Neuron Action Potential

Nerve signals are transmitted by action potentials, which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and ends with an almost equally rapid change back to the negative potential. To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end.

The upper panel of Figure (1) shows the changes that occur at the membrane during the action potential, with the transfer of positive charges to the interior of the fiber at its onset and the return of positive charges to the exterior at its end. The lower panel shows graphically the successive changes in membrane potential over a few 10,000ths of a second, illustrating the explosive onset of the action potential and the almost equally rapid recovery.

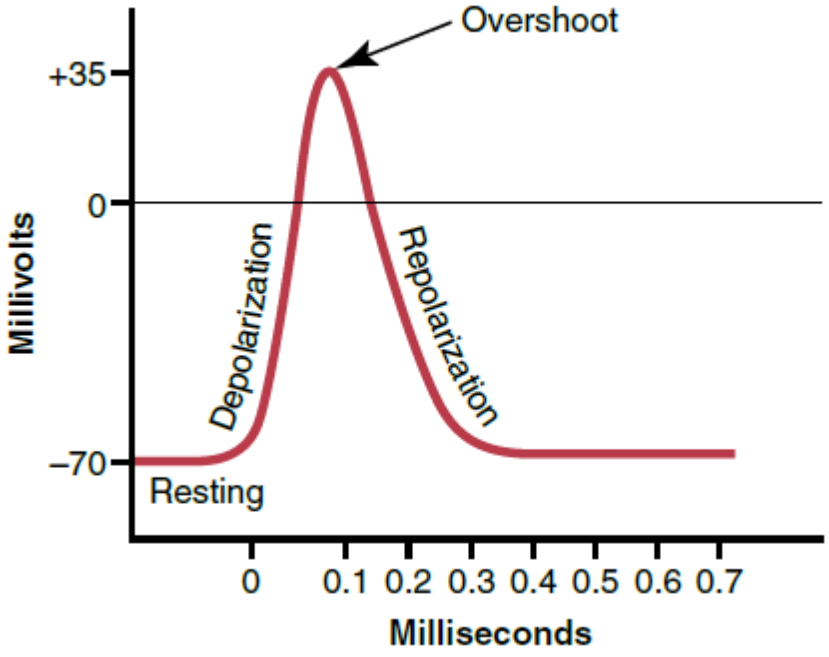

Figure (1)

The successive stages of the action potential are as follows:

Resting Stage. The resting stage is the resting membrane potential before the action potential begins. The membrane is said to be "polarized" during this stage because of the −70 millivolts negative membrane potential that is present.

Depolarization Stage. At this time, the membrane suddenly becomes permeable to sodium ions, allowing rapid diffusion of positively charged sodium ions to the interior of the axon. The normal polarized state of −70 millivolts is immediately neutralized by the inflowing, positively

charged sodium ions, with the potential rising rapidly in the positive direction—a process called depolarization.

In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually overshoot beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.

Repolarization Stage. Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close, and the potassium channels open to a greater degree than normal.

Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential, which is called repolarization of the membrane.

VOLTAGE-GATED SODIUM AND POTASSIUM CHANNELS

The necessary factor in causing both depolarization and repolarization of the nerve membrane during the action potential is the voltage-gated sodium channel. A voltage-gated potassium channel also plays an important role in increasing the rapidity of repolarization of the membrane.

These two voltage-gated channels are in addition to the Na^+-K^+ pump and the K^+ leak channels.

Activation and Inactivation of the Voltage-Gated Sodium Channel

The upper panel of Figure (2) shows the voltage-gated sodium channel in three separate states. This channel has two gates—one near the outside of the channel called the activation gate, and another near the inside called the inactivation gate. The upper left of the figure depicts the state of these two gates in the normal resting membrane when the membrane potential is −70 millivolts. In this state, the activation gate is closed, which prevents any entry of sodium ions to the interior of the fiber through these sodium channels.

Activation of the Sodium Channel. When the membrane potential becomes less negative than during the resting state, rising from −70 millivolts toward zero, it finally reaches a voltage—usually somewhere around −55 millivolts—that causes a sudden conformational change in the activation gate, flipping it all the way to the open position. During this activated state, sodium ions can pour inward through the channel, increasing the sodium permeability of the embrane as much as 500-to 5000-fold.

