MEDICINE
KING SAUD UNIVERSITY

Physiology Team 436

Action Potential of The Excitable Tissues (Nerves + Muscles)

Revised by
شوق الأحمري & طراد الوكيل

Red: very important.
Green: Doctor's notes.
Yellow: numbers.
Gray: notes and explanation.

Physiology Team 436 – Musculoskeletal Block Lectures 2 + 3

Lecture: If work is intended for initial studying.
Review: If work is intended for revision.

Objectives

- Discuss the resting membrane potential and its genesis.
- Know the ionic channels involved in resting membrane potential.
- Describe the function Na+-K+ pump and the stages of action potential.
- Explain the threshold Potential, local Response and action Potentials.
- Describe the electrical changes in membrane potential during the action potential, their chemical bases and excitability changes.
- Describe conduction along nerve fibers, role of myelination and how nerve fibers are classified.

Basic Physics of Membrane Potentials

Membrane potentials caused by ion concentration

- **Differences across a selectively permeable membrane:**

  The potassium concentration is great inside a nerve fiber membrane but very low outside the membrane. Because of the large potassium concertation gradient from inside toward outside, there is a tendency for extra numbers of potassium ions to diffuse outward through the membrane. When they do, they carry positive charge to the outside. Thus, creating negativity inside because of **negative anions (proteins, sulphate, phosphate ions, large molecules) cannot leave the cell.** that remained behind and DO NOT diffuse outward with the potassium.

(remember: diffusion from high concentration → low concentration.)

- **The Nernst equation describes the relation of diffusion potential to the ion concentration across a membrane:** we will later apply this in resting membrane potential. The Nernst equation has a physiological application when used to calculate the potential of an ion of charge z across a membrane.

$$\text{EMF (millivolts)} = \pm 61 \times \log \frac{\text{Concentration inside}}{\text{Concentration outside}}$$

EMF= *electromotive force.* **Z**= *electrical charge of an ion*

- **The Goldman Equation is used to calculate the diffusion potential when the membrane is permeable to several ions**

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

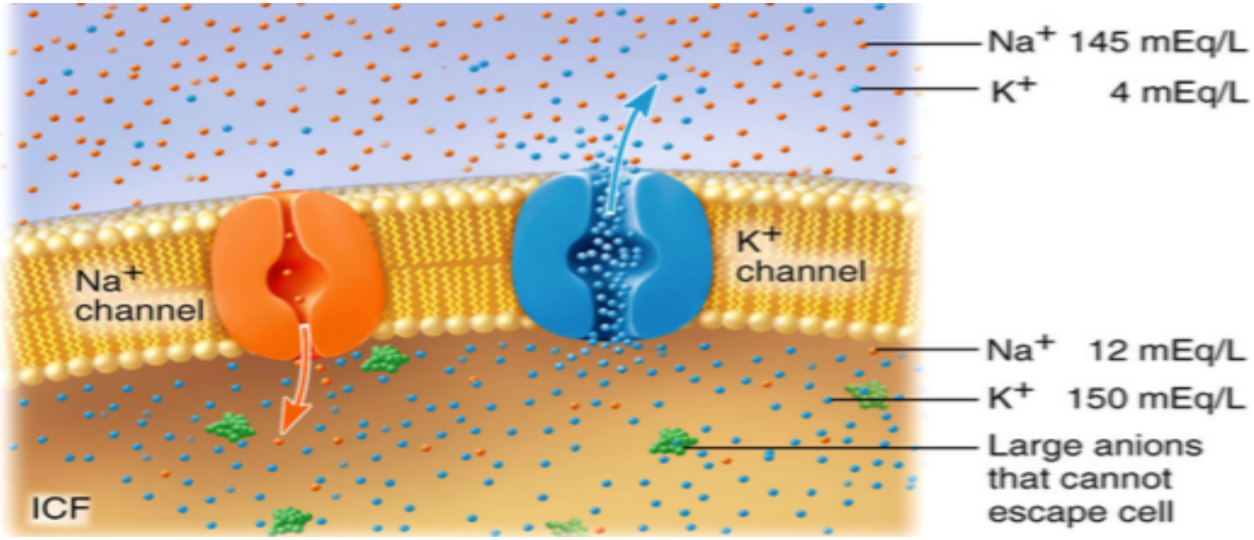
<u>ONLY IN MALES' SLIDES</u>

Resting Membrane Potential of Nerves (RMP):

- **RMP:** it is the potential difference across the cell membrane during rest, without stimulation between the inner side and the outer side, and it is relatively –ve inside.
- **Measurement of RMP:** using voltmeter
- **Normal Values :** -70 in medium sized nerves **and -90 mv in large nerve fibers**. (inside the fiber is 90 times more negative)
- **During rest, the membrane is polarized** (the membrane is a wall between the positive outside and negative inside)
- There is high molecules of K+ inside the cell and high molecules of Na+ outside the cell.

Transport properties of **the resting nerve membrane** for sodium and potassium:

- Sodium-Potassium pump (active transport)
- K+ Leak Channels:



- Potential: difference in charge across plasma membrane.
- Current: flow of charge (ions) from one point to another.

Causes (Origin) of Resting Membrane Potential (RMP):

The important factors in the establishment of the normal resting membrane potential of -90 millivolts.

- **1-** **<u>Contribution of K+ diffusion potential:-</u>**
- The cell membrane has tendency to pump **potassium (K)** (positive charge) out, from high to low, <u>(outflux)</u>, causing –ve charge inside, through <u>K leak channels</u>, down its concentration gradient.

(producing energy like Niagara falls, from high to low which gives energy to Canada)

- **Result**: Electro-positivity outside and electro-negativity inside.
- **RMP is 100 times more permeable to K+ than Na+.** (These K+ leak channels may also leak sodium ions slightly but are far more permeable to potassium than sodium)
- **K diffusion contributes far more to resting membrane potential. (most important)** ركز عليها الدكتور

- **<u>2- Contribution of Na diffusion through the nerve membrane:</u>**
- Very small amount of Na+ diffuses into the cell (from outside to inside) down its concentration gradient.
- The membrane is only <u>slightly permeable</u> to Na+ through <u>K-Na leak channels.</u>

- **<u>3- Contribution of the Na+-K+ pump:</u>**
- This is a powerful electrogenic pump on the cell membrane.
- maintains concentration gradients of K+ and Na+ between the two sides of the membrane.
- It pumps 3 Na+ to outside & 2 K+ to inside, causing a net loss of +Ve ions from inside, returning the nerve fibre to the resting state (-4 mV).

Remember: Non-diffusible anions (proteins, sulphate, phosphate ions, large molecules) cannot leave the cell. Therefore, they also <u>contribute to the negativity</u>

Cont.: Origin of the Normal Resting Membrane Potential

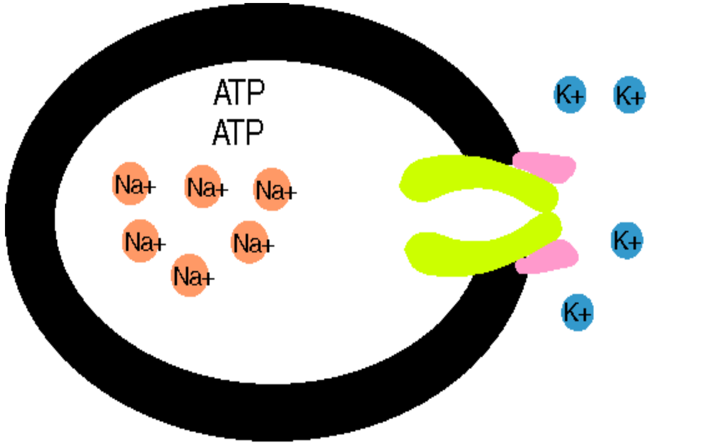
- Establishment of resting membrane potentials in nerve fibers under three conditions:

1. When the membrane potential is caused entirely by K+ diffusion: **EMF of K+= -94 mV**
2. When the membrane potential is caused by **diffusion of both Na+ & K+ = -86 mV**
3. When membrane potential is caused by **diffusion of both Na+ & k+** AND **Electrogenic Na+/K+ pump = -90 mV**

- How did we get this value? Using the **Goldman equation**:
- **E.M.F of K+** = -94 millivolts.
- **E.M.F of Na+** = +61 mV. (that's why the membrane is SLIGHTLY permeable to Na+)
- Using this value in the **Goldman equation** gives a potential inside the membrane of **−86 millivolts**.

