
PHYSIOLOGY
النادي الطبي
Lec: 13 (sun 24/3)
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General Physiology
Second Semester , 2024
Lecture 13 and 14
Part 1: Action potential of neurons
Ionic basis and properties of action potential
Part II Cardiac action potentials

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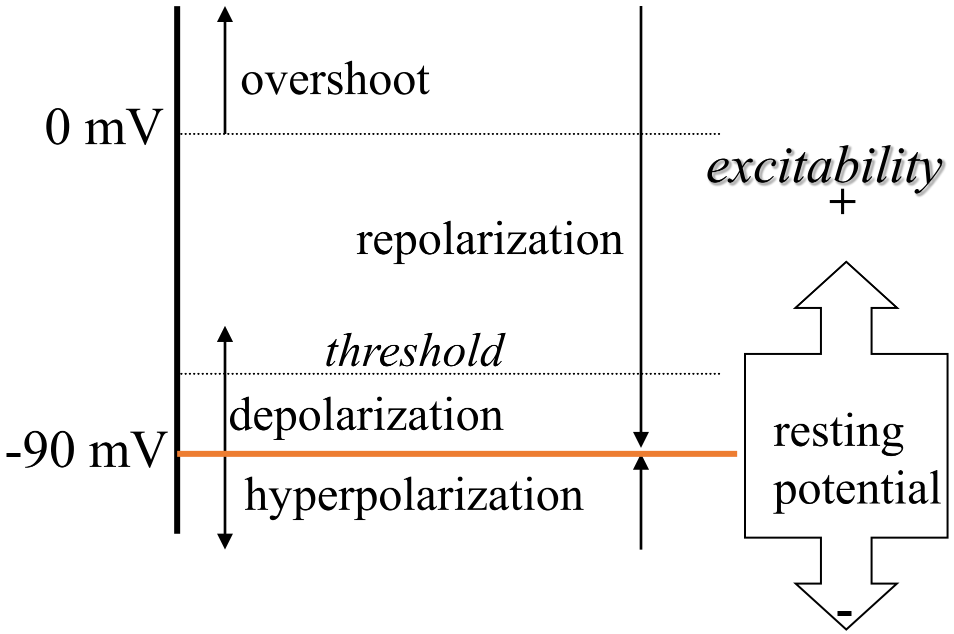
Lectures Objectives

- Define the nerve action potential and properties
- Describe the activation of action potentials and describe the ionic basis of action potential .
- Describe the membrane currents underlying action potentials.
- Describe the activity of channels producing action potentials.
- Define threshold of for initiation of action potential threshold and different phases of action potential , depolarization, overshoot , repolarization and refractory period.
- Explain the propagation of nerve impulse along axons membranes in myelinated and non myelinated nerve fibers
- Explain the consequences of myeline loss on nerve function and give example of demyelinated diseases
- Describe and explain actions of calcium, local anesthetics, and neurotoxins on action potentials.
- Define pacemaker potentials and identify phases of SA node action potential
- Identify phasis of action potential of cardiac muscles and compare neuronal action potential Skeletal muscles and cardiac muscle action potential

Action potentials : Terminology

- ***There are some terms that need to be understood & remembered*:**
  - **Depolarization**
  - **Hyperpolarization**
  - **Overshoot**
    - means positive to 0 mV
  - **Repolarization**
    - towards resting potential
  - **Excitability**
  - **Threshold** *(for action potential generation)*



-Depolarization: the membrane potential moves closer to zero (becomes less negative)

-Hyper polarization:the membrane potential goes below resting level (becomes more negative)

-Overshoot: the membrane potential goes above zero, to +35 mv (depending on the sodium ions level)

-Threshold: The minimum amount of stimulus that initiates action potential in a nerve cell

Action Potential : Terminology

- Depolarization is the process of making the membrane potential less negative
- Hyperpolarization is the process of making the membrane potential more negative
- Inward current is the flow of positive charge into the cell. Thus, inward currents depolarize the membrane potential. An example of an inward current is the flow of Na+ into the cell during the upstroke of the action potential
- Outward current is the flow of positive charge out of the cell. Outward currents hyperpolarize the membrane potential. An example of an outward current is the flow of K+ out of the cell during the repolarization phase of the action potential.

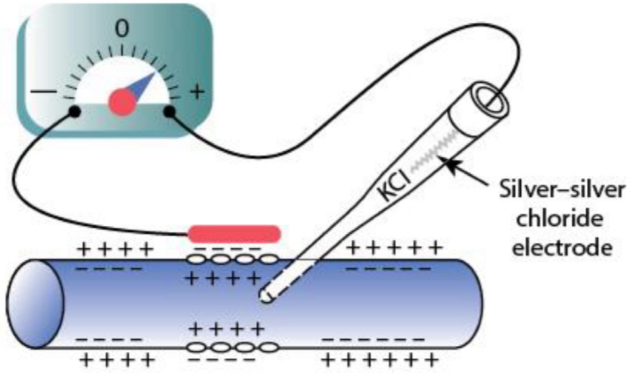
What is an action potential

- The action potential is a phenomenon of excitable cells such as nerve and muscle and consists of a rapid depolarization (upstroke) followed by repolarization of the membrane potential. It takes few mS (2 - 3 mS)
- Action potentials are the basic mechanism for transmission of information in the nervous system and in all types of muscle
- Triggered by by application of an appropriate stimulus
- For example: application of an electrical current to the nerve cells axons

