MED437
KING SAUD UNIVERSITY

جامعة
الملك سعود
King Saud University
1957

Resting membrane potential & Action potential

غيـــداء آل مصـــمع
عبدالرحمن الحيسوني
Revised by

➢ Color index:
Red: important
Green: doctor's notes
Grey: extra information
Pink: found only in females' slides
Blue: found only in males' slides

Physiology 437 team work

437
PHYSIOLOGY TEAM

objectives:

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

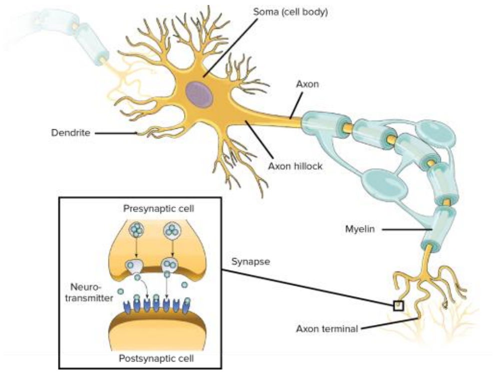
We recommend you to watch this video before you start studying it to help you understand (11:43 mins)

Background information

Neuron: Unit of function of the CNS

Neuron Components:

1. Soma (Cell body)
2. Dendrites: Carry nerve impulses from surroundings to the soma
3. Axon Hillock
4. Axon and Axon Terminal



Myelin sheath: formed by schwann cell which deposits sphingomyelin

Functions of Myelin Sheath:

1. Increase conduction velocity
2. Insulates the neuron

Histological classification of neurons

1. **Myelinated**: have myelin sheath (diameter more than 1um)
   -type A delta & Type B
1. **Unmyelinated**: (diameter less than 1um)
   -type C :postganglionic autonomic neurons & pain fibers.

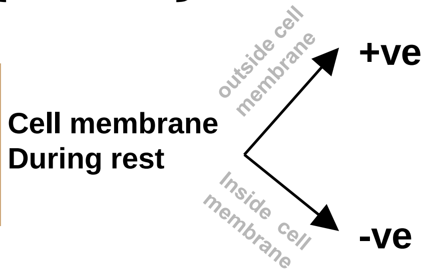
There are three types A & B are myelinated while C isn't.

Excitable Tissues: Nerves and Muscles

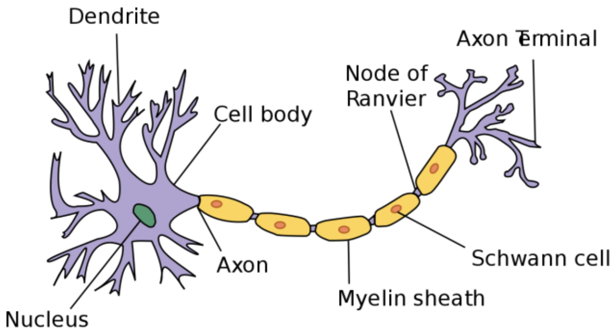
Excitable tissues have the capability to respond to an adequate stimulus

RESTING MEMBRANE POTENTIAL (RMP)

Definition	It is the <u>potential difference</u> across the membrane during rest (without stimulation) between the inner side & outer side of the membrane, and it is relatively –ve inside.
Normal Values	-70 mV in medium sized nerve -90 mV in large sized nerve.
Measurement of RMP	Using Voltmeter
During rest	The membrane is polarized



كل ما نزلنا عن الصفر أكثر كل ما احتاج أكثر Stimulus



Comments about previous slide from guyton

1. Sodium, potassium, and chloride ions are the most important ions involved in the development of membrane potentials in nerve and muscle fibers.
2. The quantitative importance of each of the ions in determining the voltage is proportional to the membrane permeability for that particular ion يعني أن أهمية العدد للايونات يخلي الميمبرين يحدد عدد الشحنات لكل أيون المسموح لها بالدخول فيحاول يوازن بينهم.
3. A positive ion concentration gradient from inside the membrane to the outside causes electronegativity inside the membrane.
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.

Causes (Origin) of RMP

Some information is from team 436

Contribution of K+ diffusion potential

The cell membrane tends to diffuse **potassium (K+)** out of the cell (outflux) “from high to low concentrations” through K leak channels.
Causes –ve charge inside.
(the diffusion of K+ is the main determinant of the RMP)
Result: Electropositivity outside and electronegativity inside.