So the **NET MEMBRANE POTENTIAL** would be:-

- **Diffusion potential** (caused by K+ & Na+ diffusion) **+** ***Electrogenic* Na+/K+ pump**
- (-86 mV) + (- 4mV) = -90 mV



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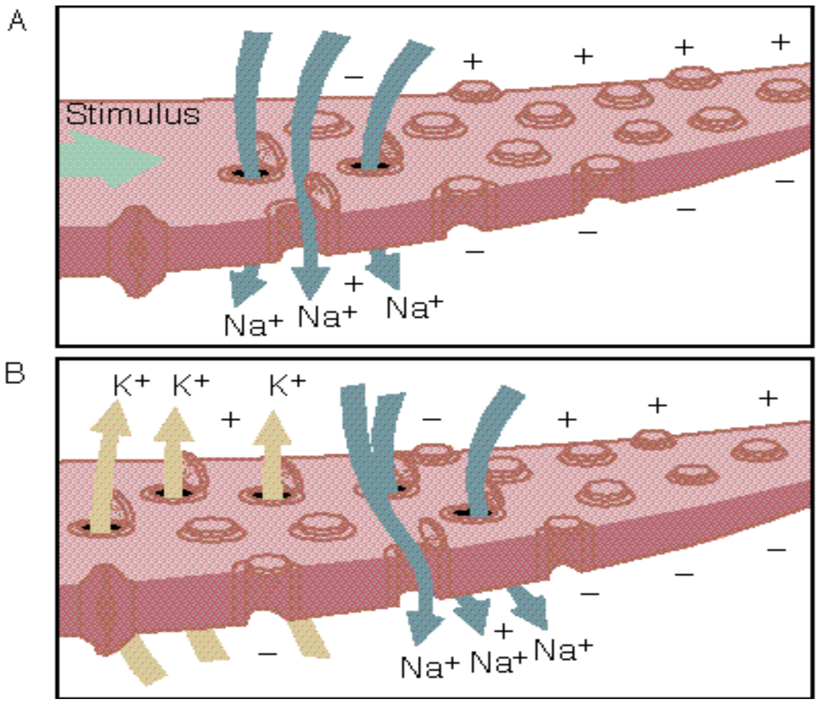
Action Potential (AP):

- 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.**
- **Action Potential**: a sudden reverse of membrane polarity (of charges) produced by a stimulus to produce a <u>physiological effect</u> such as:
  - Transmission of impulse along nerve fibers (transmission of nerve signals)
  - Release of neurotransmitters
  - Muscle contraction
  - Activation or inhibition of glandular secretion
- **Only Excitable tissue** (Nerve and muscles) respond to action potential.
- *Firing = excitability = action potential = nerve impulse*



Stages of Action Potential (AP):

I- Resting stage / Initiation of Action potential	2- Depolarization	3- Repolarization
• It is the resting membrane potential before the action potential begins. The membrane is "polarized". • Initiation: The (polarized) resting membrane potential rises from -90 to 0. (Gradual depolarization) due to threshold stimulus.	• The membrane suddenly becomes permeable to Na+ ions causing Na+ influx to the interior of the axon (upstroke) through opening **Voltage gated sodium channels** **(positive feedback).** • The membrane charges reverse (more positive inside) • Membrane potential rises from 0 to + 35 mv, so all Na channels begin to close suddenly. → (Depolarization ends) • This channel ends fast.	• K+ outflux through opening Voltage gated potassium channels, this high K conductance (flow) to outside, causes the normal negative resting membrane potential.(Negative inside) • (Na+ channels begin to close and the K+ channels open.) • This channel is slow, which leads to the next step.

A state of Hyperpolarization follows repolarization. *Will be explained later*

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 opening of sodium channels. This opening of the sodium channels can result from mechanical disturbance of the membrane, chemical effects on the membrane, or passage of electricity through the membrane

Threshold for excitation and "Acute local potentials"

Threshold stimulus:

•The membrane potential at which occurrence of the action potential is inevitable.

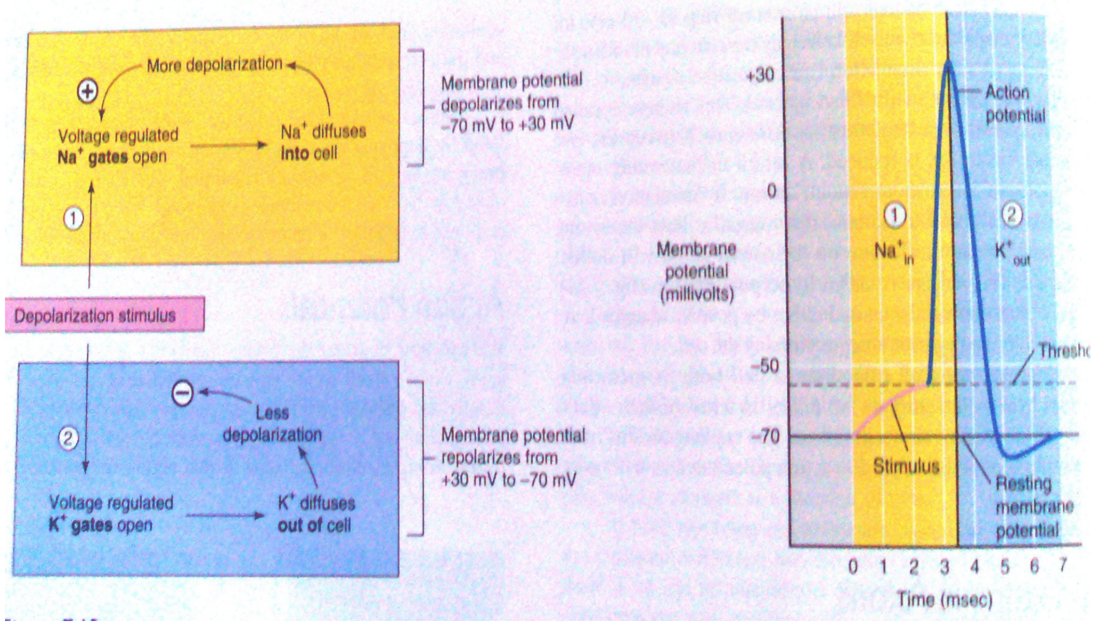
•When a stimulus is strong enough to move **RMP** from its resting value **(**-**90)** to the range of **-70mV** to **-55mV** (-65 to 55) which leads to production (start) of an **AP** or depolarization.

Subthreshold stimulus / Acute subthreshold potential:

•Stimulus that results in local depolarization. (local action potential) (does not propagate or move along).

•When stimulus is below the threshold.

All or nothing principle: When threshold value for excitation is reached, a full Action Potential is produced, so its intensity can not be increased by increasing stimulus intensity (suprathreshold).



Types of Transport Channels Through the Nerve Membrane

- **There are two types:**
1. Voltage gated Na+ channels
2. Voltage gated K+ channels.
- **What opens the voltage gated channels?** A stimulus strong enough to depolarize them to threshold.

The voltage gated Na+ channel has two gates:

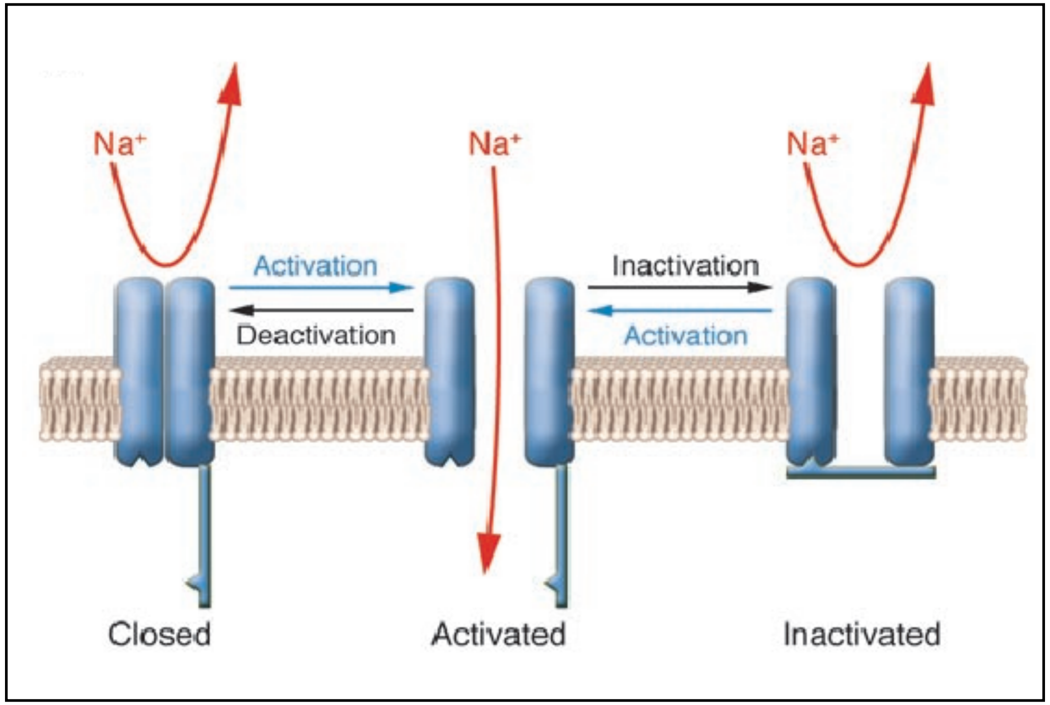
Has 2 gates

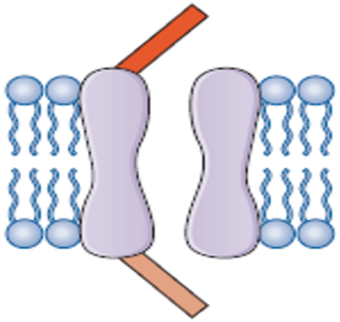
Activation gate

on the outer side of membrane

Inactivation gate

on the inner side of membrane





First: The Na+ Voltage-Gated Channel: Has three states.