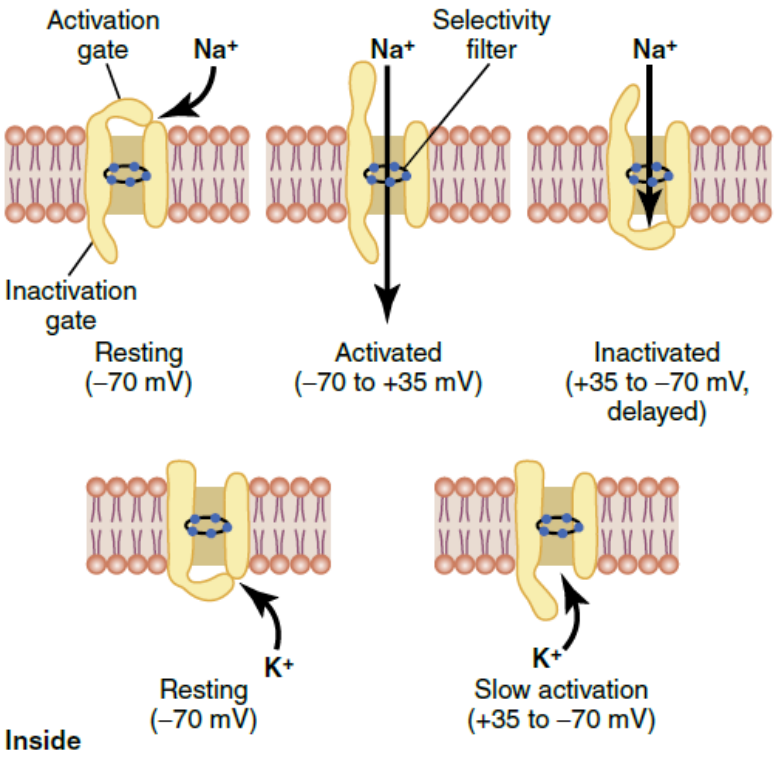

Figure (2)

Inactivation of the Sodium Channel. The upper right panel of Figure (2) shows a third state of the sodium channel. The same increase in voltage that opens the activation gate also closes the inactivation gate. The inactivation gate, however, closes a few 10,000ths of a second after the activation gate opens. That is, the conformational change that flips the inactivation gate to the closed state is a slower process than the conformational change that opens the activation gate. Therefore, after the sodium channel has remained open for a few 10,000ths of a second, the inactivation gate closes, and sodium ions no longer can pour to the inside of the embrane. At this point, the membrane potential begins to return toward the resting membrane state, which is the repolarization process.

Another important characteristic of the sodium channel inactivation process is that the inactivation gate will not reopen until the membrane potential returns to or near the original resting membrane potential level. Therefore, it is usually not possible for the sodium channels to open again without first repolarizing the nerve fiber.

Voltage-Gated Potassium Channel and Its Activation

The lower panel of Figure (2) shows the voltage-gated potassium channel in two states—during the resting state(left) and toward the end of the action potential (right).

During the resting state, the gate of the potassium channel is closed, and potassium ions are prevented from passing through this channel to the exterior. When the membrane potential rises from −70 millivolts toward zero, this voltage change causes a conformational opening of

the gate and allows increased potassium diffusion outward through the channel. However, because of the slight delay in opening of the potassium channels, they open, for the most part, at about the same time that the sodium channels are beginning to close because of inactivation.

Thus, the decrease in sodium entry to the cell and the simultaneous increase in potassium exit from the cell combine to speed the repolarization process, leading to full recovery of the resting membrane potential within another few 10,000ths of a second.

The Voltage Clamp Method for Measuring the Effect of Voltage on Opening and Closing of Voltage-Gated Channels

The original research that led to quantitative understanding of the sodium and potassium channels was so ingenious that it led to Nobel Prizes for the scientists responsible, Hodgkin and Huxley, in 1963. The essence of these studies is shown in Figures. (3) and (4).

Figure (3) shows the voltage clamp method, which is used to measure the flow of ions through the different channels. In using this apparatus, two electrodes are inserted into the nerve fiber. One of these electrodes is used to measure the voltage of the membrane potential, and the other is used to conduct electrical current into or out of the nerve fiber.

This apparatus is used in the following way. The investigator decides which voltage to establish inside the nerve fiber. The electronic portion of the apparatus is then adjusted to the desired voltage, automatically injecting either positive or negative electricity through the current

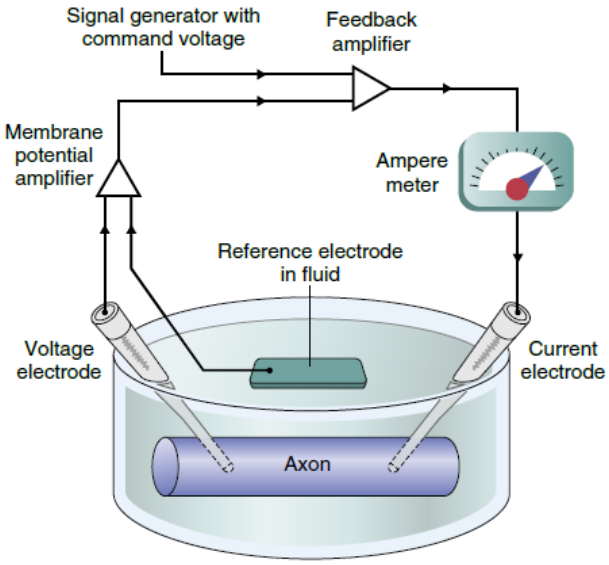

Figure (3)

electrode at whatever rate is required to hold the voltage, as measured by the voltage electrode, at the level set by the operator.

