CHAPTER 5
MEMBRANE POTENTIALS AND ACTION POTENTIALS

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DIFFUSION POTENTIAL

A **diffusion potential** is the **potential** difference generated across a membrane when a charged solute (an ion) diffuses down its concentration gradient. Therefore, a **diffusion potential** is caused by **diffusion** of ions.

A diffusion potential can be generated *only* if the membrane is permeable to that ion. Furthermore, if the membrane is not permeable to the ion, no diffusion potential will be generated no matter how large a concentration gradient is present.

EQUILIBRIUM POTENTIAL

The **equilibrium potential** is the diffusion potential that exactly balances or opposes the tendency for diffusion down the concentration difference.
At **electrochemical equilibrium**, the chemical and electrical driving forces acting on an ion are equal and opposite, and no further net diffusion occurs.

NERNST POTENTIAL

The diffusion potential across a membrane that exactly opposes the net diffusion of a particular ion through the membrane is called the Nernst potential for that ion.

The magnitude of the Nernst potential is determined by the ratio of the concentrations of that specific ion on the two sides of the membrane. The greater this ratio, the greater the tendency for the ion to diffuse in one direction, and

therefore the greater the Nernst potential required to prevent additional net diffusion.

The following equation, called the Nernst equation, can be used to calculate the Nernst potential for any univalent ion at the normal body temperature of 98.6°F (37°C):

EMF (in mV) = ±61/z x log C1/C2

Z is electrical charge (e.g +1 for K+)

C1 is inside concentration

C2 is outside concentration

When using this formula, it is usually assumed that the potential in the extracellular fluid outside the membrane remains at zero potential, and the Nernst potential is the potential inside the membrane. Also, the sign of the potential is positive (+) if the ion diffusing from inside to outside is a negative ion, and it is negative (–) if the ion is positive. Thus, when the concentration of positive potassium ions on the inside is 10 times that on the outside, the log of 10 is 1, so the Nernst potential calculates to be –61 millivolts inside the membrane.

GOLDMAN EQUATION

Goldman equation or Goldman-Hodgkin-Katz equation is used to calculate the diffusion potential when the membrane is permeable to several different ions.

When a membrane is permeable to several different ions, the diffusion potential that develops depends on three factors:

1. The polarity of electrical charge of each ion
2. The permeability of the membrane to each ion (P)
3. The concentration of the respective ions on the inside (Ci) and on the outside (Co) of the membrane

This equation gives the calculated membrane potential on the inside of the membrane when two univalent positive ions, sodium (Na+) and potassium (K+), and one univalent negative ion, chloride (Cl−), are involved

$$\text{EMF (millivolts)} = -61 \times \log \frac{C_{Na_i^+} P_{Na^+} + C_{K_i^+} P_{K^+} + C_{Cl_o^-} P_{Cl^-}}{C_{Na_o^+} P_{Na^+} + C_{K_o^+} P_{K^+} + C_{Cl_i^-} P_{Cl^-}}$$

Several key points become evident from the Goldman equation:

1. Sodium, potassium, and chloride ions are the most important ions involved in the development of membrane potentials in nerve and muscle fibers, as well as in the neuronal cells in the nervous system. The concentration gradient of each of these ions across the membrane helps determine the voltage of the membrane potential.
2. The quantitative importance of each of the ions in determining the voltage is proportional to the membrane permeability for that particular ion. That is, if the membrane has zero permeability to potassium and chloride ions, the membrane potential becomes entirely dominated by the concentration gradient of sodium ions alone, and the resulting potential will be equal to the Nernst potential for sodium. The same holds for each of the other two ions if the membrane should become selectively permeable for either one of them alone.
3. A positive ion concentration gradient from inside the membrane to the outside causes electronegativity inside the membrane. The reason for this phenomenon is that excess positive ions diffuse to the outside when their concentration is higher inside than outside. This diffusion carries positive charges to the outside but leaves the no diffusible negative anions on the inside, thus creating electronegativity on the inside. The opposite effect occurs when there is a gradient for a negative ion. That is, a chloride ion gradient from the outside to the inside causes negativity inside the cell

because excess negatively charged chloride ions diffuse to the inside, while leaving the non-diffusible positive ions on the outside.

4. The permeability of the sodium and potassium channels undergoes rapid changes during transmission of a nerve impulse, whereas the permeability of the chloride channels does not change greatly during this process. Therefore, rapid changes in sodium and potassium permeability are primarily responsible for signal transmission in neurons.

ELECTROCHEMICAL DRIVING FORCE

When an ion is not at its electrochemical equilibrium, an electrochemical driving force (V_{DF}) acts on the ion, causing the net movement of the ion across the membrane down its own electrochemical gradient.

The electrochemical driving force is generally expressed in millivolts and is calculated according the following equation:

$$V_{DF} = V_m - V_{eq}$$

where V_{DF} is the electrochemical driving force, V_m is the membrane potential, and V_{eq} is the equilibrium potential.

The arithmetic sign of V_{DF} (positive or negative) and the valence of the ion (cation or anion) can be used to predict the direction of ion flow across the membrane, into or out of the cell.

- For cations such as Na+, a positive V_{DF} predicts ion movement out of the cell down its electrochemical gradient, and a negative V_{DF} predicts ion movement into the cell.
- For anions such as Cl-, a positive V_{DF} predicts ion movement into the cell, and a negative V_{DF} predicts ion movement out of the cell.
- When $V_m = V_{eq}$, there is no net movement of ion into or out of the cell.
- The direction of ion flux through the membrane reverses as V_m becomes greater than or less than V_{eq} hence, the equilibrium potential is also called the reversal potential.

MEASURING MEMBRANE POTENTIAL

A small pipette is filled with an electrolyte solution. The pipette is impaled through the cell membrane to the interior of the fiber. Another electrode, called the "indifferent electrode," is then placed in the extracellular fluid, and the potential difference between the inside and outside of the fiber is measured using an appropriate voltmeter. This voltmeter is a highly sophisticated electronic apparatus that is capable of measuring small voltages despite extremely high resistance to electrical flow through the tip of the micropipette, which has a lumen diameter usually less than 1 micrometer and a resistance more than a million ohms. For recording rapid changes in the membrane potential during transmission of nerve impulses, the microelectrode is connected to an oscilloscope

RESTING MEMBRANE POTENTIAL OF DIFFERENT CELL TYPES

Cell Type	Resting Potential (mV)
Neurons	–60 to –70
Skeletal muscle	–85 to –95
Smooth muscle	–50 to –60
Cardiac muscle	–80 to –90
Hair (cochlea)	–15 to –40
Astrocyte	–80 to –90
Erythrocyte	–8 to –12
Photoreceptor	–40 (dark) to –70 (light)

RESTING MEMBRANE POTENTIAL OF NEURONS

- The membrane potential when large nerve fibers are not transmitting nerve signals is called resting membrane potential.