1.Resting state

- **The activation gate is closed** in the resting cell, when the MP* = RMP* is:
- **-70 to -90 mV.**

✓This prevents entry of Na+ to the interior of the cell through this gate

2.Activated state

Threshold Depolarizing Stimulus: moves the MP from its **resting value** (-90 mV) to its **threshold value** (-65 to -55mV)

This opens the activation gate.

(NB in this case BOTH the activation gate & inactivation gate are open) → permeability to Na+ becomes increased 500 to 5000 times → Na+ influx

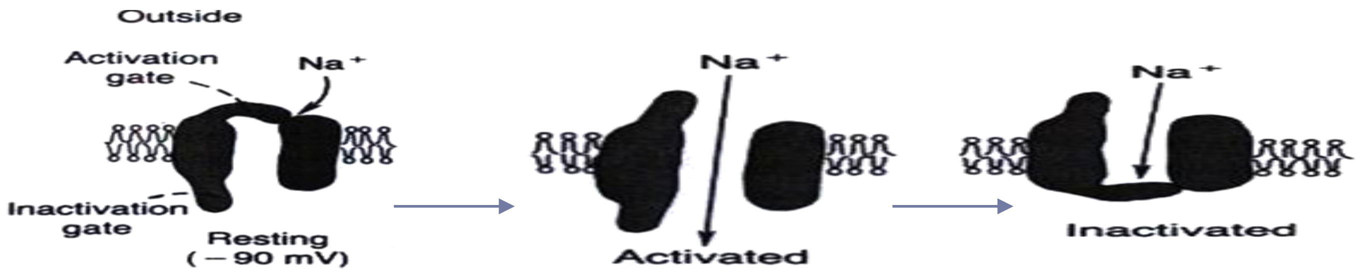
Na+ flows into the cell in large amounts

3.Inactivated state

A few milliseconds after the activation gate opens, **the channel becomes inactivated**: At the peak of AP the inactivation gate will close the inactivation gate will **NOT** open by a second stimulus → & **the cell becomes Refractory(ممانعة) to another stimulation**

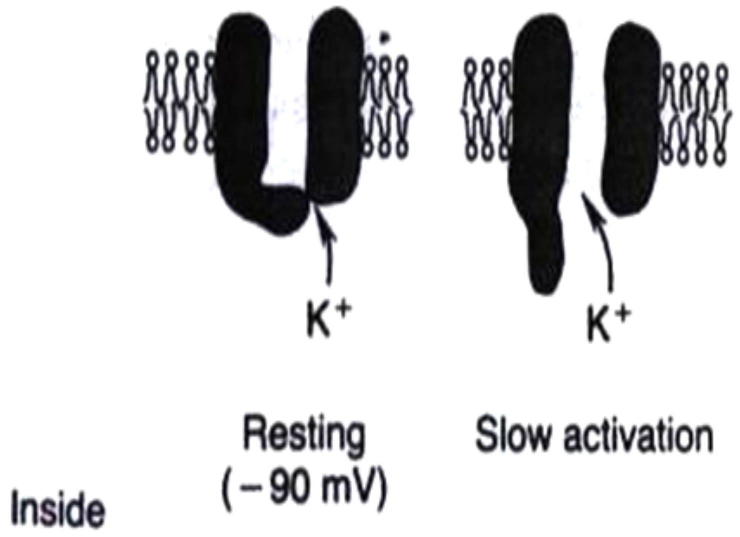
This goes on until the MP has gone back to its resting (RMP) level (-70 to -90mV)

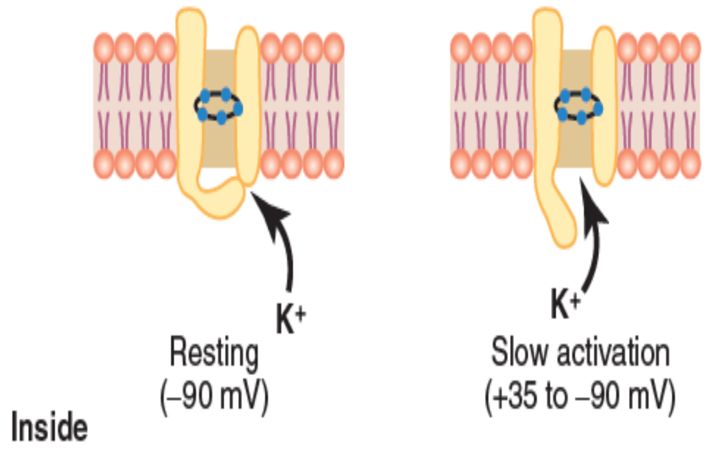
The activation gate is still open the inactivation gate is closed



Second: Potassium Voltage Gated Channel (Repolarization)

- Has one gate only .
1. **During the resting state:-** the gate is closed and K+ can not go out to the exterior
2. Shortly **after depolarization** (when the membrane potential rises from -90 mV towards zero):-
- The **sodium channel** begins to be inactivated
- The **potassium channel** opens
- K+ exits (called K+ Efflux)* → Repolarization





#435 TEAM

بوابات الصوديوم : سريعة الفتح, سريعة الإغلاق فبمجرد حدوث تغير في الفولت تفتح البوابة ويدخل فوج من الصوديوم.

sodium voltage-gated channel opens and closes in only milliseconds. And if it reaches 35mV and doesn't close it may cause epilepsy الصرع

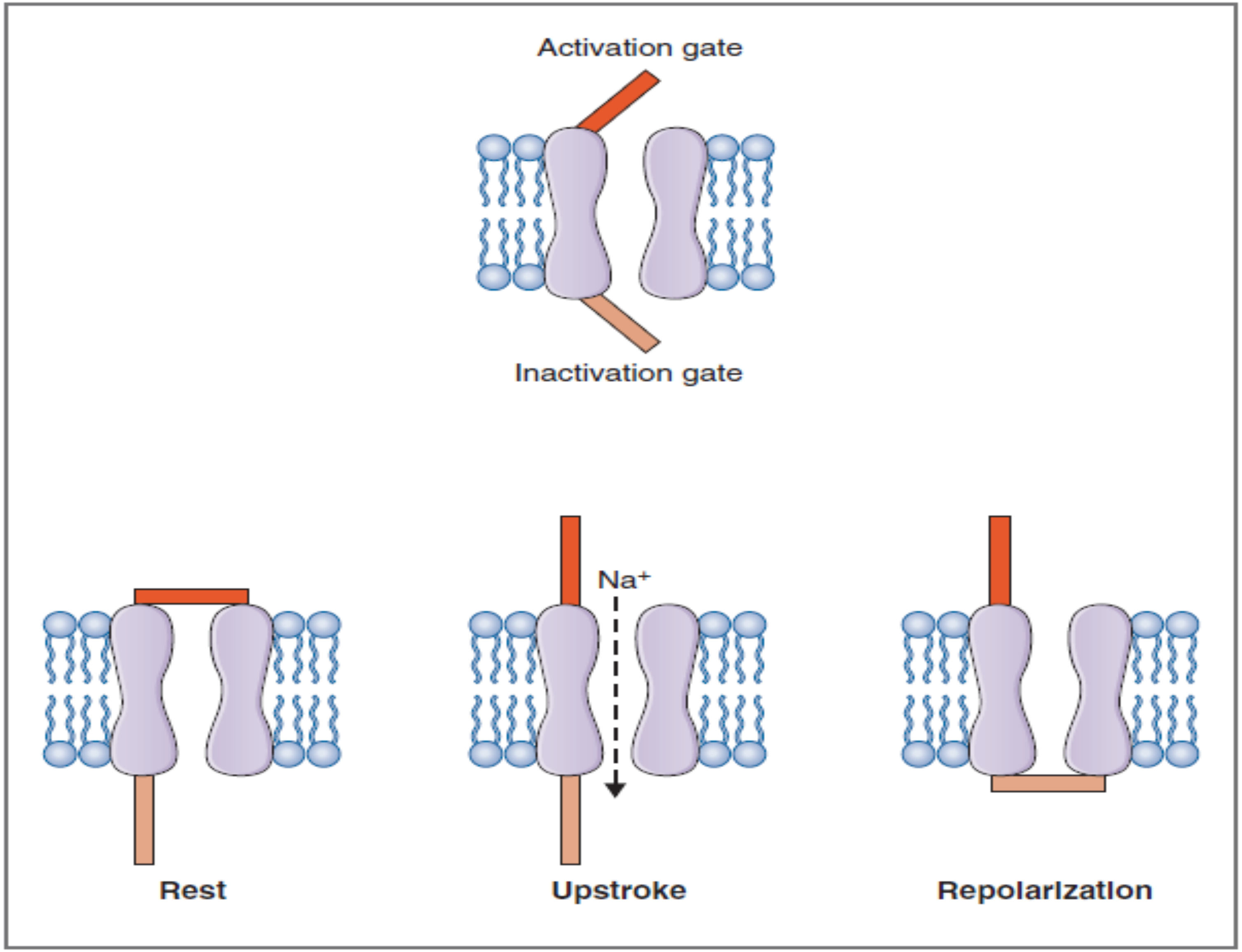
بوابات البوتاسيوم: بطيئة الفتح , بطيئة الإغلاق

potassium voltage-gated channels open and close slowly and that's what causes hyperpolarization