Contribution of Na+ diffusion potential

The cell membrane tends to diffuse **Sodium (Na+)** into the cell (influx) “from high to low concentrations” through Na leak channels. The membrane is almost impermeable to Na+

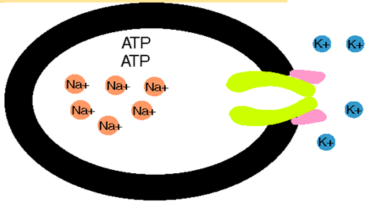
ICF concentration : 14
ECF concentration :142

Contribution of Na+/K+ ATPase PUMP

This is a powerful electrogenic (كهربائية) pump on the cell 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)**. It maintains conc. gradients of K+ and Na+ between the two sides of the membrane.

Cell membrane is 100 times more permeable to K+ than Na+.
K diffusion contributes far more to resting membrane potential than Na
Non-diffusible anions (proteins, sulphate, and phosphate ions) cannot leave the cell. **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.**



Continued

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

E.M.F(mV)=(-61/z)*log(conc. inside/conc. outside)

1-When the membrane potential is caused entirely by K+ diffusion (outflux): **EMF of K+**= **-94 mV**

2-When the membrane potential is caused entirely by Na+ diffusion (influx): **EMF of Na+** = **+61 mV**

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

Then, using these values in the **Goldman equation** we get a potential inside the membrane of **−86 mV.** This potential is the result of Goldmann equation(ليس الجمع) of the ions' diffusions only (without Na/K pump).

3-When membrane potential is caused by diffusion of both **Na+ & k+** and **Na+/K+ pump** = **-90 mV**

The membrane is highly permeable to potassium but only slightly permeable to sodium, it is logical that the diffusion of potassium contributes far more to the membrane potential than does the diffusion of sodium.

ions	EMF
K+	-94
Na+	+61
All ions	-86
Na+/K+ pump	-4
Net	-90

(-86) + (-4) = -90

Only in males' slides

Extra information about previous slide

where EMF is electromotive force and z is the electrical charge of the ion

Diffusion potential depends on three factors: (1) the polarity of the electrical charge of each ion, (2) the permeability of the membrane (P) to each ion, and (3) the concentrations (C) of the respective ions on the inside (i) and outside (o) of the membrane.

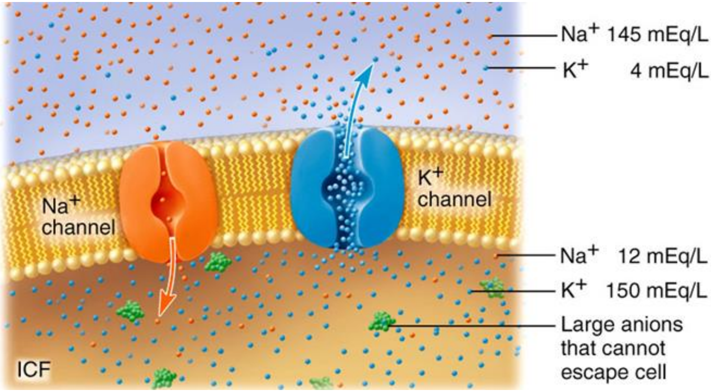
What does it mean when a neuron “fires”?

Firing → Excitability → Action potential → Nerve impulse

Recall resting potential of all cells

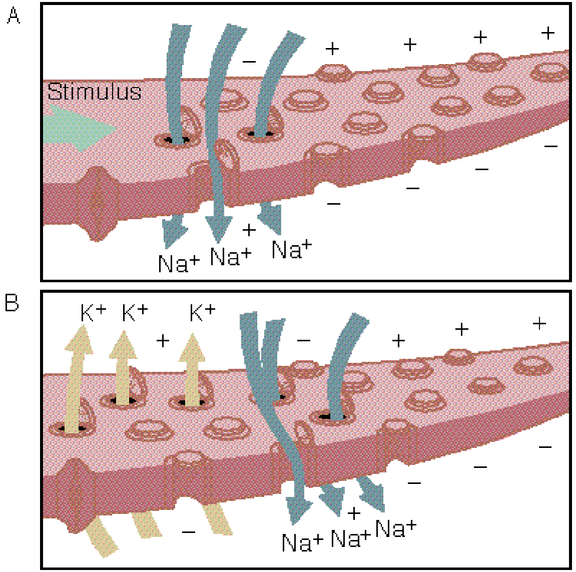
- High k+ inside; High Na+ outside
- Cell overall negative charge inside is due to molecules like proteins, RNA, DNA
- Cell is polarized