- Its value is -70mV
- It is due to :
    1. Sodium-potassium pump
    2. Leakage of potassium through nerve cell membrane
- SODIUM POTASSIUM PUMP

  The sodium potassium pump causes large concentration gradients for sodium and potassium across the resting nerve membrane. These gradients are as follows :

Na^+(outside): 142 mEq/L

Na^+(inside): 14 mEq/L

K^+(outside): 4 mEq/L

K^+(inside): 140 mEq/L

The ratios of these two respective ions from the inside to the outside are as follows:

$$Na^+_{inside}/Na^+_{outside} = 0.1$$

$$K^+_{inside}/K^+_{outside} = 35.0$$

- If potassium ions were the only factor causing the resting potential, the resting potential inside the fiber would be equal to -94mV
- Considering only sodium and potassium gives the potential inside the membrane of -86 mV
- The net membrane potential when all these factors are operative at the same time is about -90mV

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

Voltage clamp method 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 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 –90 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 oscilloscope that records the current flow, as demonstrated on the screen of the oscilloscope in Figure 5-8. 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 instance, 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

ACTION POTENTIAL

DEFINITION

- An action potential is defined as a sudden, fast, transitory, and propagating change of the resting membrane potential. Only neurons and muscle cells are capable of generating an action potential; that property is called the excitability.

What causes action potential?

- Not all stimuli can cause an action potential. Adequate stimulus must have a sufficient electrical value which will reduce the negativity of the nerve cell to the threshold of the action potential.
- In this manner, there are subthreshold, threshold, and suprathreshold stimuli.

- Subthreshold stimuli cannot cause an action potential
- Threshold stimuli are of enough energy or potential to produce an action potential (nerve impulse).
- Suprathreshold stimuli also produce an action potential, but their strength is higher than the threshold stimuli.

ELICITING 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 can be caused by :
    - Mechanical disturbance of the membrane (such as mechanical pressure to excite sensory nerve endings)
    - Chemical effects on the membrane (such as neurotransmitters)
    - Passage of electricity through membrane

Resting Membrane Potential

- The **resting membrane potential** of a **neuron** is about -70 mV (mV=millivolt) - this means that the inside of the **neuron** is 70 mV less than the outside.
- Because there is a **potential** difference across the cell **membrane**, the **membrane** is said to be **polarized**.
- At **rest**, there are relatively more sodium ions outside the **neuron** and more potassium ions inside that **neuron**.
- All voltage-gated ion channels are closed. Leakage-gated ion channels and the sodium-potassium pump helps to keep the resting potential stable.

Threshold Potential

- an action potential is generated when a stimulus changes the membrane potential to the values of threshold potential. The threshold potential is

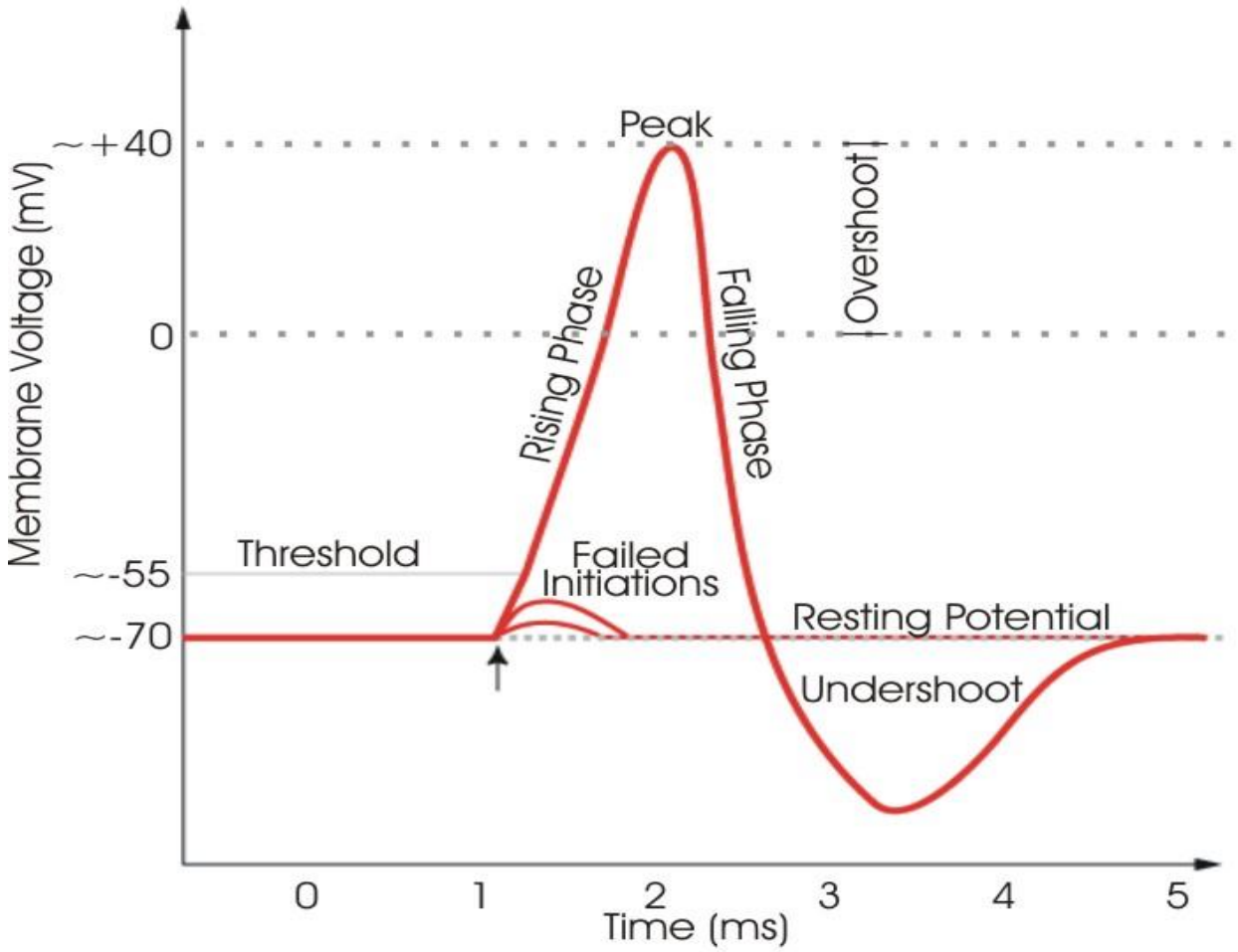
usually around -50 to -55 mV. It is important to know that the action potential behaves upon the *all-or-none law*. This means that any subthreshold stimulus will cause nothing, while threshold and suprathreshold stimuli produce a full response of the excitable cell.

- The value of threshold potential depends on the membrane permeability, intra- and extracellular concentration of ions, and the properties of the cell membrane.