Voltage gated Na+ channels

video

الدكتور نبه على الرسمة وقال انها
مهمة مرة



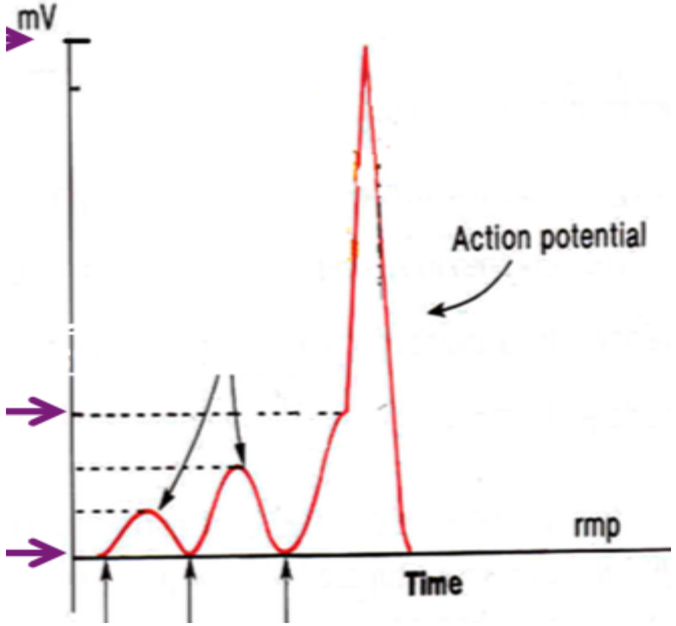
[redacted] **Functions of activation and inactivation gates on the nerve Na^+ channel.** At rest, the activation gate is closed and the inactivation gate is open. During the upstroke of the action potential, both gates are open and Na^+ flows into the cell down its electrochemical potential gradient. During repolarization, the activation gate remains open but the inactivation gate is closed.

Action Potential (AP)

Reversal Potential = + 35 mV

Threshold Potential (Firing Level) = -50 to -65 mV

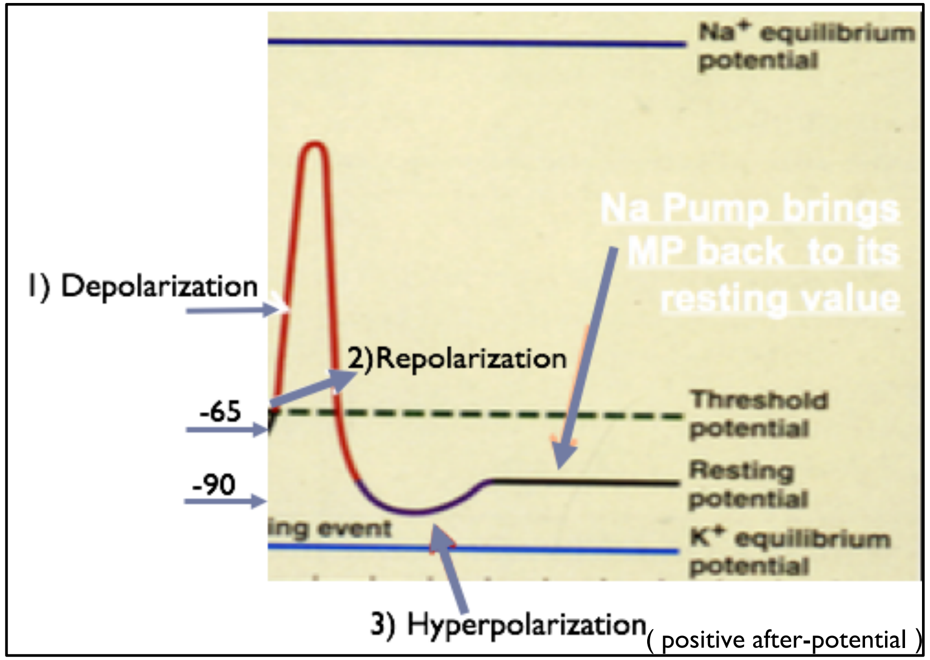
RMP= -90 mV



Increasing Stimulation

We need to start from the baseline (Resting State of the cell, RMP)A threshold Stimulus will lead to:

1) Depolarization.
2) Repolarization phase.
3) In some neurons there is a 3rd phase called :Hyperpolarization



* Action potential occurs when voltage-gated channels are opened!!

Q :What opens the voltage gated channels ?
Opened by a stimulus strong enough to depolarize them to threshold.