Assume that I touch a hot plate, I should apply depolarization for the receptors and the receptors must do action potential in the sensory fibers for the signal to move to the brain. Otherwise, I will never be able to feel the touch, I will never be able to feel the hot temperature so the main objective of the action potential is to move the signal from one place to another.
sometimes the signal moves from the hand (peripheral) by feeling temperature or pressure or heat stimulation, and sometimes this action potential moves from the cortex to the peripheral.
for example: I want to move my hand, the brain sends a signal using action potential to the motor neurons that are in the spinal cord so they can move to the muscle and the muscle contracts and move my hand. The objective of action potential is to move the signal from one place to another, (to move the signal from the central nervous system to the peripheral nervous system or vice versa), and sometimes the action potential is referred to as a nerve impulse

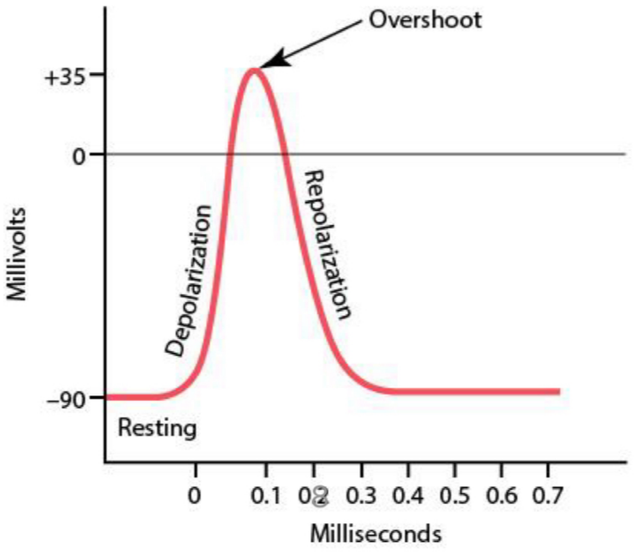
Intracellular recording of action in the axon of a nerve cell via microelectrodes

Assume here that you have an axon of a cell and somehow you apply and electrical current, (that's how they did the experiment) -the passed through the cell a depolarized electrical current, so to make slight depolarization, and if the slight depolarization reaches the threshold, it will initiate this rapid change in membrane potential which is the action potential, and the action potential as you can see is the resting potential. When we depolarize the cell we get this phase depolarization phase or sometimes it is called the



Now you see in this case the membrane potential during depolarization phase overshoots the zero and you can see the peak here reaches about +35 mv which is equivalent to the equilibrium potential of Na ions cuz the permeability during depolarization becomes higher to the Na, after that the membrane potential goes back to the normal state this is called the falling phase or repolarization phase

Based on our last discussion, the depolarization is caused by the activation of Na ions channel, on the other hand in the repolarization phase we start to close The Na ion channels and open the K ion channels, the K ions start to go out and the Na ions start to get in and the membrane potential goes back to its normal level.



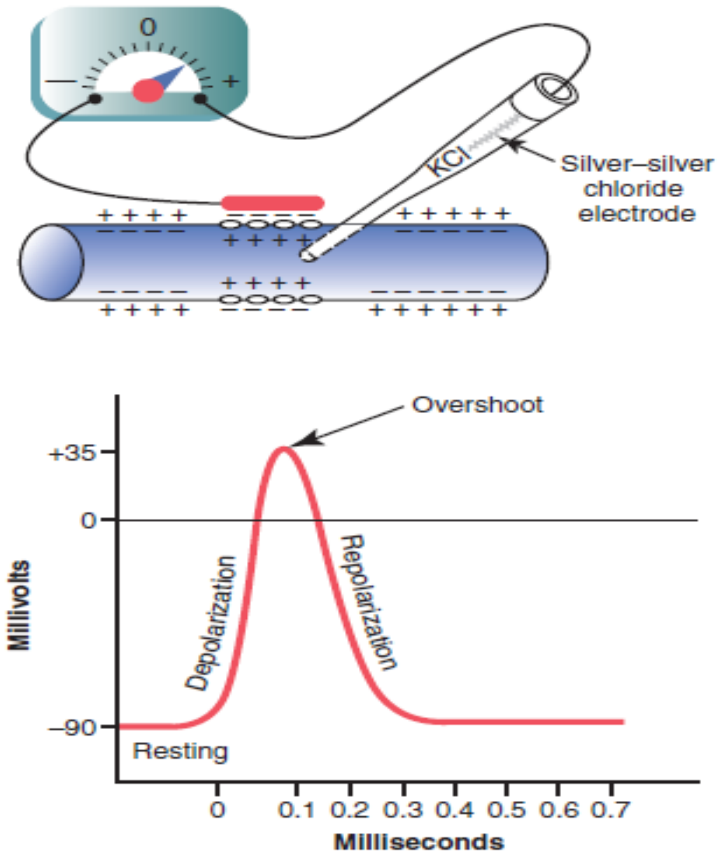
Schematic Diagram of action potential and membrane potential changes during the successive stages of action potential