Phases Of Action Potential

- An action potential has several phases:

1. Threshold Potential
2. Depolarization
3. Overshoot
4. Repolarization
5. Hyperpolarization.



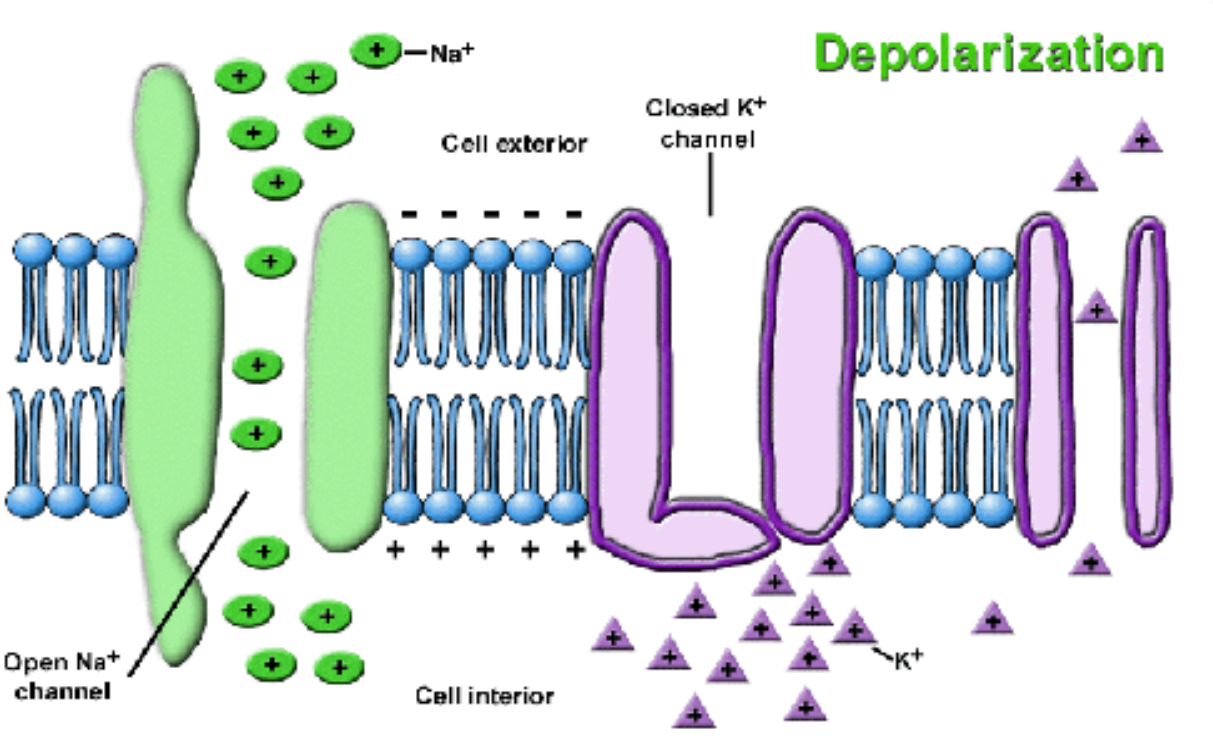
1. Threshold Potential

A stimulus from a sensory cell or another neuron causes the target cell to depolarize toward the **threshold potential**.

Most often, the threshold potential is a membrane potential value between –50 and –55 mV, but can vary based upon several factors. A neuron's resting membrane potential (–70 mV) can be altered to either increase or decrease likelihood of reaching threshold via **sodium** and **potassium** ions.

2. Depolarization

- The threshold potential opens voltage-gated sodium channels and causes a large influx of sodium ions. This phase is called the depolarization.
- During depolarization, the inside of the cell becomes more and more electropositive
- If any event causes enough initial rise in membrane potential from -70 mV towards the zero level, the rising voltage will cause many voltage-gated sodium channels to begin opening through positive feedback.

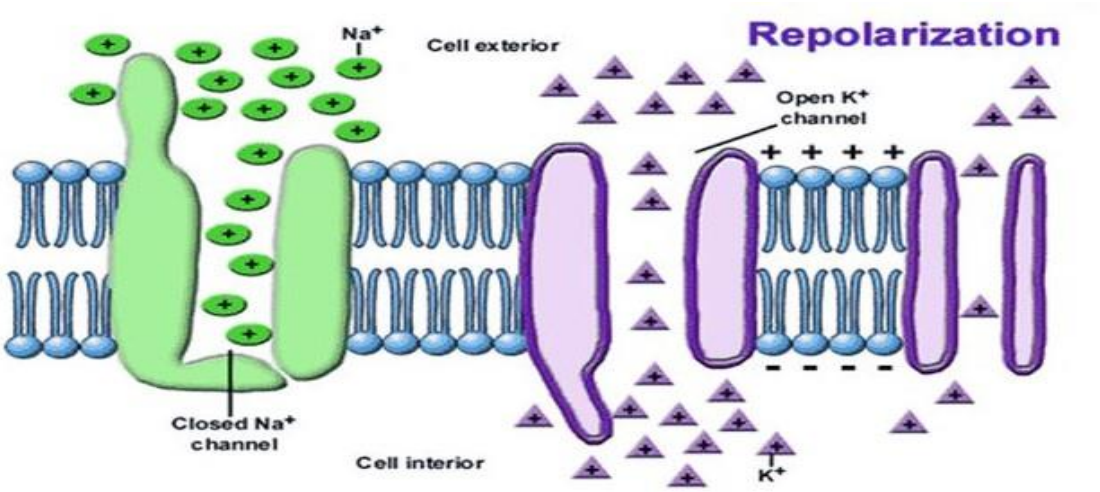


3. OVERSHOOT

- The peak of action potential
- At the peak action potential, K^+ channels open and K^+ begins to leave the cell. At the same time, Na^+ channels close.