video

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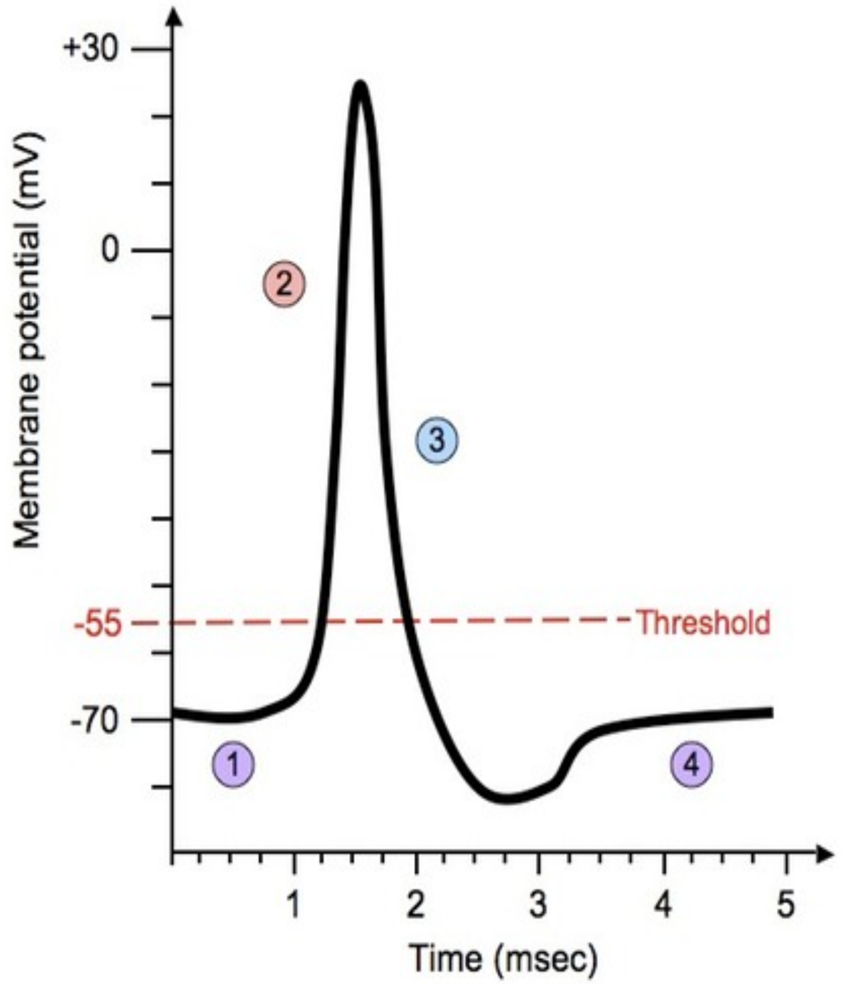
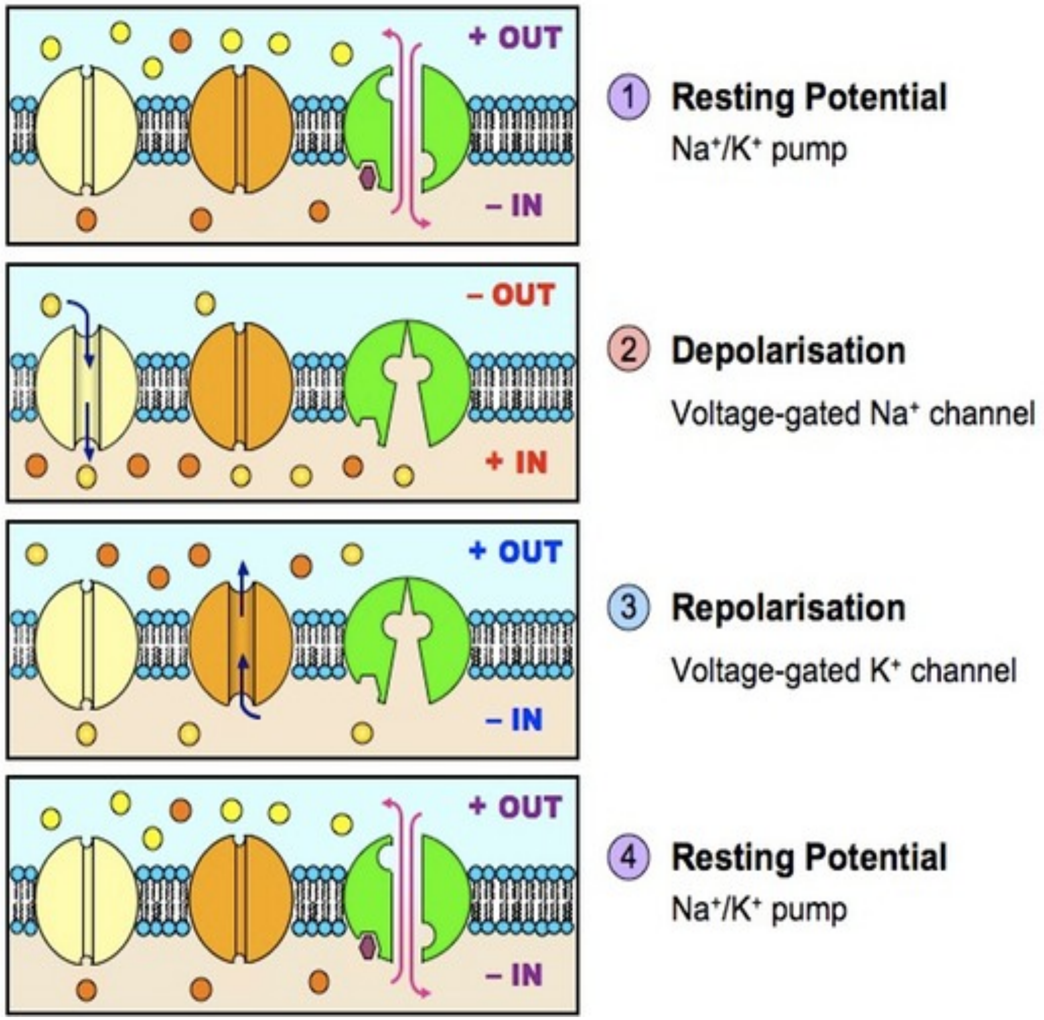
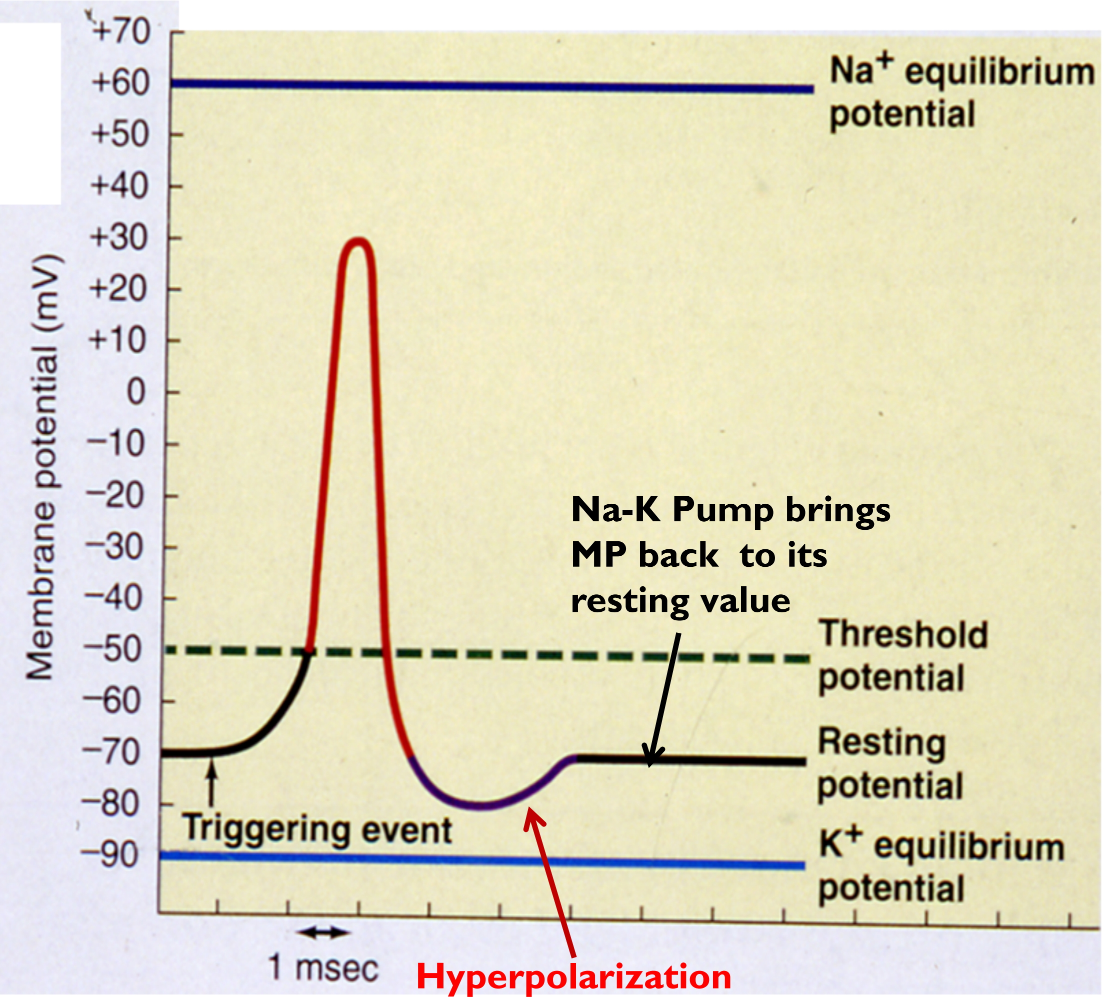
Further Explanation:





Hyperpolarization:

- **Hyperpolarization (Positive after-potential):** Hyperpolarization is a change in a cell's membrane potential that makes it more negative inside and more positive outside, more than resting membrane potential.)
- It inhibits action potentials by increasing the stimulus required to move the membrane potential to the action potential threshold.
- Towards the end of each action potential (following repolarization) and continuing for a short period of time, **the membrane becomes more permeable to potassium ions.** The increased outflow of potassium ions carries positive charges. **(the K+ conductance is higher than at rest.)**
- Na-K pump now starts to move Na+ out & K+ in against their concentration gradient.
- While hyperpolarized, the neuron is in a refractory period.



What Happens After Action Potential? video

- **Refractory period**: few milliseconds
  - Time during which can't stimulate neuron a second time
  - Happens until recovery of resting potential
- **Two stages:**

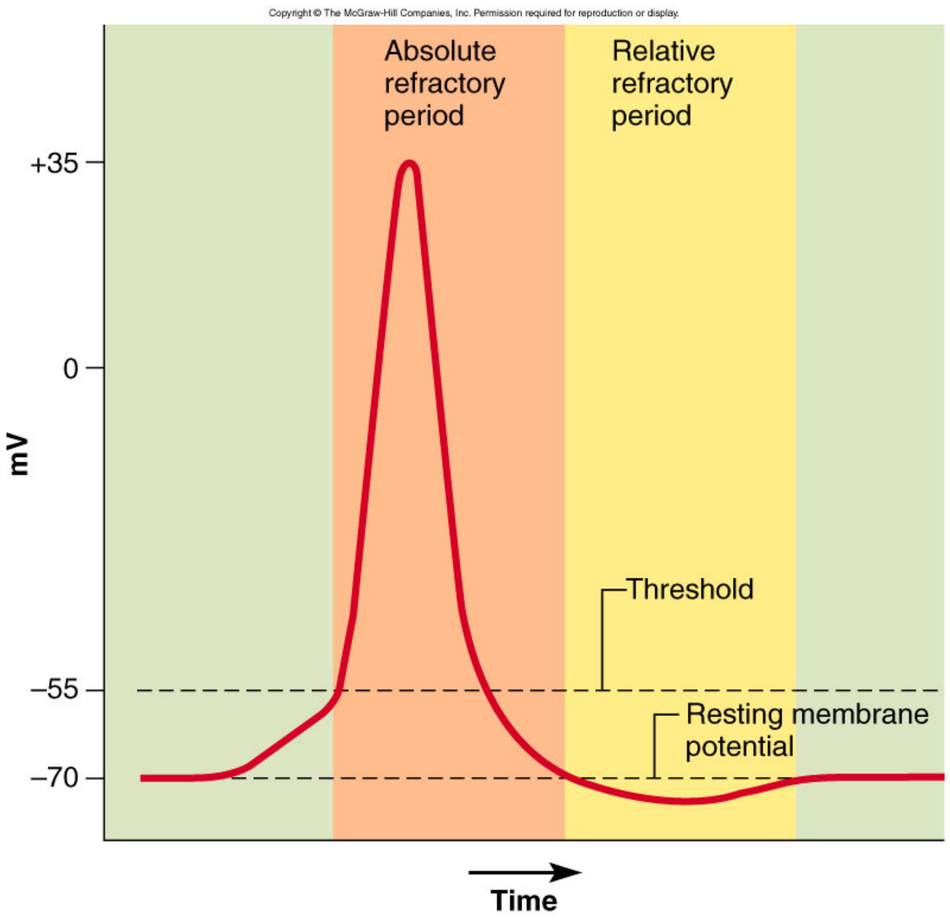
1. **Absolute refractory period:**

- The period during which a second action potential cannot be elicited, even with a strong stimulus. (No new action potential possible).