When the membrane potential is suddenly increased by this voltage clamp from −70 millivolts to zero, the voltage-gated sodium and potassium channels open, and sodium and potassium ions begin to pour through the channels. To counterbalance the effect of these ion movements on the desired setting of the intracellular voltage, electrical current is injected automatically through the current electrode of the voltage clamp to maintain the intracellular voltage at the required steady zero level. To achieve this level, the current injected must be equal to but of opposite polarity to the net current flow through the membrane channels.

To measure how much current flow is occurring at each instant, the current electrode is connected to an ampere meter that records the current flow, as demonstrated in Figure (3).

Finally, the investigator adjusts the concentrations of the ions to other than normal levels both inside and outside the nerve fiber and repeats the study. This experiment can be performed easily when using large nerve fibers removed from some invertebrates, especially the giant squid axon, which in some cases is as large as 1 millimeter in diameter.

When sodium is the only permeant ion in the solutions inside and outside the squid axon, the voltage clamp measures current flow only through the sodium channels. When potassium is the only permeant ion, current flow only through the potassium channels is measured.

Another means for studying the flow of ions through an individual type of channel is to block one type of channel at a time. For example, the sodium channels can be blocked by a toxin called tetrodotoxin when it is applied to the outside of the cell membrane where the sodium activation gates are located. Conversely, tetraethylammonium ion blocks the potassium channels when it is applied to the interior of the nerve fiber.

Typical changes in conductance of the voltage-gated sodium and potassium channels when the membrane potential is suddenly changed through use of the voltage clamp, from −70 millivolts

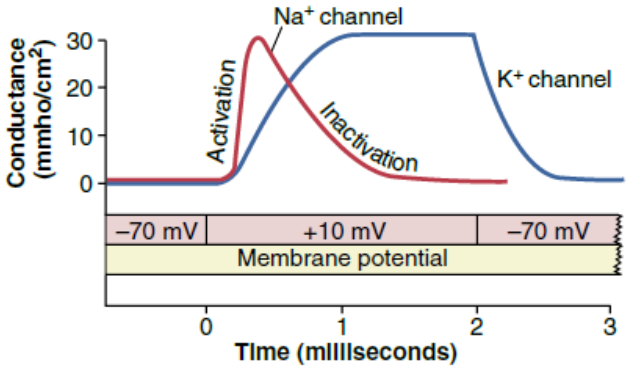

Figure (4)

to +10 millivolts and then, 2 milliseconds later, back to −70 millivolts.The sudden opening of the sodium channels (the activation stage) within a small fraction of a millisecond after the

membrane potential is increased to the positive value. However, during the next millisecond or so, the sodium channels automatically close (the inactivation stage).

Note the opening (activation) of the potassium channels, which open less rapidly and reach their full open state only after the sodium channels have almost completely closed. Furthermore, once the potassium channels open, they remain open for the entire duration of the positive membrane potential and do not close again until after the membrane potential is decreased back to a negative value.

SUMMARY OF EVENTS THAT CAUSE THE ACTION POTENTIAL

The sequential events that occur during and shortly after the action potential. The bottom of the figure shows the changes in membrane conductance for sodium and potassium ions. During the resting state, before the action potential begins, the conductance for potassium ions is 50 to 100 times as great as the conductance for sodium ions. This disparity is caused by much greater leakage of potassium ions than sodium ions through the leak channels. However, at the onset of the action potential, the sodium channels almost instantaneously become activated and allow up to a 5000-fold increase in sodium conductance. The inactivation process then closes the sodium channels within another fraction of a millisecond.

The onset of the action potential also initiates voltage gating of the potassium channels, causing them to begin opening more slowly, a fraction of a millisecond after the sodium channels open.