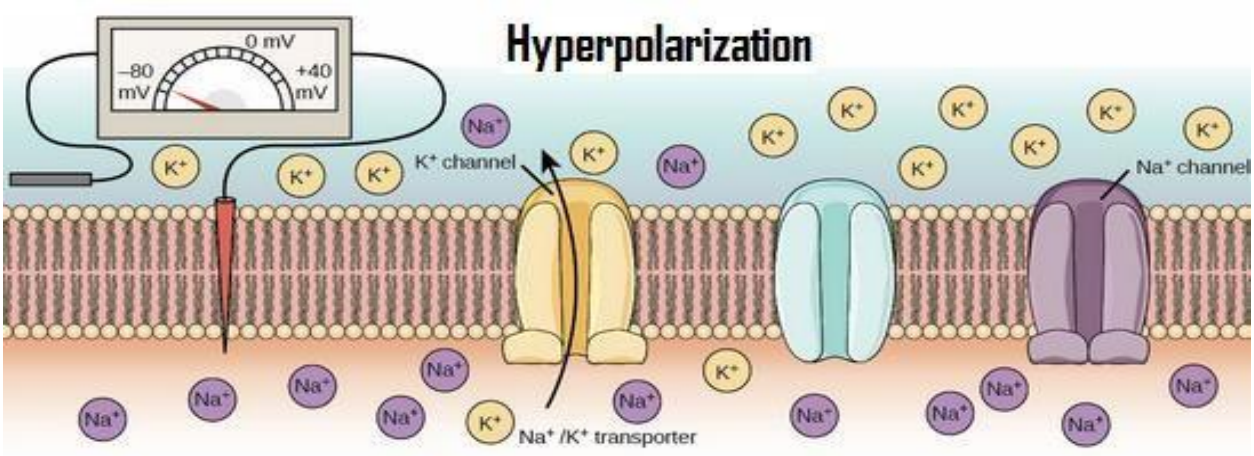
4. REPOLARIZATION

- After the overshoot, the sodium permeability suddenly decreases due to the closing of its channels. The overshoot value of the cell potential opens voltage-gated potassium channels, which causes a large potassium efflux, decreasing the cell's electropositivity. This phase is the repolarization phase, whose purpose is to restore the resting membrane potential.



5. HYPERPOLARIZATION

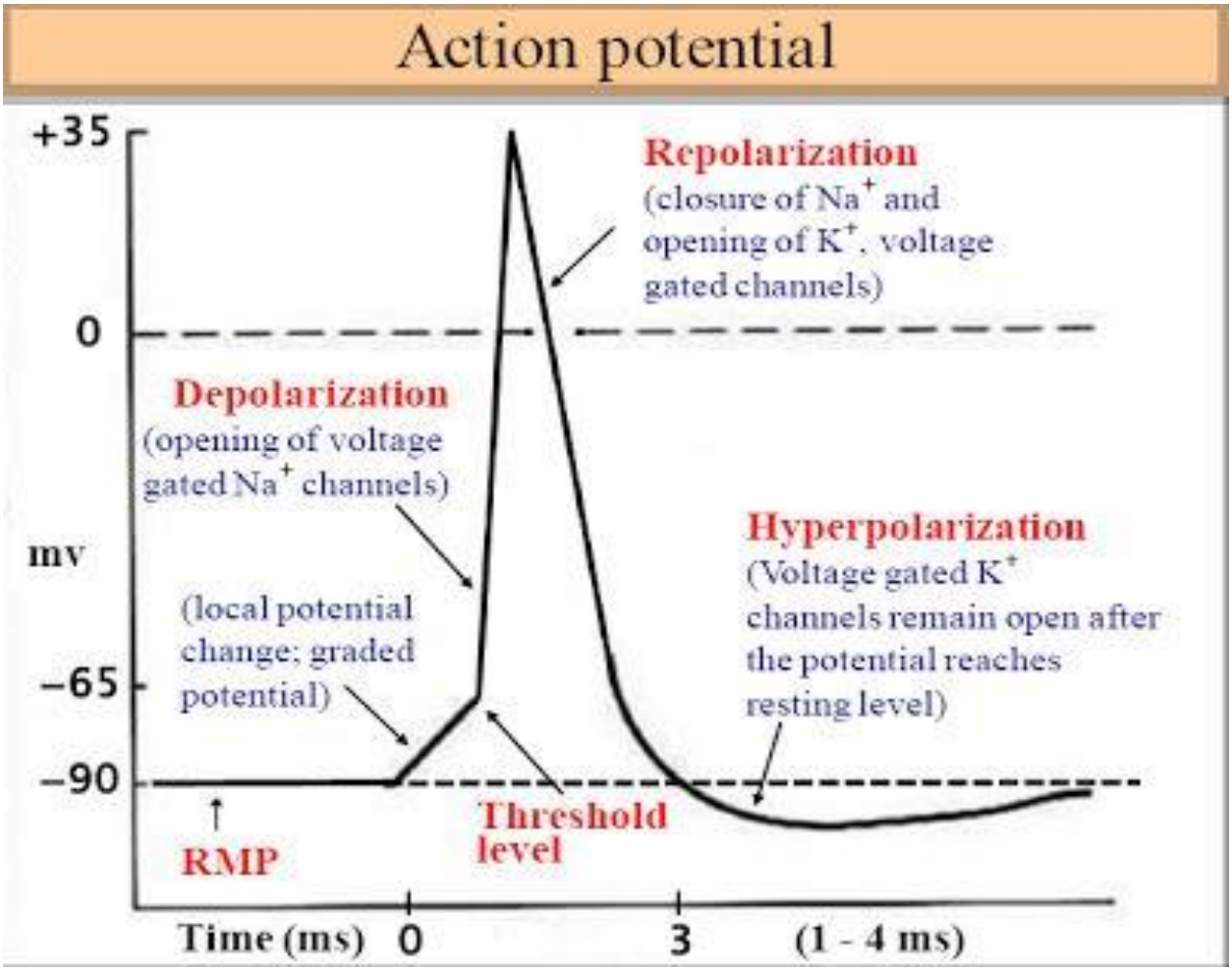
- The voltage-gated potassium channels stay open a little longer than needed to bring the membrane back to its resting potential. This results in a phenomenon called "undershoot," in which the membrane potential briefly dips lower (more negative) than its resting potential and is called hyperpolarization.



At the peak action potential, Na^+ channels close while K^+ channels open. K^+ leaves the cell, and the membrane eventually becomes hyperpolarized.

REFRACTORY PERIOD

- 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.
- Eventually, the voltage-gated potassium channels close and the membrane potential stabilizes at resting potential. The sodium channels return to their normal state. The action potential cycle may then begin again.