"يعني مهما عطينا محفز ثاني مايستجيب"

2. **Relative refractory period:**

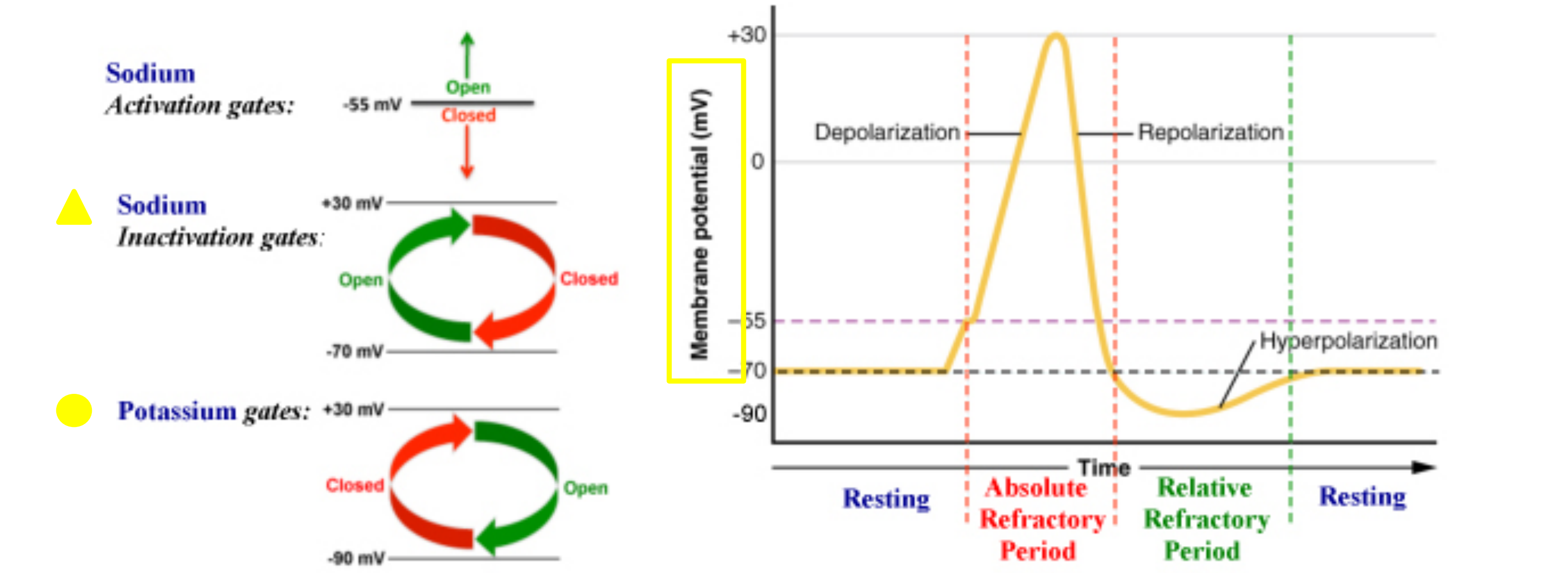
- Can trigger new action potential if stimulus is very strong.



Summary of Action Potential : “EXTRA”

- When membrane potential (mV) reaches - 70 Na gates will <u>open</u> , and the gates will <u>close</u> when (mV) reaches + 30.

- K gates will be open when (mV) reaches +30 , and close when it reaches -90 .



		Resting	Threshold	Peak	Repolarization		Hyperpoloarization
		-70 mV →	-55 mV →	+30 mV →	-55 mV →	-70 mV →	-90 mV
Na-Gates	Activation	Closed	Open	Open	Closed	Closed	Closed
	Inactivation	Open	Open	Closed	Closed	Open	Open
		~~Na^+~~	Na^+	~~Na^+~~	~~Na^+~~	~~Na^+~~	~~Na^+~~
			ABSOLUTE REFRACTORY PERIOD			RELATIVE REFRACTORY PERIOD	
K-Gates		Closed	Closed	Open	Open	Open	Closed
		~~K^+~~	~~K^+~~	K^+	K^+	K^+	~~K^+~~

The Neuron

- **Definition:** Unit of function of the central nervous system.

1- Soma: cell body

2- Dendrites: carry nerve impulses from surroundings to soma.

3- **<u>Axon hillock</u>**: start of action potential (because it has a lot of voltage gated Na channels)

4- Axon and axon terminal.

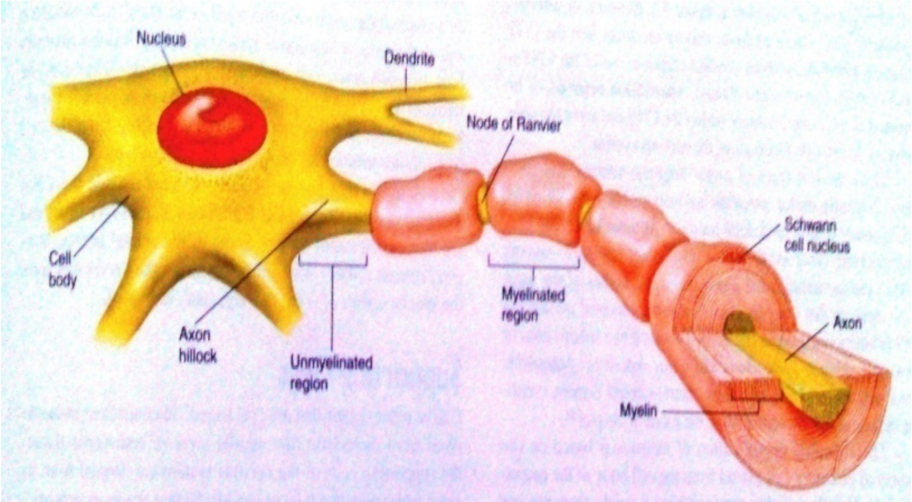


Figure 7.2 Parts of a neuron. The axon of this neuron is wrapped by Schwann cells, which form a myelin sheath.

Axon with myelin sheath	Axon without myelin sheath
Myelinated axons diameter: >1um <u>Schwann cells</u> deposit sphingomyelin (which wraps around the axon) 1- increases conduction velocity 2- insulation by the membrane of Schwann cells. (عزل)	Unmyelinated axon diameter: <1um - Type C: in the Post ganglionic Autonomic fibers, and Pain fibers. Also has schwann cells but not wrapped around the axon.

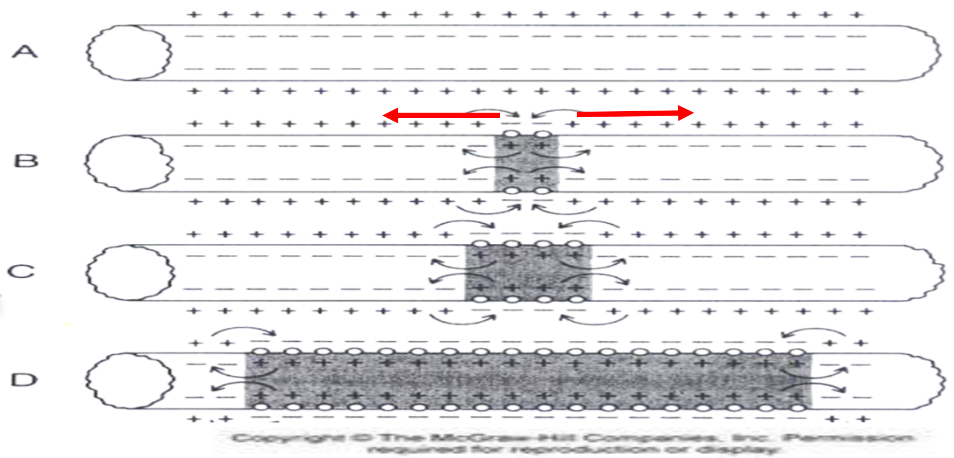
<u>Only in male slides:</u>

- An <u>Excitable tissue</u> is the tissue has the capability to respond to an adequate stimulus.
- Examples are: nerves and muscles

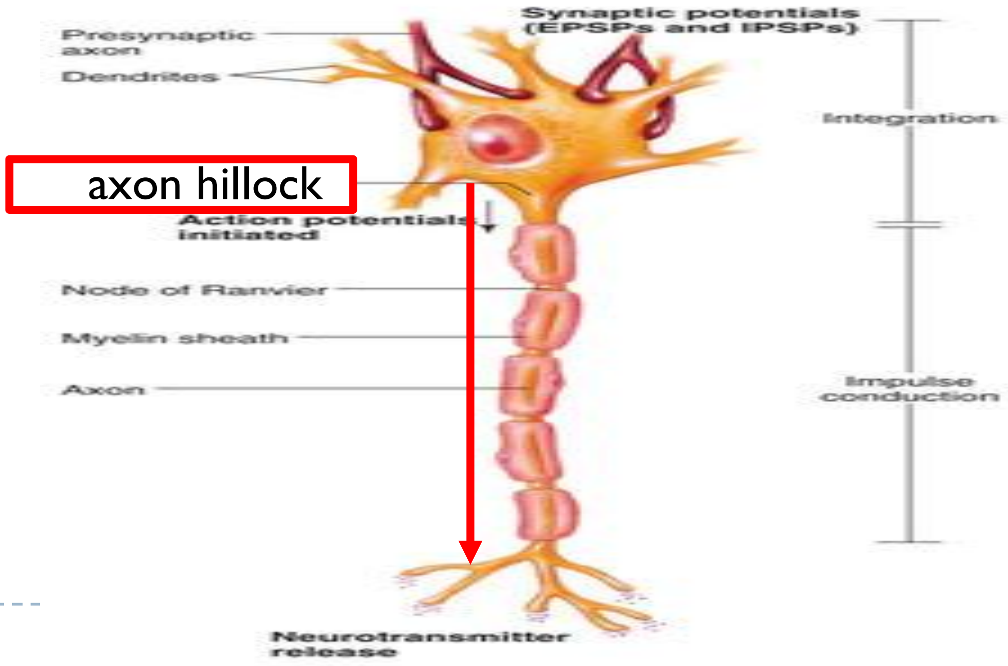
<u>ONLY IN FEMALES' SLIDES</u>

Direction of AP Propagation (Conduction) video

- Artificial Electrical Stimulation :-
- Under Artificial condition of electrical stimulation in the laboratory , the AP propagates in both directions .