Stages of action potential

Resting Stage::
Membrane is polarized

Depolarization Stage

Repolarization Stage

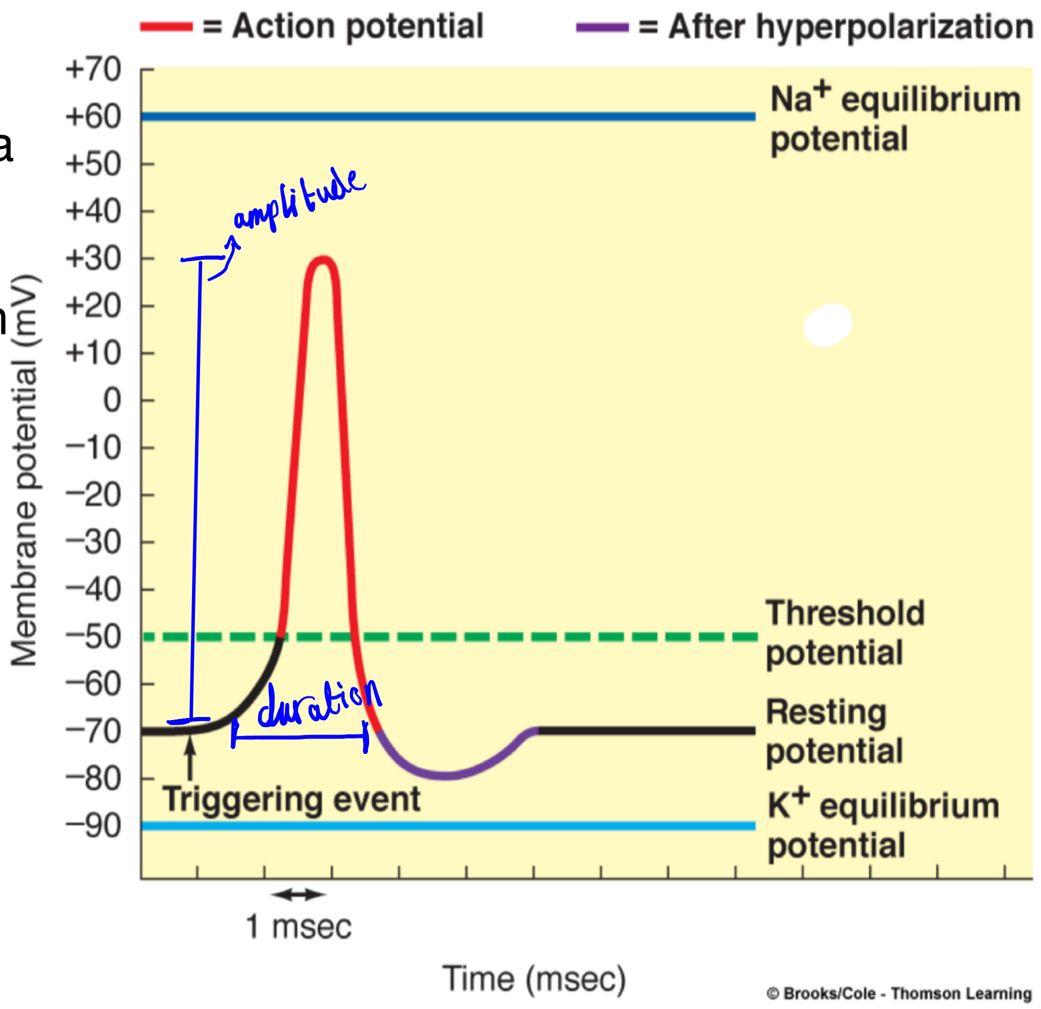


nerve, muscle (skeletal) cells

Initiation of Action Potential

-You can see here, we have a resting potential now when you apply a current you cause a depolarization state here, this depolarization is due to the application of the current, you inject a depolarizing current, and this potential when it reaches the threshold level The volted-gated channels are open, and we activate the sodium channels, to get this depolarization, and then we go back (repolarization) and in some cases you see the membrane potential going beyond zero or beyond the - 70 mv which is called hyperpolarization or they call it positive after potential and this is probably caused by the prolonged activation of the potassium ion channels, and that's only in some cases.

-Notice that every signal in the nervous system has its own amplitude and duration, as we see in the chart The duration of the action potential is 2 ms, however not all action potentials last that long some have longer durations. But in general nerve cells, muscle cells (skeletal) have a duration of about 2 ms



NEURON ACTION POTENTIAL
Successive stages of the action potential

- **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**. 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.
- At this time, the membrane suddenly becomes permeable to sodium ions, allowing positively charged sodium ions to diffuse to the interior of the axon. The normal “polarized” state of −90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction in some nerve cells
- **Repolarization Stage**. Within a few msec 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,

Changes in sodium and potassium conductance during the course of the action potential. Sodium conductance increases several thousand–fold during the early stages of the action potential, whereas potassium conductance increases only about 30-fold during the latter stages of the action potential and for a short period there after.