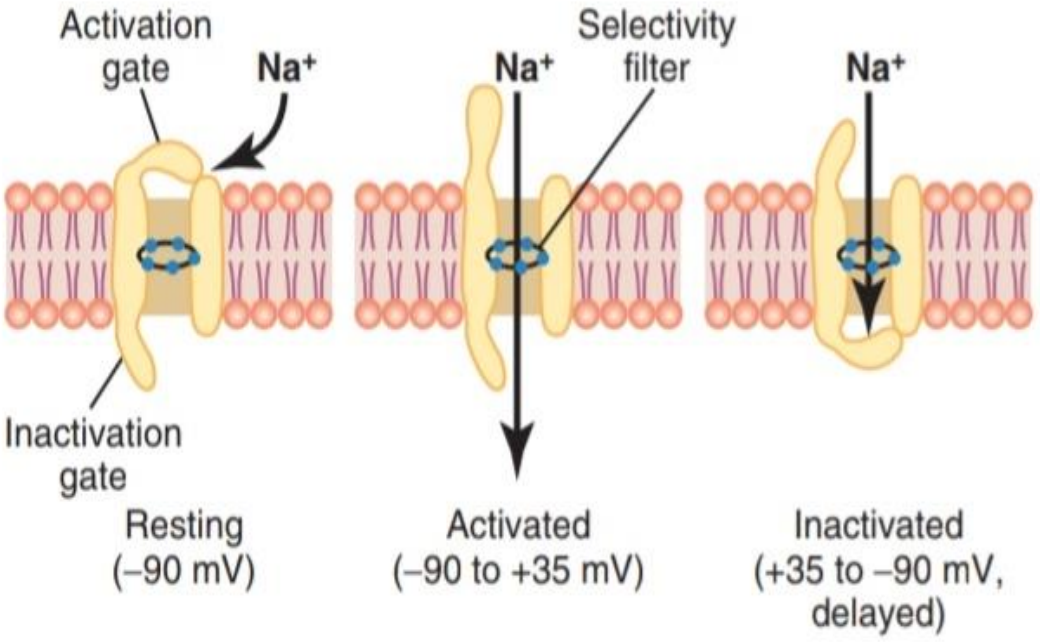
WORKING OF SODIUM GATES

- A strong negative charge on the inside of the cell membrane may cause the outside sodium gates to remain tightly closed.
- When the inside of the membrane loses its negative charge, these gates open suddenly and allow sodium to pass inward through the sodium pores.

STRUCTURE OF VOLTAGE GATED SODIUM CHANNEL

- Two gates:
    - Activation gate outside the channel
    - Inactivation gate near the inside

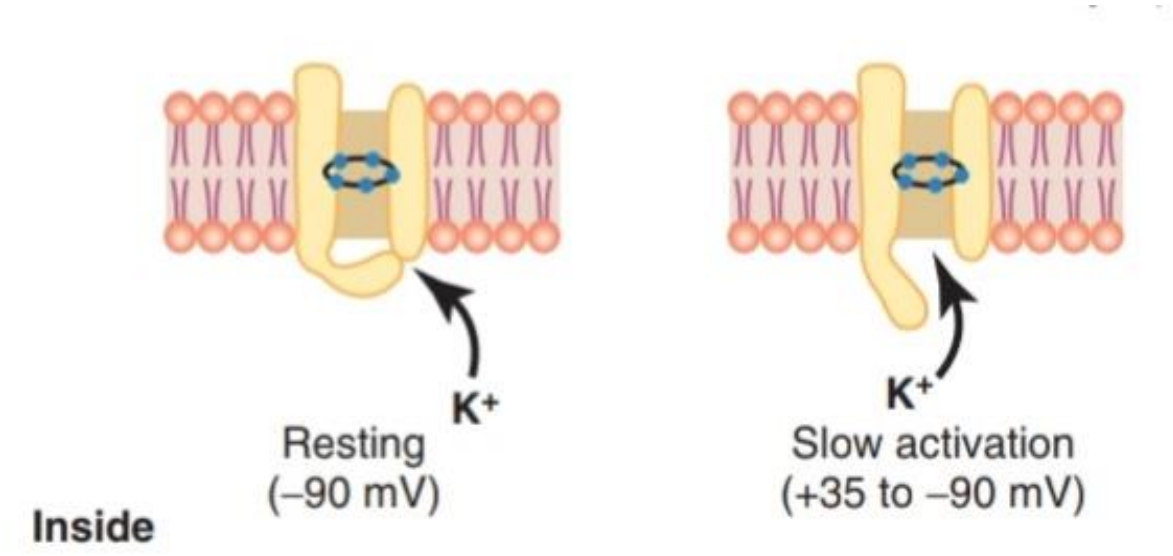
- Activation gate is closed in resting membrane which prevents any entry of sodium ions to interior of the fiber.
- When membrane potential reaches a voltage somewhere around -55 mV, a sudden conformational change in the activation gate takes place, flipping it all the way to the open position. This activation can increase sodium permeability of the membrane as much as 500 to 5000 fold.
- Inactivation gate close during repolarization. Closure of the **inactivation gate** causes **Na^+** flow through the **channel** to stop, which in turn causes the membrane potential to stop rising.



Working of Potassium Gates

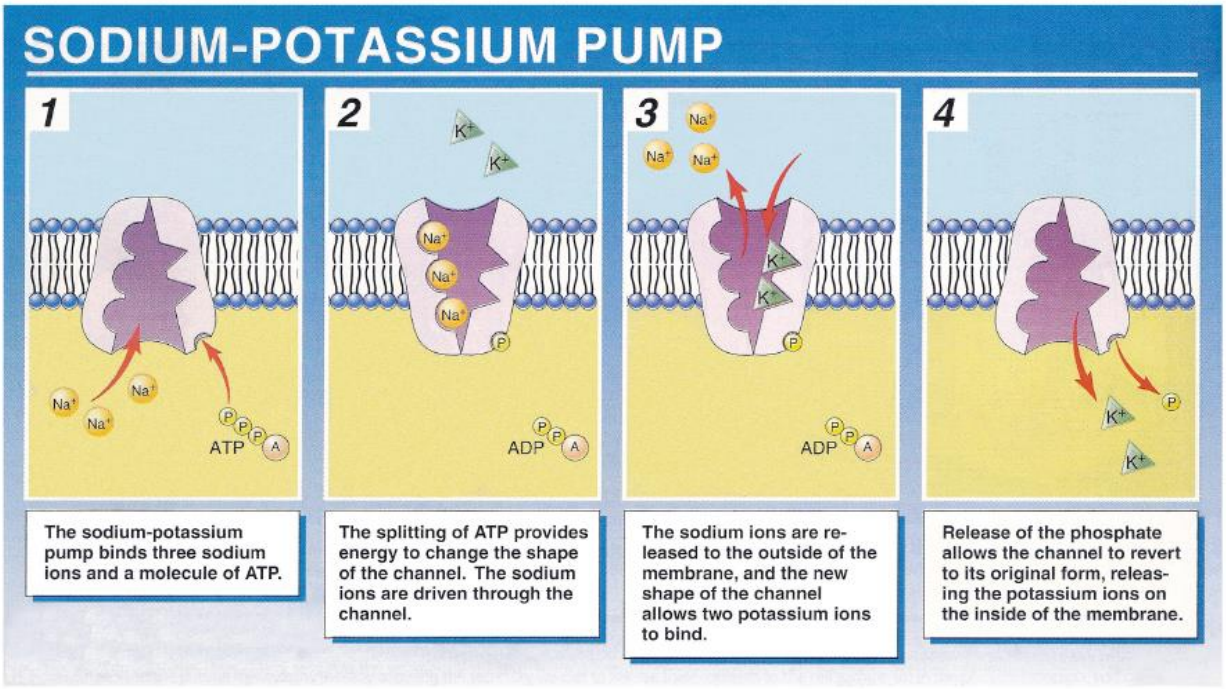
- The potassium gates are on the intracellular ends of the potassium channels.
- During resting stage, potassium gates are closed, thus preventing passage of potassium to exterior.