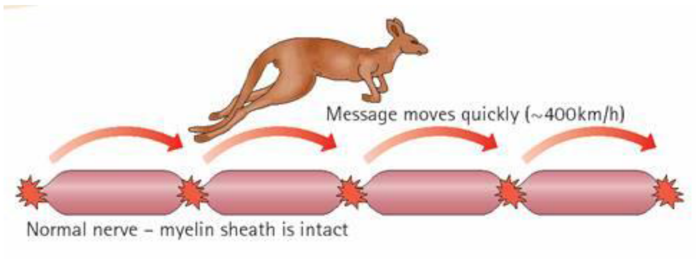


- But normally, AP starts in axon hillock & propagates distally in one direction
- AP starts at axon hillock Because it is full of voltage gated Na channels

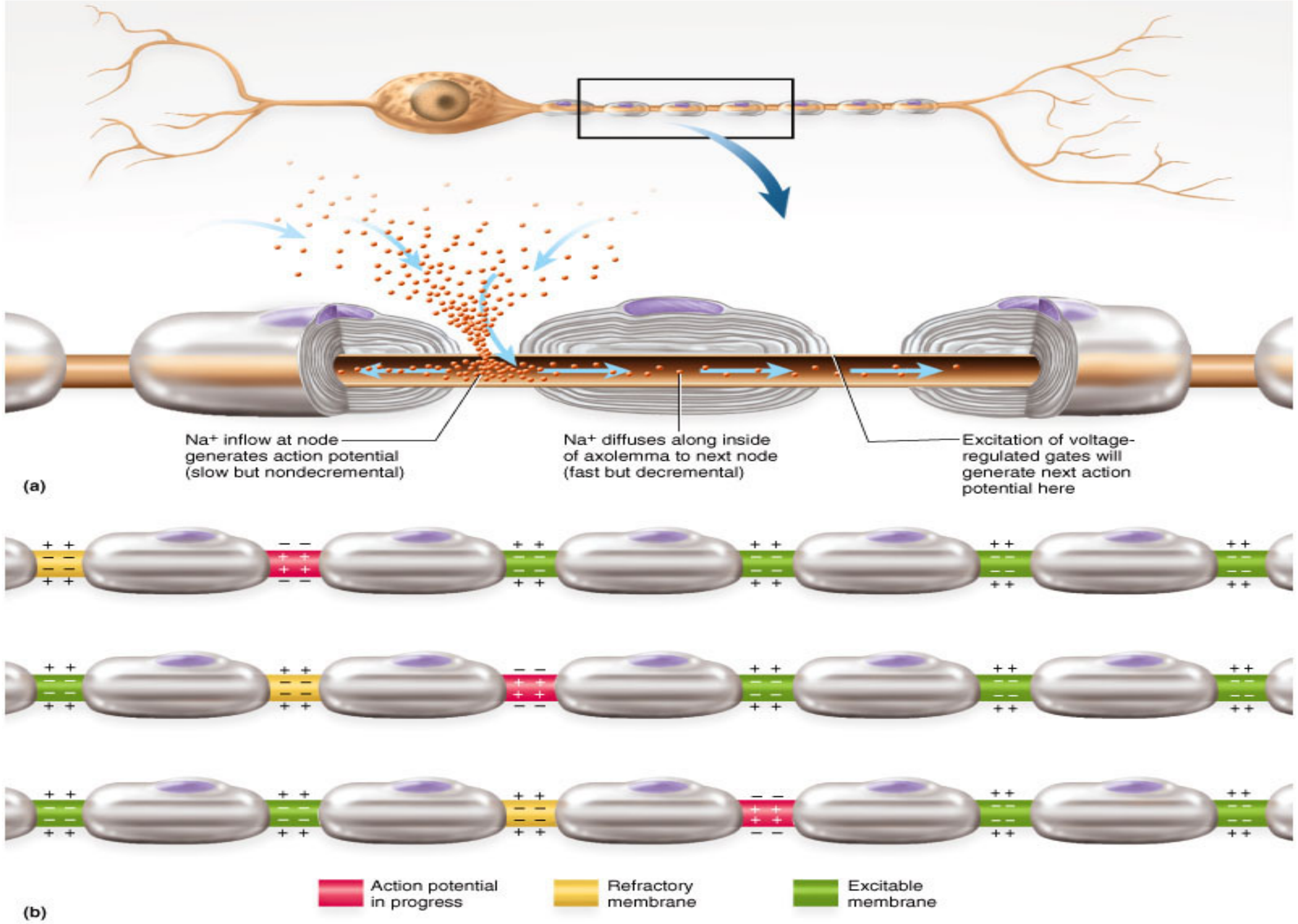


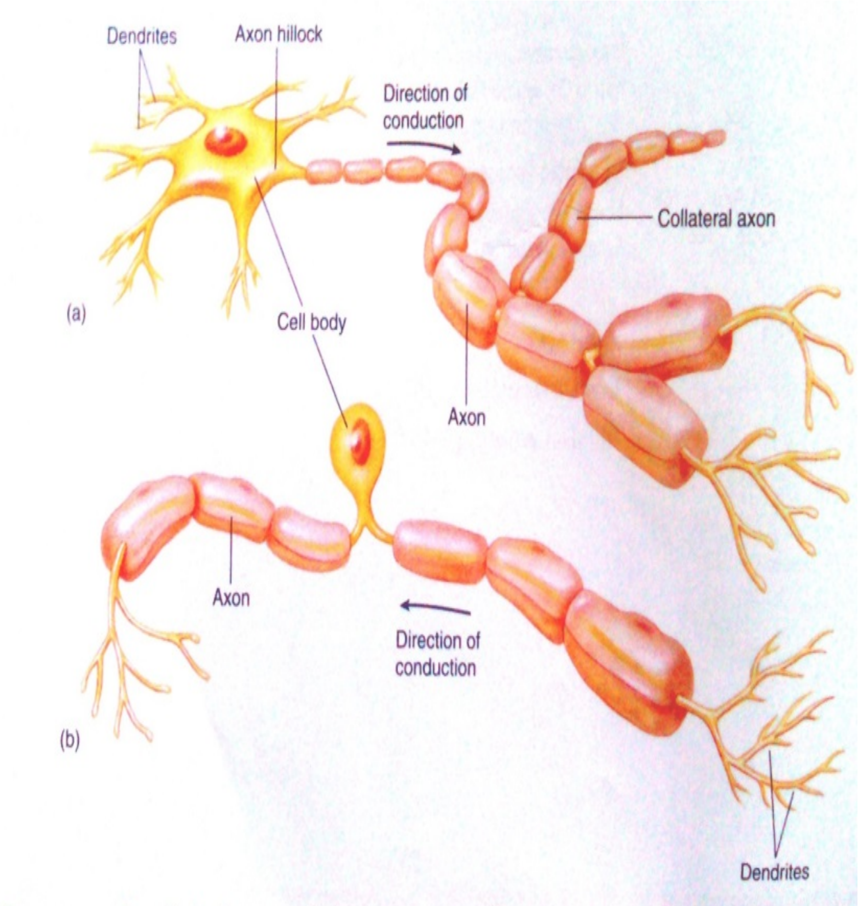
Propagation of Action Potential

Myelinated nerve fibers	Non- myelinated nerves
<u>Saltatory conduction (jumping)</u> ○ Many times faster transmission ○ Action potential skips from one node of Ranvier to the next <u>Value:-</u> 1- ↑ velocity of conduction of nerve impulses 2- Conserve energy for axon because only nodes depolarize لان عدد AP أقل بالتالي يحتاج طاقة أقل لذلك يعتبر energy conserving	<u>(local circuits)=point to point</u> ○ Slower ○ Depolarization pass by local circuits.



Propagation of Action Potential





The structure of two kinds of neurons. (a) A motor neuron and (b) a sensory neuron are depicted here.