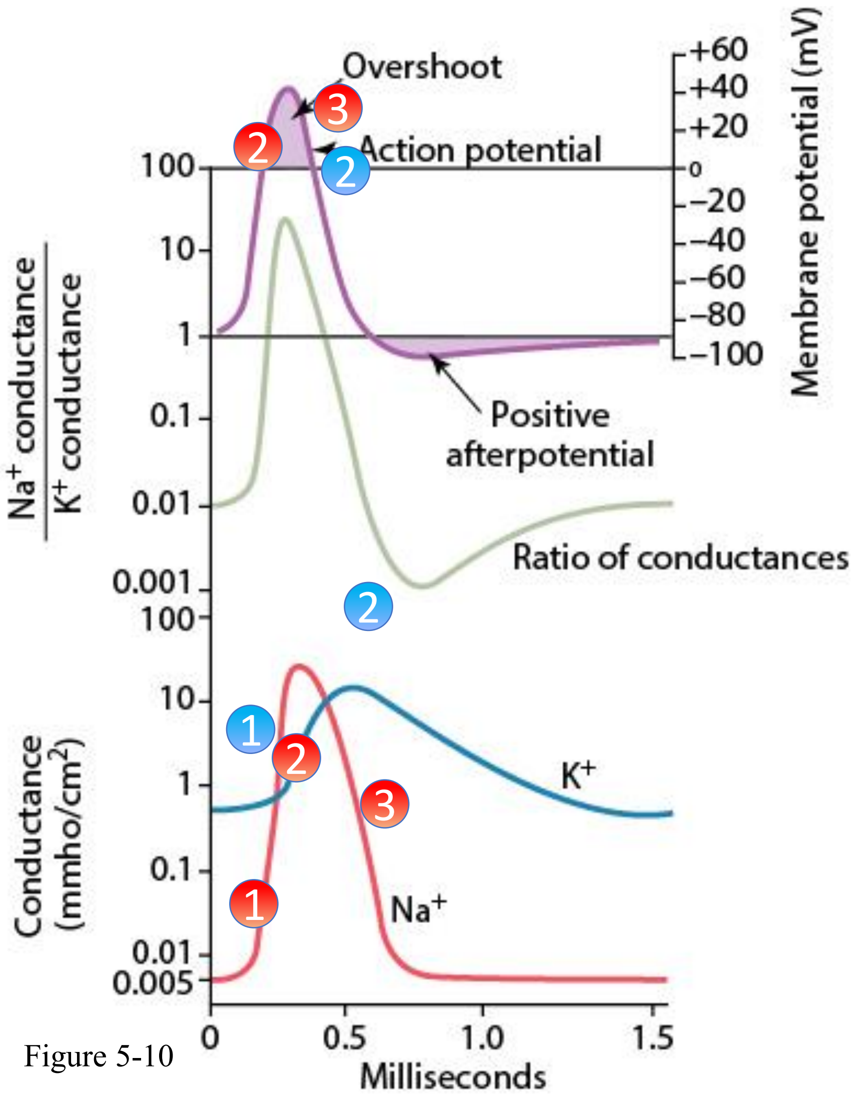


Figure 5-10

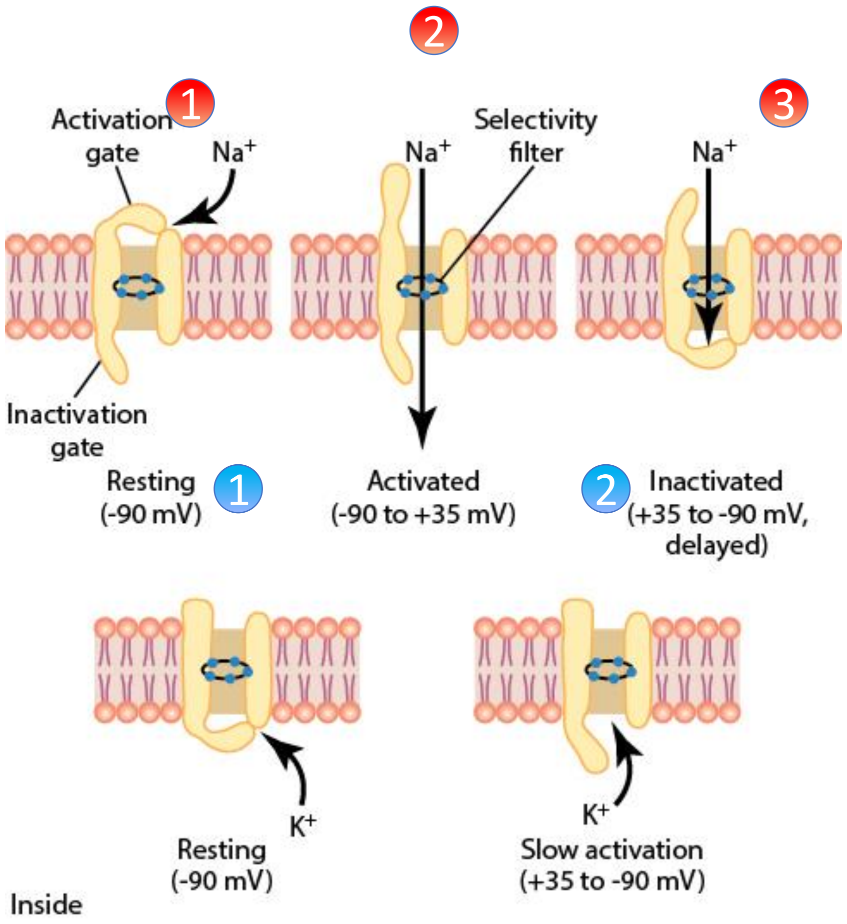


Figure 5-7

In the previous slide, it shows us what happens in an action potential in terms of the channels thatwe talked about (na,k) . In the resting state the activation gate is closed, when depolarization happens the gate will be activated, Na channels are open, an increase in Na permeability, Na will move on and cause depolarization .

When we reach the peak of the action potential we will activate The inactivation gate, so the Na channels close and the sodium's stops from entering the cell,

At the same time we have another set of channels (for K ions) once we reach the peak of action potential these k channels open, sodium ions will move out and the membrane goes back to its resting potential level (repolarization) and as we said sometimes hyper-polarization (positive after potential) happens which is the small curve below the resting state (-70mv).