- Charge measured in millivolts
- Potential; difference in charge across PM
- Current; flow of charge (ions) from one point to another



Changes that occur through the nerve after stimulation by threshold (effective) stimulus:

- Electrical changes (nerve action potential)
- Excitability changes
- Thermal changes
- Chemical changes

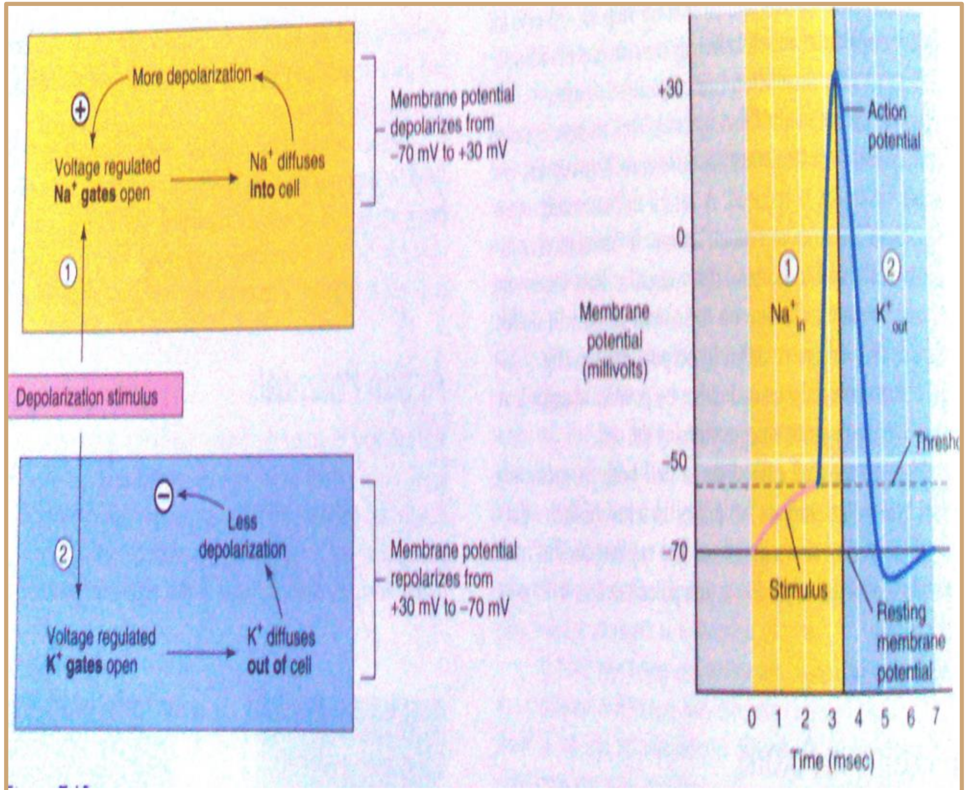


Extra

Excitation

The process of eliciting the action potential

"Understanding Excitation" In the generation of the action potential, stimulation of the cell by neurotransmitters or by sensory receptor cells partially opens channel-shaped protein molecules in the membrane. Sodium diffuses into the cell, shifting{converting} that part of the membrane toward a less-negative polarization.If this local potential reaches a critical state called the "**Threshold Potential**" (measuring about −60 mV), then sodium channels open completely to undergo Action Potentials.On the other hand, if Sodium influx does not reach the threshold potential, so the cell will return to resting potential"**Acute subthreshold potential**".



The 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 to produce <u>physiological effects</u> **such as:**
    - Transmission of impulse along nerve fibres
    - Release of neurotransmitters
    - Muscle contraction
    - Activation or inhibition of glandular secretion

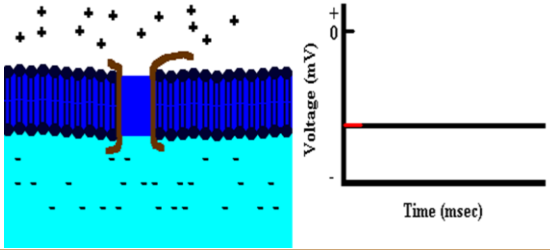
الاكشن بوتنشال مهم جدا فبدونه لا تتحرك
العضلات ولا تفرز الهرمونات)هو نقطة
التحكم من المخ إلى جميع المواقع بالجسم(

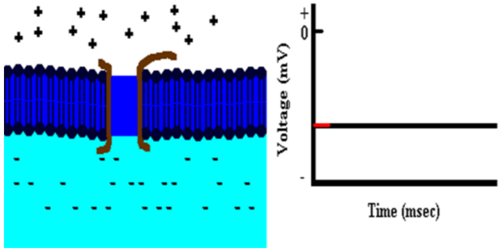
- Each action potential begins with a **<u>sudden change</u>** from the normal resting negative membrane potential to a positive potential and ends with an almost equally rapid change back to the negative potential.