Conduction Velocity

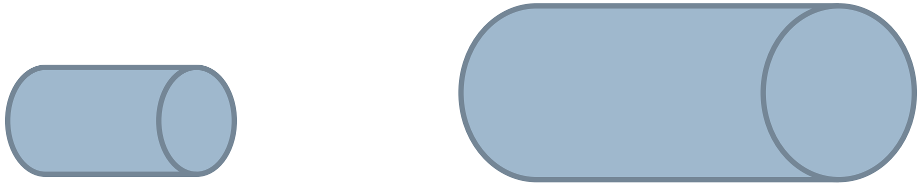
- It is the speed at which action potentials are conducted (propagated) along a nerve or muscle fiber.
- Mechanisms that increase conduction velocity along a nerve (influences speed of action potential):

1. **Axon / Nerve diameter:**

- The larger the diameter, the faster the speed of transmission because large fibers offers less resistance to local current flow so, more ions will flow.
- كل ما زاد الdiameter قلت المقاومة فيزيد AP
- (علاقة عكسية)

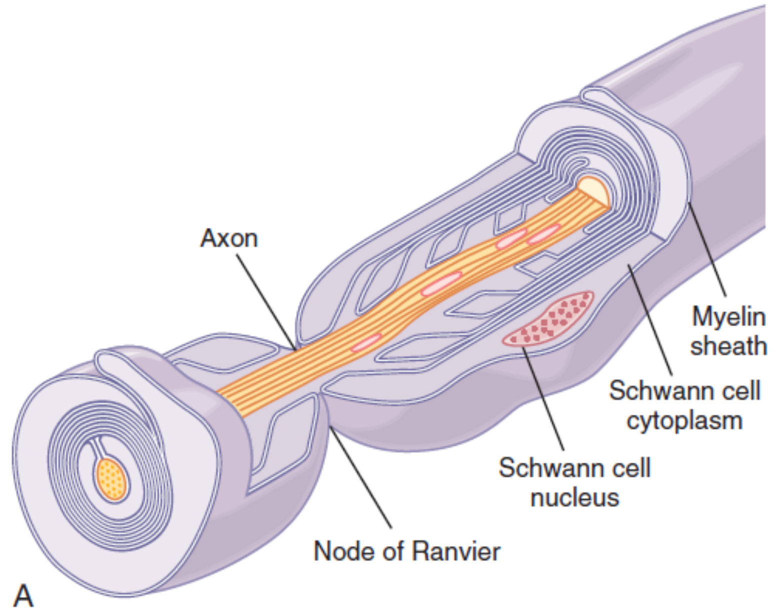
2. **Myelination:**

- Myelin is an **insulator** that makes it more difficult for charges to flow between intracellular and extracellular fluids.
- The layers of Schwann cell membrane contain the lipid substance **sphingomyelin** (a lipid substance) which is excellent **electrical insulator** that decreases ion flow through the membrane.
- **Node of Ranvier**: small uninsulated area where ions can flow with ease.



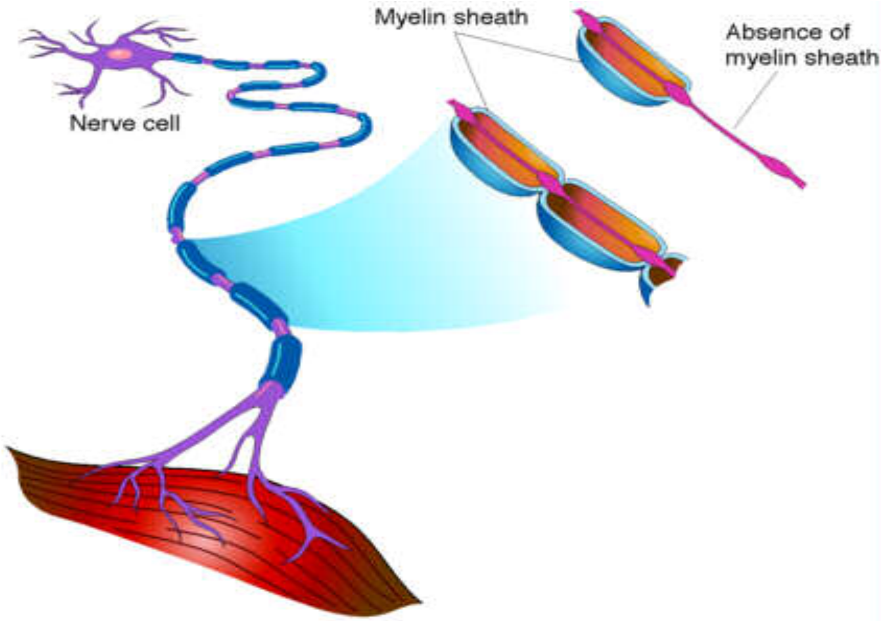
Small diameter →slower transduction

large diameter →faster transduction



What Happens if Myelination is Lost? video

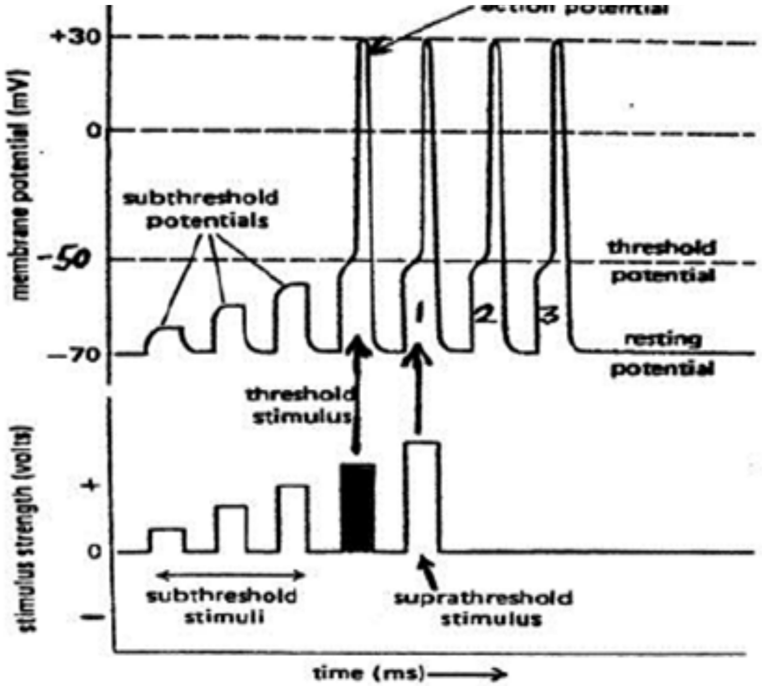
- Multiple sclerosis:
  - Autoimmune disease (Immune system attacks the myelin sheaths surrounding axons as well as the axons themselves).
  - Usually affect young adults.
  - Causes blindness, problems controlling muscles ,ultimately paralysis.



The myelin sheaths are lost → Scar tissue (scleroses) replaces some damaged cells → Other now unmyelinated axons sprout Na+ channels

Extra: “435” Excitation-the process of eliciting the action potential (**Threshold for excitation and “Acute Local Potentials”**)

1. when we give a really weak stimulus (slowly going to a stronger one) we have this small little response labeled subthreshold potential. not an action potential it is **“local depolarization”**
2. If we keep giving it a stronger and stronger stimulus, strong enough to pass the threshold potential
3. Any stimulus greater than threshold give us a repeated action potential called **Suprathreshold** potential



In this we are shown a neuron and it shows how different intensities of stimuli affect the voltage changes.

If something tickles your nose but it’s not enough to make you sneeze, that’s a subthreshold stimulus. If something tickles your nose just enough to make you sneeze once, that’s a threshold stimulus. If something tickles your nose intensely and makes you sneeze three times in a row, that’s a suprathreshold stimulus.

Example

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- **Changes** (a series of changes in polarity) **that occur through the nerve after stimulation by threshold stimulus:**
- **1- Chemical changes.**
- **2- Thermal changes.**
- **3- Excitability changes.**
- **4- Electrical changes (nerve action potential):**
- It is the **potential difference** along the nerve membrane after stimulation by one threshold stimulus.
- **Most important factors:**
  - Threshold stimulus, and Voltage-gated Na and K channels.
  - Nerve signals (impulses) which are transmitted via nerve action. They're transmitted as a wave of depolarization.
- **- Oscilloscope**: Measures rapid changes in membrane potential.

Propagation: action potential propagates through the nerve to stimulate other neurons (starts from axon hillock because it has the most Voltage gated sodium channels)

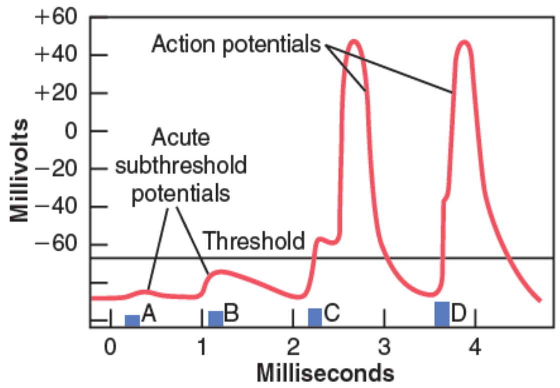

Figure 5-18. Effect of stimuli of increasing voltages to elicit an action potential. Note development of acute subthreshold potentials when the stimuli are below the threshold value required for eliciting an action potential.

Quiz

- https://www.onlineexambuilder.com/rmp-ap/exam-117621

Link to Editing File

(Please be sure to check this file frequently for any edits or updates on all of our lectures.)

References:

- Girls' and boys' slides.
- Guyton and Hall Textbook of Medical Physiology (Thirteenth Edition.)

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

The Physiology 436 Team:

Nouf Aloqaili
Rana Barasain
Norah Alshabib
Sundus Alhawamda
Ruba Barnawi
Heba Alnasser
Lama Alfawzan
Fahad Al Fayez
Muhammad Al Mutlaq

Team Leaders:
Qaiss Almuhaideb
Lulwah Alshiha

Contact us:
Physiology436@gmail.com
@Physiology436