Q:in the resting state, which is higher, the ratio of k ions conductance to Na conductance or the other way around?

A N S:
-resting state: if we measured the permeability of Na ions we will notice that Its a lot less than the permeability of K ions

Depolarization: its the other way around the relative permeability of sodium becomes a lot higher than the permeability of potatoes

Note: Conductance is a physics term that refers to permeability but in electricity) when they calculated the action potential they used thermoconductors

(الدكتور خربط وحكى Potassium بدل sodium)

at resting state, the conductance of Na is way less the the conductance ratio of potassium, but during an action potential the conductance of sodium becomes 10 times larger than potassium, be cause the channels open up and Na will move through the activation of those channels

If you compare the permeability or The conductance during an action potential:

-In the resting state sodium permeability is very low, but it gets very high at the peak of action potential and then during repolarization goes back down to its normal state

-If you take the potassium conductance or permeability during an action potential, you see that at the peak of action potential it starts to go up, so it can bring back the membrane potential to its normal state,also you will notice that the k channels open slowly and not as fast as the Na channels, and it may stay open a bit longer causing hyperpolarization (positive after potential)

So this diagram shows you the phases of action potential (depolarization vs repolarization) and it shows you the relative changes in the permeability of Na and K

Assume for one reason or the other the sodium concentration outside the cell decreased dramatically (a lot), ex. From 140 meq to 100 meq
A - what do you expect to happen to the amplitude of the action potential? Is it going to go up or stay the same or go down?

B- and would it affect the resting membrane potential significantly or no?

A- ANS: yes it would cuz the concentration gradient will decrease so the amount of sodium that will enter the cell would be lower, of course we will not get to this state in the real world,also the amount of Na and K ions that go in or out during action potential are minude(very small amount) so realistically they will not change the concentration gradient, even if some particles got inside, the Na - k pump will restore it to its normal levels

B- ANS: no it want affect the RMP cuz its dependent on the k ions

-Influx: means from the inside of the cell to the outside
-Efflux: means from the outside of the cell to the inside

-The electrical current which is carried by sodium ions is known as inward sodium current, which happens in the depolarization phase
-The outward potassium current happens in the repolarization phase
-The current is curried by ions

