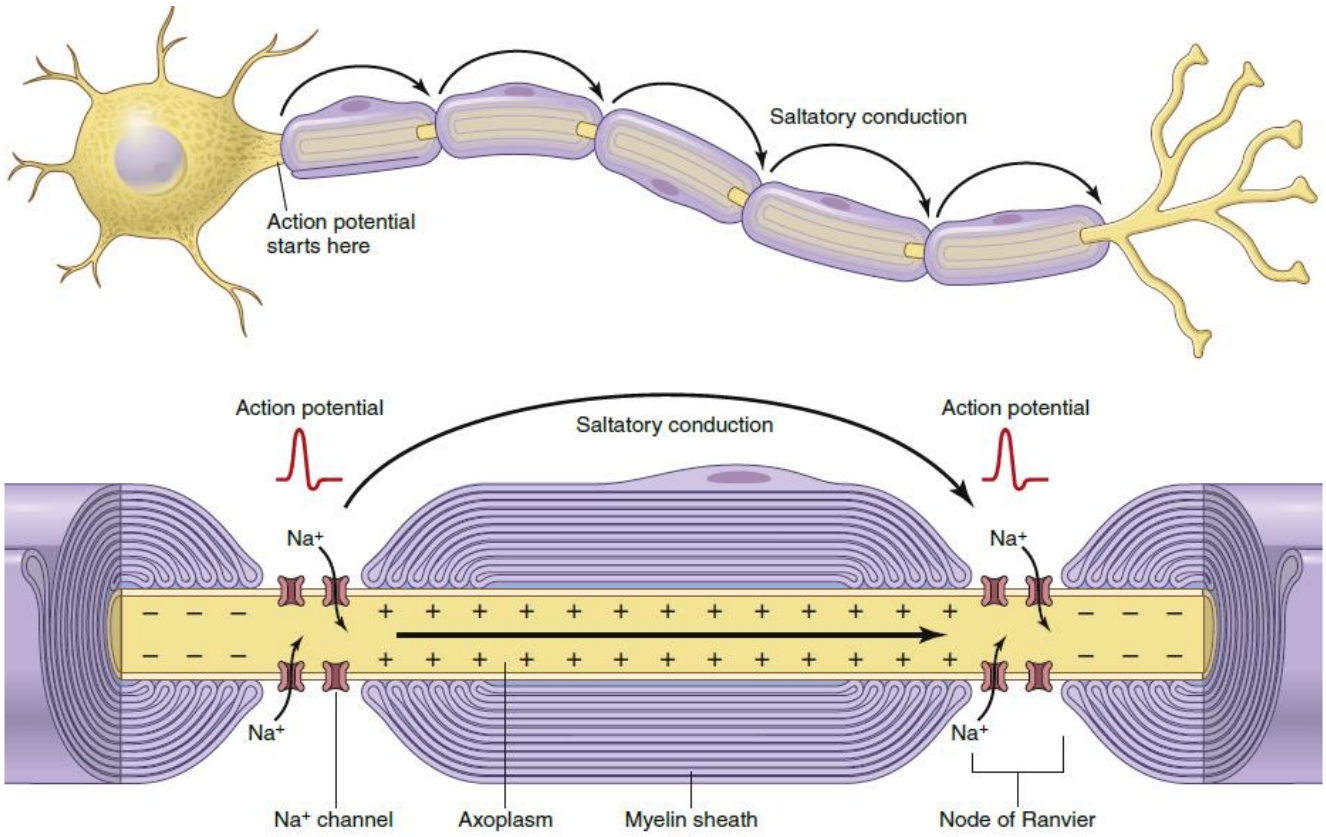

Figure 11

EXCITATION—THE PROCESS OF ELICITING THE ACTION POTENTIAL

Basically, any factor that causes sodium ions to begin to diffuse inward through the membrane in sufficient numbers can set off automatic regenerative opening of the sodium channels. This automatic regenerative opening can result from mechanical disturbance of the membrane, chemical effects on the membrane, or passage of electricity through the membrane. All these approaches are used at different points in the body to elicit nerve or muscle action potentials: mechanical pressure to excite sensory nerve endings in the skin, chemical neurotransmitters to transmit signals from one neuron to the next in the brain, and electrical current to transmit signals between successive muscle cells in the heart and intestine.

Threshold for Excitation and Acute Local Potentials. A weak negative electrical stimulus may not be able to excite a fiber. However, when the voltage of the stimulus is increased, there comes a point at which excitation does take place. Figure 12 shows the effects of successively applied stimuli of progressing strength. A weak stimulus at point A causes the membrane potential to change from −70 to −65 millivolts, but this change is not sufficient for the automatic regenerative processes of the action potential to develop. At point B, the stimulus is greater, but the intensity is still not enough. The stimulus does, however, disturb the membrane potential locally for as long as 1 millisecond or more after both of these weak stimuli. These

local potential changes are called acute local potentials and, when they fail to elicit an action potential, they are called acute subthreshold potentials.

At point C in Figure 12, the stimulus is even stronger. Now, the local potential has barely reached the threshold level required to elicit an action potential, but this occurs only after a short "latent period." At point D, the stimulus is still stronger, the acute local potential is also stronger, and the action potential occurs after less of a latent period.

Thus, this figure shows that even a weak stimulus causes a local potential change at the membrane, but the intensity of the local potential must rise to a threshold level before the action potential is set off.

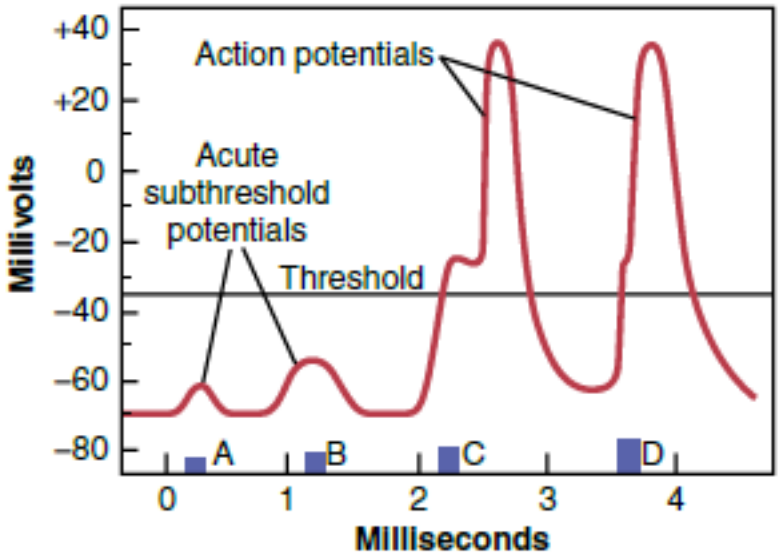

Figure 12

REFRACTORY PERIOD AFTER AN ACTION POTENTIAL, DURING WHICH A NEW STIMULUS CANNOT BE ELICITED

A new action potential cannot occur in an excitable fiber as long as the membrane is still depolarized from the preceding action potential. The reason for this restriction is that shortly after the action potential is initiated, the sodium channels (or calcium channels, or both) become inactivated, and no amount of excitatory signal applied to these channels at this point will open the inactivation gates.

The only condition that will allow them to reopen is for the membrane potential to return to or near the original resting membrane potential level. Then, within another small fraction of a second, the inactivation gates of the channels open, and a new action potential can be initiated.

The period during which a second action potential cannot be elicited, even with a strong stimulus, is called the absolute refractory period. This period for large myelinated nerve fibers is about 1/2500 second. Therefore, one can readily calculate that such a fiber can transmit a maximum of about 2500 impulses per second.