- 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, for the most part, they open just at 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
- The opening of these gates is partly responsible for terminating the action potential



SODIUM-POTASSIUM PUMP

- also known as the Na+/K+ pump or Na+/K+-ATPase, this is a protein pump found in the cell membrane of neurons
- It acts to transport sodium and potassium ions across the cell membrane in a ratio of 3 sodium ions out for every 2 potassium ions brought in.
- In the process, the pump helps to stabilize membrane potential, and thus is essential in creating the conditions necessary for the firing of action potentials.



ACTION POTENTIAL SUMMARY

- RESTING STAGE
    - Conductance for K+ ions is 50 to 100 times as great as conductance for sodium ions.
    - Leakage of K+ ions through leak channels.
- ONSET OF ACTION POTENTIAL
    - Sodium channels instantaneously become activated and allow upto 500 fold increase in sodium conductance
- PEAK OF ACTION POTENTIAL
    - Sodium channels close
    - Opening of potassium channels slowly
- REPOLARIZATION
    - Return of membrane potential to negative state

ROLES OF OTHER IONS DURING ACTION POTENTIAL

- Anions inside the nerve axons
    - Anions of protein molecules and many organic phosphate compounds and sulfate compounds.
- Calcium ions
    - A major function of voltage gated calcium ion channels is to contribute to the depolarizing phase of the action potential in some cells
    - 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.

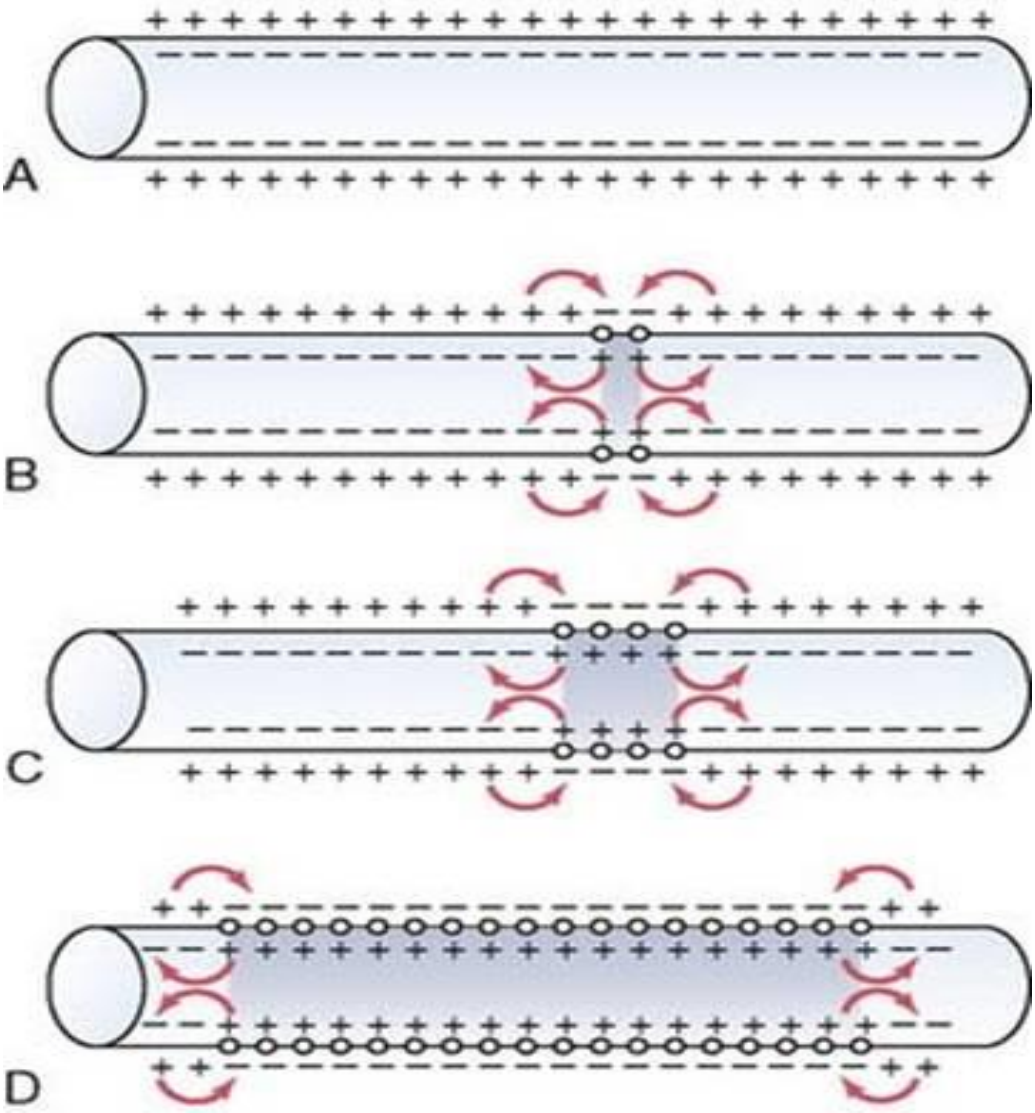
Increased permeability of sodium ions due to deficit of calcium ions

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 percent 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 molecule. 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.

PROPAGATION OF ACTION POTENTIAL

- Action potentials are propagated along the axon without losing strength by active propagation as follows:
  The passive spread of depolarization causes cations (mostly potassium) to spread to adjacent regions of the axon's cytoplasm.
  As the depolarization spreads, it loses its magnitude and MUST be actively generated (propagated) to move far.
  Propagation depends upon the passive spread of depolarization to induce the membrane potential in adjacent parts of the axon to reach the threshold potential which then triggers the intake of sodium ions and continuation of the cycle.
  For example, signals move from the dendrites through the cell body to the base of the axon (the axon hillock) where sodium channels are concentrated. At the axon hillock, a great influx of sodium ions can occur which specify that action potentials initiated here are propagated down the axon.
  The propagated action potential is the nerve impulse.
  The rate of impulse transmission depends on electrical properties of the axon such as the electrical resistance of the cytosol and the ability to retain electric charge (capacitance) of the plasma membrane.



RESTORING IONIC CONCENTRATIONS AFTER COMPLETION OF ACTION POTENTIAL

- The concentration of sodium and potassium ions are reduced during action potential as sodium ions diffuse to the inside during depolarization, and K+ ions diffuse to outside during repolarization.
- This concentration is re-established by sodium-potassium pump which requires energy ie ATP for operating.
- A special feature of the Na+ -K+ adenosine triphosphatase pump is that its 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 ACTION POTENTIALS

- In some instances, 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, and only then does repolarization begin.
- 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.