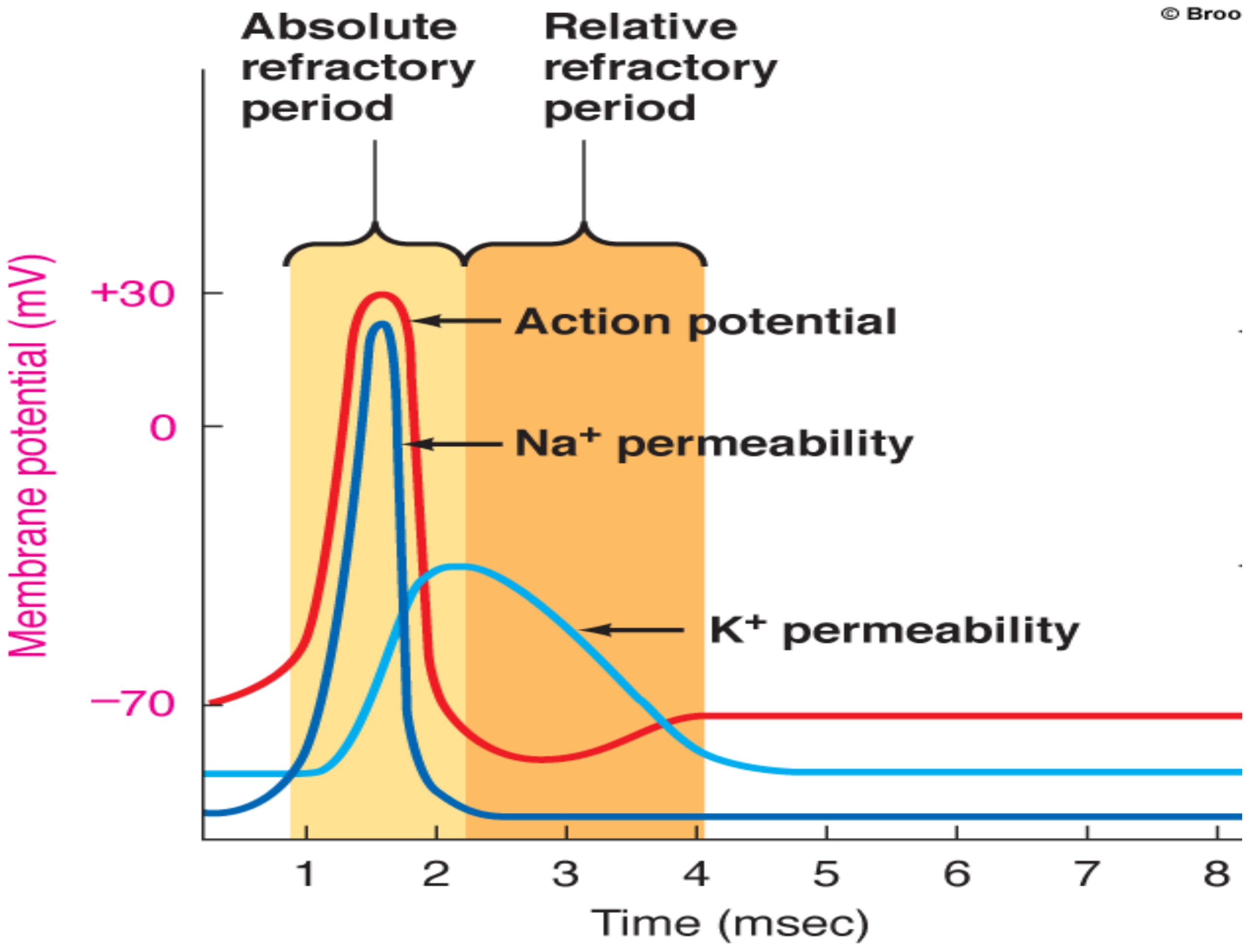
* influx : out -> in

* efflux : in ⟶ out

The absolute and relative refractory periods during an action potential

During the absolute refractory period no stimulus, however large, can elicit a second action potential.

During the relative refractory period a second action potential can be elicited but it requires a larger stimulus than that in the resting state



-There’s one important property of the action potential wether its in the heart, nerve cell, muscle (skeletal) cell, something known as the refractory period, refractory means (doesn't respond) for example: if we stimulated a nerve or a muscle cell, and we had another stimulus during the first action potential (1-2 ms), the cell wouldn’t respond to this stimulus with a second action potential

-So, the period of time that the nerve cell doesn't respond to the second stimulus is called refractory period, and of course in the nerve cell and the muscle cell the R.P. is very short (2-3 ms), but not all cells have the same R.P., in the cardiac muscles the R.P. Is about (300 ms) which is too long

Physiologists decided to divide the refractory period to 2 parts,

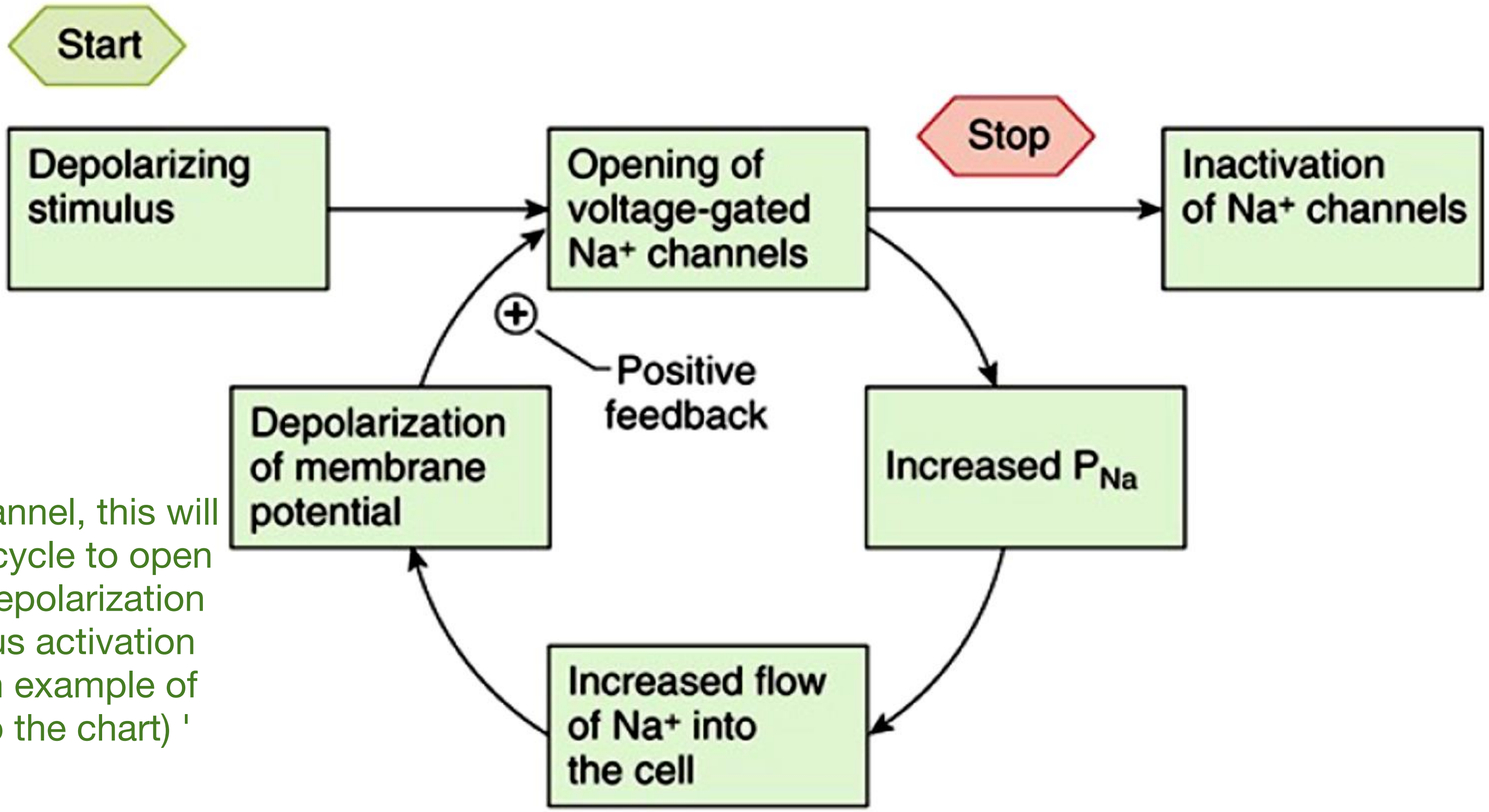
A- the relative refractory period:
B- the absolute refractory period:

Ex. We have an electrical current (10 A), in the (absolute refractory period)
No matter how strong the current or the stimulus is no action potential would happen, the A.R.P. Usually happens during The depolarization state or during the activation of the voltage-gated sodium channels, cuz the channels are not available for another cycle,

However, if we stimulated the nerve during the (dark orange part of the graph) the nerve may respond to the stimulus with a second action potential, but the intensity of the stimulus (electrical current) must be higher, this period of the action potential where the nerve may respond to the second stimulus is called relative refractory period (R.R.P)

INITIATION OF THE ACTION POTENTIAL

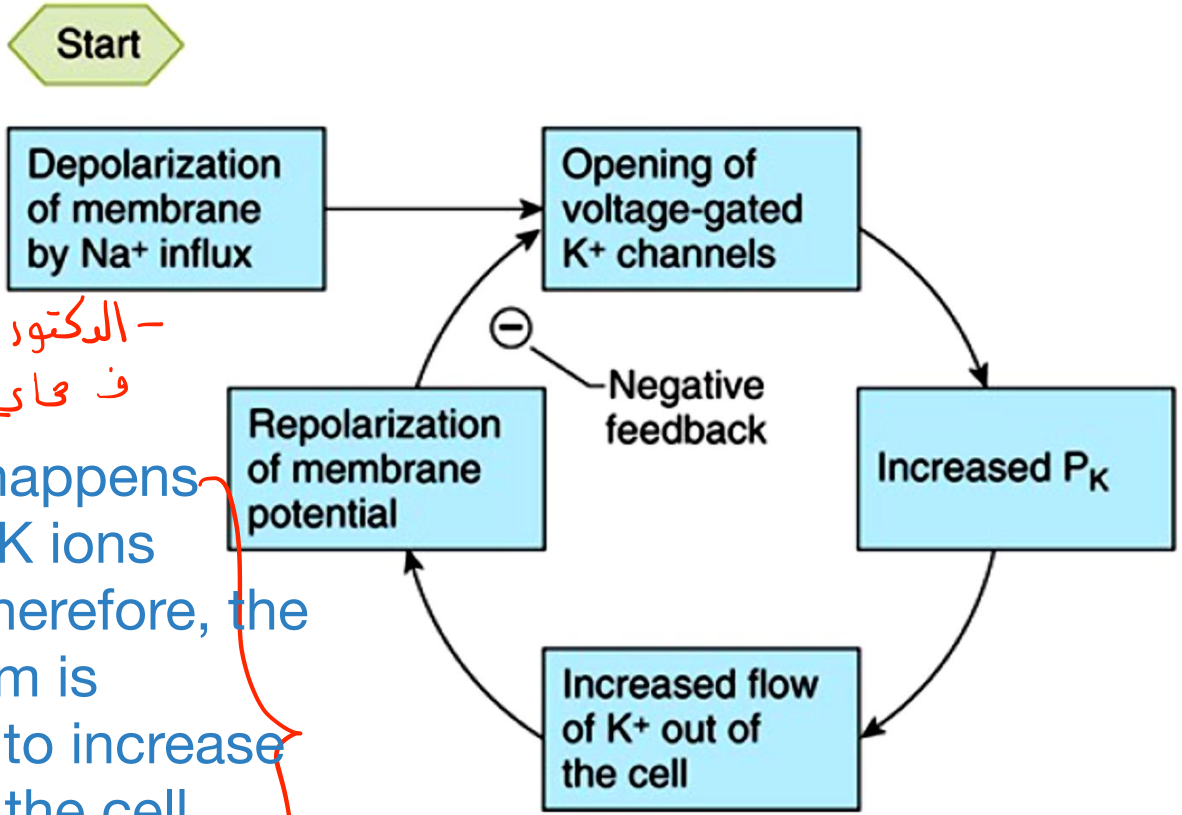
Positive-Feedback Cycle Opens the Sodium Channels.



Once you open a Na channel, this will set a positive feedback cycle to open more channels, so the depolarization phase and the continuous activation of the Na channels, is an example of positive feedback, (go to the chart) '

K channels exert negative feed back and cause repolarization

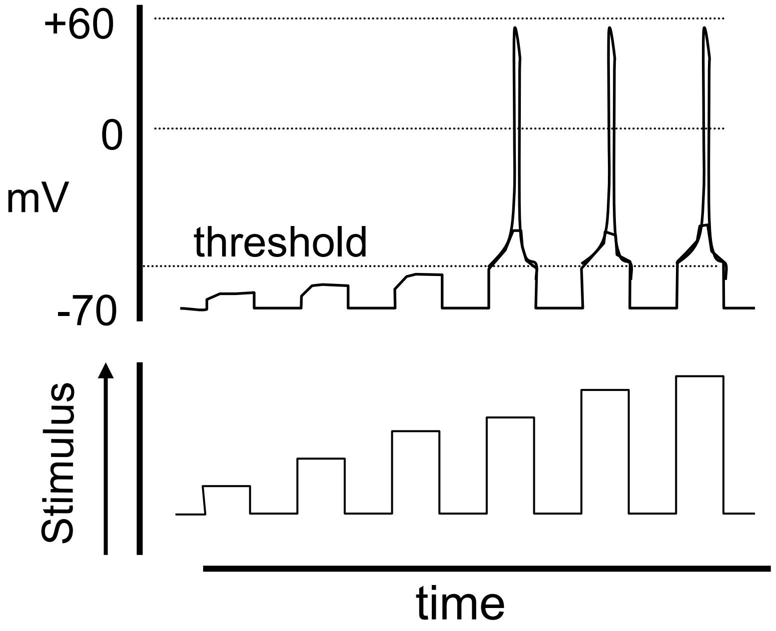
- الدكتور ما حكى كثير عن هذا الموضوع
ف هاي إضافة خارجية