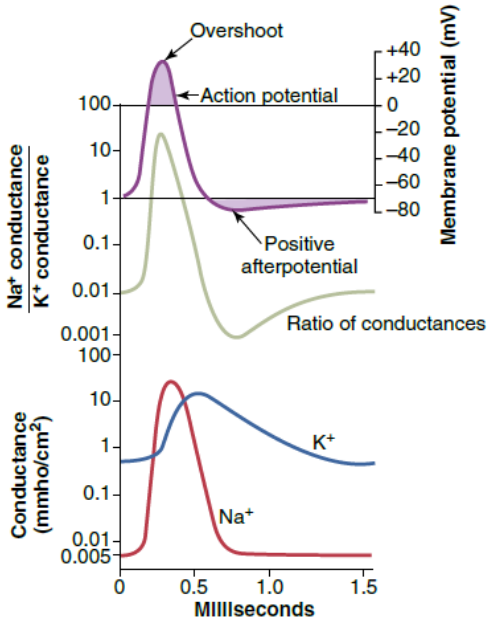

Figure (5)

At the end of the action potential, the return of the membrane potential to the negative state causes the potassium channels to close back to their original status but, again, only after an additional millisecond or more delay.

The middle portion of Figure (5) shows the ratio of sodium to potassium conductance at each instant during the action potential, and above this depiction is the action potential itself. During the early portion of the action potential, the ratio of sodium to potassium conductance increases more than 1000-fold.

Therefore, far more sodium ions flow to the interior of the fiber than potassium ions to the exterior. This is what causes the membrane potential to become positive at the action potential onset. Then, the sodium channels begin to close, and the potassium channels begin to open; thus, the ratio of conductance shifts far in favor of high potassium conductance but low sodium conductance. This shift allows for a very rapid loss of potassium ions to the exterior but virtually zero flow of sodium ions to the interior. Consequently, the action potential quickly returns to its baseline level.

Roles of Other Ions During the Action Potential

Thus far, we have considered only the roles of sodium and potassium ions in generating the action potential. At least two other types of ions must be considered, negative anions and calcium ions.

Impermeant Negatively Charged Ions (Anions) Inside the Nerve Axon. Inside the axon are many negatively charged ions that cannot go through the membrane channels. They include the anions of protein molecules and of many organic phosphate compounds and sulfate compounds, among others. Because these ions cannot leave the interior of the axon, any deficit of positive ions inside the membrane leaves an excess of these impermeant negative anions. Therefore, these impermeant negative ions are responsible for the negative charge inside the fiber when there is a net deficit of positively charged potassium ions and other positive ions.

Calcium Ions. The membranes of almost all cells of the body have a calcium pump similar to the sodium pump, and calcium serves along with (or instead of) sodium in some cells to cause most of the action potential. Like the sodium pump, the calcium pump transports calcium ions from the interior to the exterior of the cell membrane (or into the endoplasmic reticulum of the cell), creating a calcium ion gradient of about 10,000-fold.

This process leaves an internal cell concentration of calcium ions of about 10−7 molar, in contrast to an external concentration of about 10−3 molar.

In addition, there are voltage-gated calcium channels. Because the calcium ion concentration is more than 10,000 times greater in the extracellular fluid than in the intracellular fluid, there is

a tremendous diffusion gradient and elec-trochemical driving force for the passive flow of calcium ions into the cells. These channels are slightly permeable to sodium ions and calcium ions, but their permeability to calcium is about 1000-fold greater than to sodium under normal physiological conditions. When the channels open in response to a stimulus that depolarizes the cell membrane, calcium ions flow to the interior of the cell.

A major function of the voltage-gated calcium ion channels is to contribute to the depolarizing phase on the action potential in some cells. The gating of calcium channels, however, is relatively slow, requiring 10 to 20 times as long for activation as for the sodium channels. For this reason, they are often called slow channels, in contrast to the sodium channels, which are called fast channels.

Therefore, the opening of calcium channels provides a more sustained depolarization, hereas the sodium channels play a key role in initiating action potentials.

Calcium channels are numerous in cardiac muscle and smooth muscle. In fact, in some types of smooth muscle, the fast sodium channels are hardly present; therefore, the action potentials are caused almost entirely by the activation of slow calcium channels.

Increased Permeability of the Sodium Channels When There Is a Deficit of Calcium Ions. The concentration of calcium ions in the extracellular fluid also has a profound effect on the voltage level at which the sodium channels become activated. When there is a deficit of calcium ions, the sodium channels become activated (opened) by a small increase of the membrane potential from its normal, very negative level. Therefore, the nerve fiber becomes highly excitable, sometimes discharging repetitively without provocation, rather than remaining in the resting state. In fact, the calcium ion concentration needs to fall only 50% below normal before spontaneous discharge occurs in some peripheral nerves, often causing muscle “tetany.” Muscle tetany is sometimes lethal because of tetanic contraction of the respiratory muscles.

The probable way in which calcium ions affect the sodium channels is as follows. These ions appear to bind to the exterior surfaces of the sodium channel protein. The positive charges of these calcium ions, in turn, alter the electrical state of the sodium channel protein, thus altering the voltage level required to open the sodium gate.