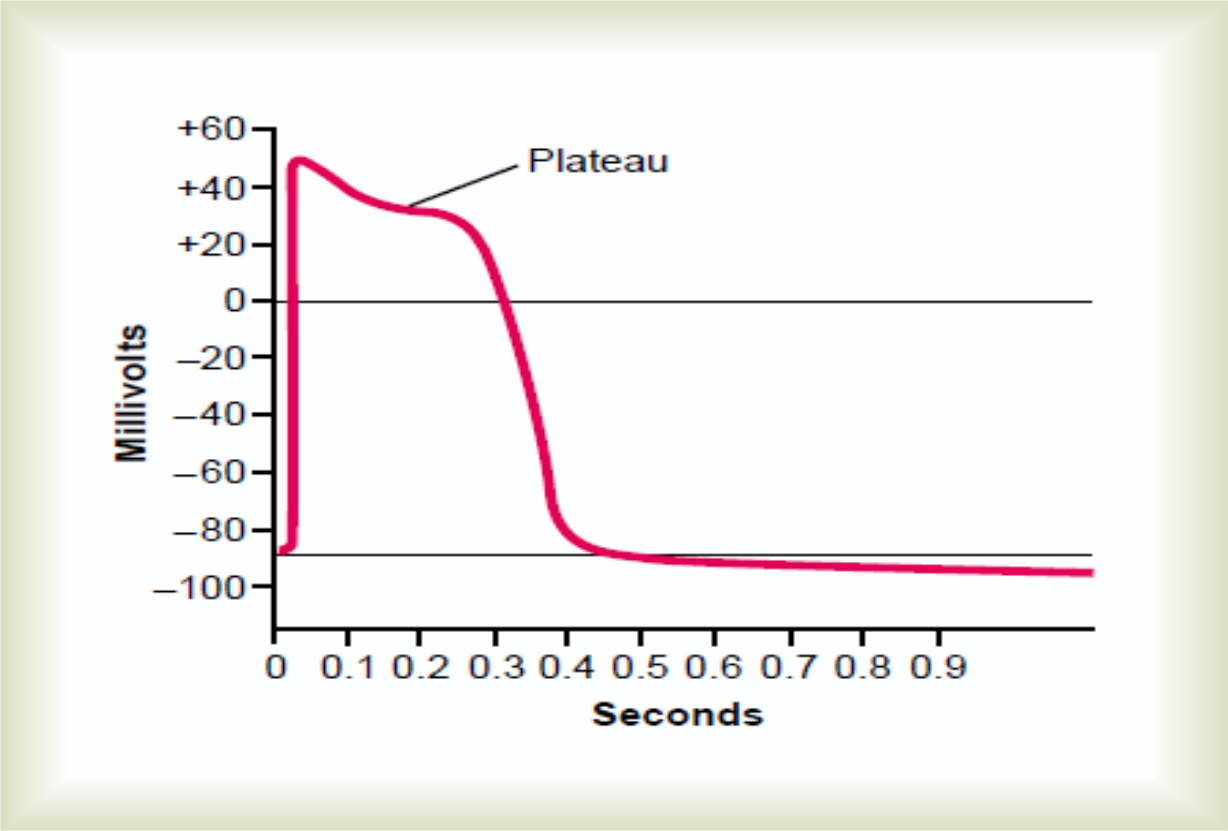


Figure 5–13

Action potential (in millivolts) from a Purkinje fiber of the heart, showing a "plateau."

CAUSES OF PLATEAU

- 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.

- A second 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 −70millivolts. The plateau ends when the calcium-sodium channels close and permeability to potassium ions increases.

REPITITIVE DISCHARGE – RHYTHMICITY OF SOME EXCITABLE TISSUES

- 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

(1) the rhythmical beat of the heart,

(2) rhythmical peristalsis of the intestines, and

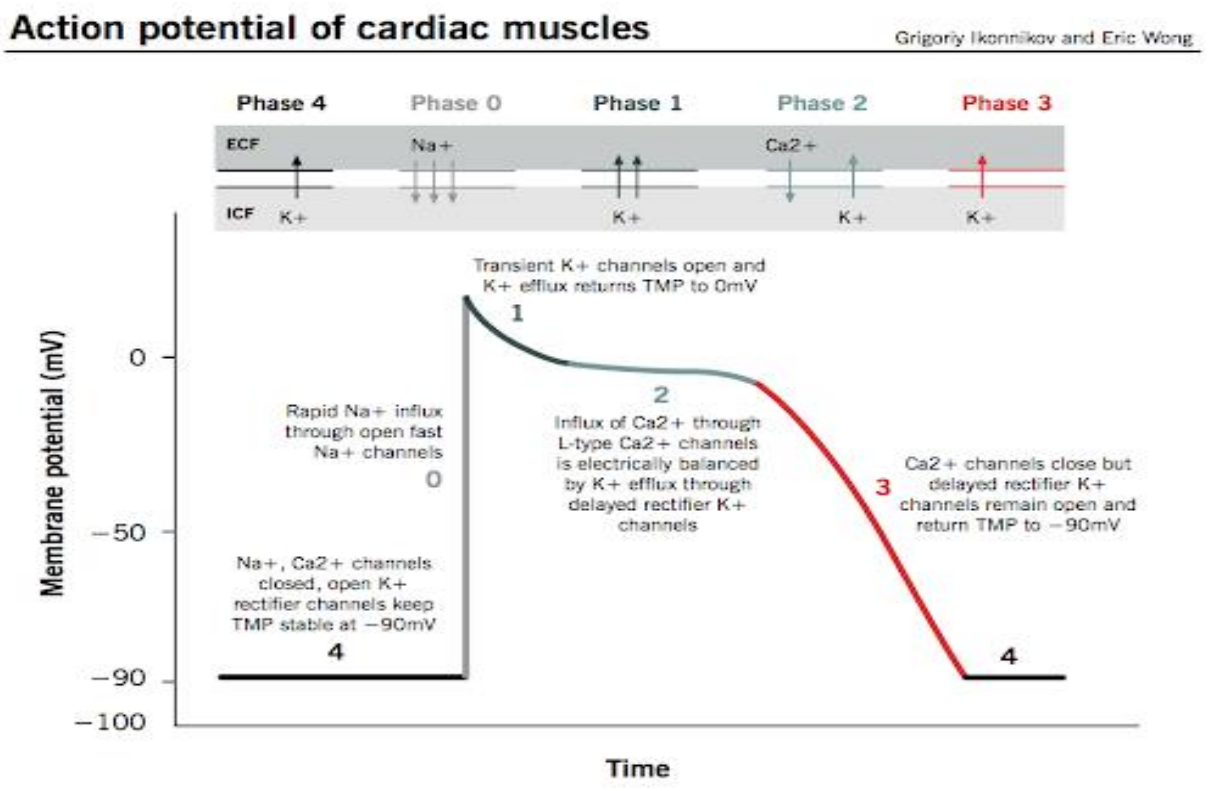
(3) such neuronal events as the rhythmical control of breathing.