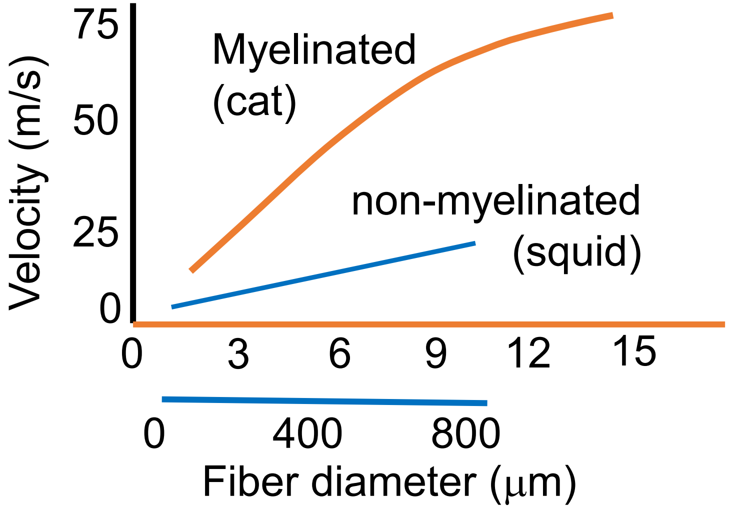


The negative feedback happens when the voltage gated K ions channels start to open therefore, the permeability of potassium is increased, which allows to increase flow of the K ions out of the cell (efflux) leading to the repolarization of the membrane potential

Properties of action potentials

- **Action potentials:**
  - **are all-or-none events**
    - threshold voltage (usually 15 mV positive to resting potential)
    - **Self-propagation**
  - **are initiated by depolarization**
    - action potentials can be induced in nerve and muscle by extrinsic (percutaneous) stimulation
  - **have constant amplitude**
    - APs do not summate - information is coded by frequency not amplitude.
  - **have constant conduction velocity**
    - True for given fiber.
    - Fibers with large diameter conduct faster than small fibers. As a general rule:
      - ***myelinated*** fiber diameter (in mm) x 4.5 = velocity in m/s.
      - Square root of ***unmyelinated*** fiber diameter = velocity in m/s





Main objective of the action potential:
move the signal from one place to another, cur the brain acts like electrical wires, so to transport the heat there is a wire that goes from the hand and to the spinal cord and then to the brainstem, to the thalamus and then to the cortex, but not one wire, there are several stations just like the electrical fuses of the house.

The only way to transmit signals across neurons in the nervous system (or via neurons is more accurate) is by action potential

First property of action potential:

-ALL-OR-NONE: if the action potential happens or not:
If we applied a stimulus, wether it is due to chemical transmission or mechanical stimulation or whatever, if the stimulus makes a depolarization phase that doesn't cause the opening of voltage-gated ion channels, an action potential won't happen.

If an action potential happens, increasing the stimulus wont matter,

sometimes the action potential happens and sometimes it doesn't, depending wether the stimulus is above the threshold or below it, if the stimulus is above the threshold we get an action potential, if it's below the threshold we don't get an action potential

Second property of action potential:

once the action potential is initiated it propagates, or the nerve impulse propagates,
the meaning of propagates is: assume the action potential happens in the first part of the axon, it keeps going until it reaches the last part of the nerve cell (terminal) , so the action potential travels on its own (self-propagation) until it reaches the final destination

Also the amplitude of the wave stays the same, so even if we measure the amplitude of the A.P. At different points it will stay the same it won't change (the start of the axon and its end)

Also for a given fiber or a nerve cell, the rate of propagation or how fast an action potential moves from one point of the nerve cell to another is fixed (stays the same and doesn't change) and of course different nerve cells myelinated or non-myelinated) there are nerves with a small diameter and others with a huge diameter, for ex: the pain nerve cells have a small diameter and un-myelinated, but the cells responsible for the touch and pressure feelings are thicker in diameter and are myelinated, the rate of propagation of an action potential or the conduction velocity across the nerve fibers depend mainly on 2 things assuming that the body temp is constant (it might increased by body temp, but we assume it is constant) the rate of conduction of an A.P. From one point of the nerve cell to the other, will be determined by diameter and myelin, increasing the diameter or if the nerve is myelinated, the rate of propagation of an action potential would be faster

Sometimes the myelin is damaged, it happens, and some immune diseases that may ruin the myelin sheath and we have failure of conduction of the A.P. And slow loss of action potential and a 100 other problems, so the myelin is important it increases the speed of conduction and the conduction ability of the nerve impulse,

We calculate the speed action potential in m/s, The rate of conduction from 70 m/s, there are some nerves that transmit the signed fast and there are nerves which are a bit slower, and much much slower, depending on the Rate