- 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 instance, 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 sodium permeability of the membrane.

- . 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.

CARDIAC ACTION POTENTIAL

- The cardiac action potential is very different to that seen in nerves. It has a prolonged plateau phase lasting around 300 ms compared with 1 ms in nerves. The cardiac action potential has five phases.
- During phase 0, membrane permeability to potassium decreases and fast sodium channels open, producing rapid depolarization from −90 mV to +10 mV.
- During phase 1, there is partial repolarization, because of a decrease in sodium permeability.
- Phase 2 is the plateau phase of the cardiac action potential. Membrane permeability to calcium increases during this phase, maintaining depolarization and prolonging the action potential. Membrane permeability to calcium decreases somewhat towards the end of phase 2, and the plateau is partially maintained by an inward sodium current. Sodium flows into the cell through the sodium–calcium exchanger. The exchanger transfers three sodium ions into the cell in exchange for one calcium ion flowing out, and so produces a net inward positive current.
- As calcium channels inactivate towards the end of the plateau phase, an inward potassium current produces repolarization in phase 3.
- The resting membrane potential in phase 4 is approximately −90 mV. This is produced mainly by the selective permeability of the cell membrane to potassium and the concentration gradient for potassium that exists across the cell membrane and is close to the Nernst equilibrium potential for potassium.



SPONTANEOUS CARDIAC RHYTHMICITY

- **Cardiac rhythmicity** is the **spontaneous** depolarization and repolarization event that occurs in a repetitive and stable manner within the **cardiac muscle**. **Rhythmicity** is often abnormal or lost in cases of **cardiac** dysfunction or **cardiac** failure.
- 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.

NERVE FIBERS

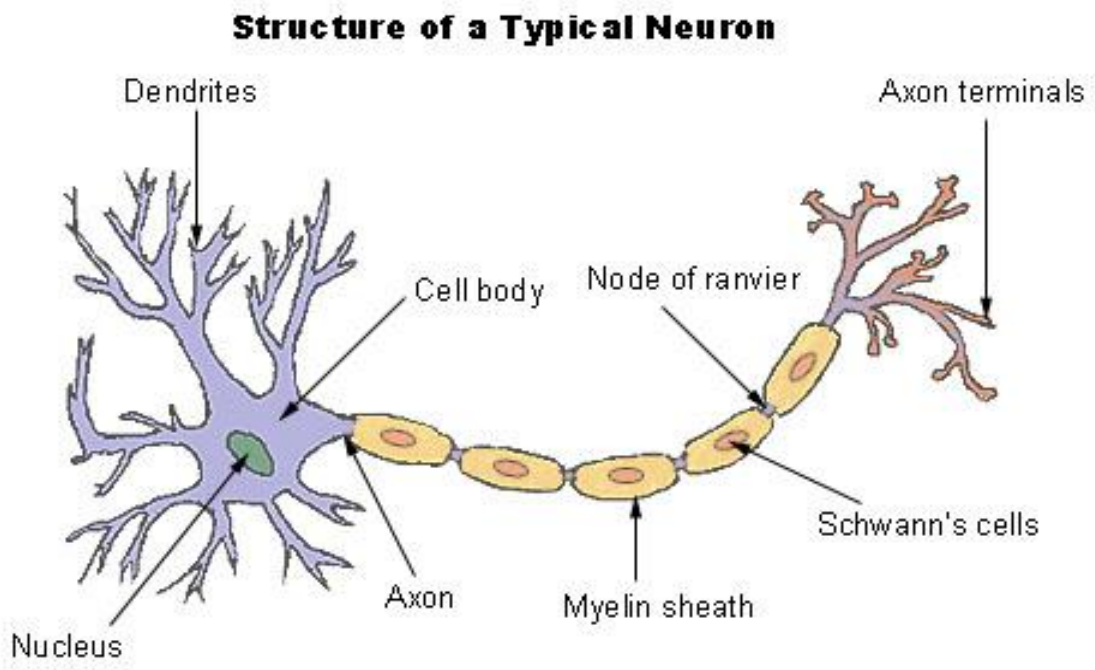
1. Myelinated fibers
2. Unmyelinated fibers

- 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.
- The velocity of action potential conduction in nerve fibers varies from as little as 0.25 m/sec in small unmyelinated fibers to as great as 100 m/sec in large myelinated fibers.

MYELINATED FIBER

- Axon – central core of the fiber filled with axoplasm.
- Membrane of axon conducts action potential.
- Axon is surrounded by a myelin sheath which is often much thicker than the axon.
- About once every 1 to 3 millimeters along the length of the myelin sheath is a node of Ranvier across which ion flow takes place. Action potential occur only at the nodes by saltatory conduction.
- 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.



SALTATORY CONDUCTION

- Saltatory conduction is of value for two reasons.
    - 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.
    - 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 little 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.

EXCITING A NERVE EXPERIMENTALLY

- Exciting a Nerve Fiber by a Negatively Charged Metal Electrode. The usual means for exciting a nerve or muscle in the experimental laboratory is to apply electricity to the nerve or muscle surface through two small electrodes, one of which is negatively charged and the other positively charged. When electricity is applied in this manner, the excitable membrane becomes stimulated at the negative electrode.

- Remember that the action potential is initiated by the opening of voltage-gated sodium channels. Further, these channels are opened by a decrease in the normal resting electrical voltage across the membrane—that is, negative current from the electrode decreases the voltage on the outside of the membrane to a negative value nearer to the voltage of the negative potential inside the fiber. This effect decreases the electrical voltage across the membrane and allows the sodium channels to open, resulting in an action potential. Conversely, at the positive electrode, the injection of positive charges on the outside of the nerve membrane heightens the voltage difference across the membrane rather than lessening it. This effect causes a state of hyperpolarization, which actually decreases the excitability of the fiber rather than causing an action potential.

Stabilizers and Local Anesthetics

- In contrast to the factors that increase nerve excitability, still others, called membrane-stabilizing factors, can decrease excitability. For instance, a high extracellular fluid calcium ion concentration decreases membrane

permeability to sodium ions and simultaneously reduces excitability. Therefore, **calcium ions** are said to be a "stabilizer."

- **Local Anesthetics.** Among the most important stabilizers are the many substances used clinically as local anesthetics, including ***procaine*** and ***tetracaine***. Most of these substances act directly on the activation gates of the sodium channels, making it much more difficult for these gates to open, thereby reducing membrane excitability. When excitability has been reduced so low that the ratio of action potential strength to excitability threshold (called the "safety factor") is reduced below 1.0, nerve impulses fail to pass along the anesthetized nerves.