Stages Of Action Potential:

After depolarization it must return to resting stage if not it will cause continuous contraction leads to tetany

Resting stage	depolarization stage	Repolarization stage
It is the resting membrane potential before the action potential begins. The membrane is "polarized".	The membrane suddenly becomes permeable to **Na+** ions, allowing tremendous numbers of positively charged **Na+** to diffuse to the interior of the axon (Upstroke). Membrane potential reaches zero value to reach +35 mV, at +35 mV all Na channels begin to close suddenly (depolarization ends).	**Na+** channels begin to close and the **K+** channels open. Rapid diffusion of **K+** ions to the exterior re-establishes the normal negative resting membrane potential.





Cont.

Initiation of Action Potential (AP):
-70 to -90 mv is the resting potential
Threshold stimulus opens voltage gated Na channels & Na influx raises resting potential from -90 towards zero (gradual depolarization)
As membrane potential rises more Na channels open & Na influx increases (+ve feedback) until all voltage gated Na channels open.

Electrical changes:

The nerve action potential

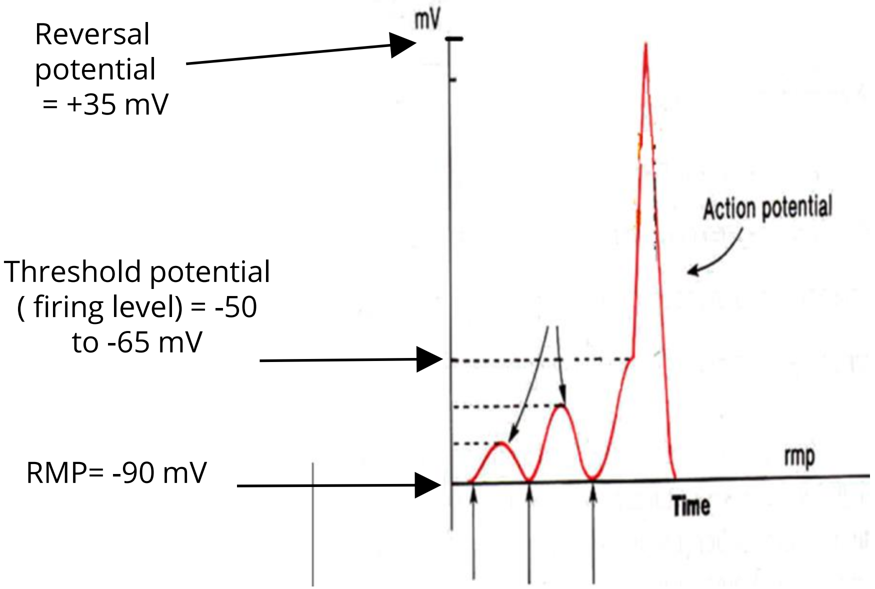
It is the potential difference along the nerve membrane after stimulation by threshold (effective) stimulus

Oscilloscope is used to measure the rapid changes in membrane potential

Nerve signals (impulses) are transmitted as nerve action potentials conducted along the nerve fiber as a wave of depolarization to its end

Factors necessary for nerve action potential:

1. Voltage gated Na channels
2. Voltage gated K channels
3. Threshold stimulus

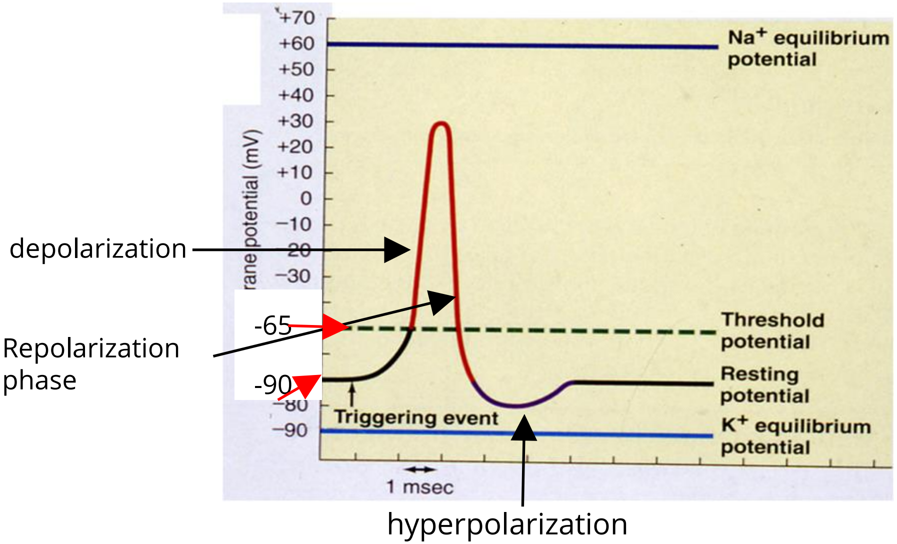


Increasing stimulation

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

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



Threshold Stimulus: The membrane potential at which occurrence of the **action potential** is inevitable{certain to happen} سيحدث لا محالة.

When a **stimulus is strong** enough to move **RMP** from its resting value **(-70 mV)** to the level of **-55 mV** which leads to production of an Action Potential.

Will open all na+ channels

This occurs when the number of sodium ions entering the fiber becomes greater than the number of potassium ions leaving the fiber.

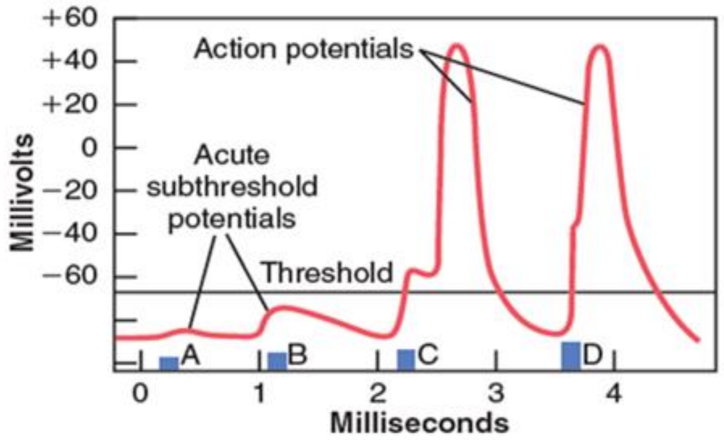


Figure 5-18. Effect of stimuli of increasing voltages to elicit an action potential. Note development of acute subthreshold potentials when the stimuli are below the threshold value required for eliciting an action potential.

Subthreshold stimulus / Acute subthreshold potential:
Stimulus that results in local depolarization. (local action potential)
(does not propagate or move along)" Weak Stimulus".
When stimulus is below the threshold.

All-or-nothing principle:

Once threshold value for excitation is reached a full AP is produced, its intensity can not be increased by increasing stimulus intensity (suprathreshold)

Types of Transport Channels Through the Nerve Membrane

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

A) Voltage gated Na+ channels

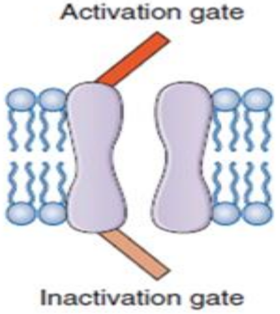
Na Channel has <u>two gates</u>:

- **Activation gate:** on the outer side of Membrane.
- **Inactivation gate:** on the inner side of Membrane.

Na channel <u>has three states</u>:

- **Resting state**
- **Activated state**
- **Inactivated state**

We will talk about these states in detail in the next slide.



B) Voltage gated K+ Channels

Kindly understand the next slide before you read this" "يسهل عليك فهم الكلام الذي بالاسفل"

- Has **one gate** only .
- 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**"Extracellular fluid.
- Shortly **after depolarization**, when the **sodium** channel begins to be **inactivated**, the **potassium** channel **opens**.
- K+ **exits (Efflux)** → **Repolarization**

Once the cell reaches +35mV, Voltage gated K+ channels open its gate.

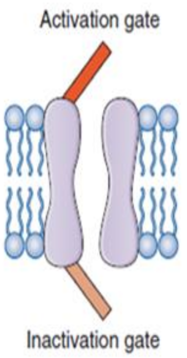
Voltage gated Na+ channels states

<u>1-Resting state :</u> The **activation** gate is **closed** in the resting cell which means the MP"Membrane Potential" = RMP "Resting Membrane Potential" is between **-70** to **-90 mV**.This **prevents** the **entry of Na+** to the intracellular. The **inactivation** gate is **open.**

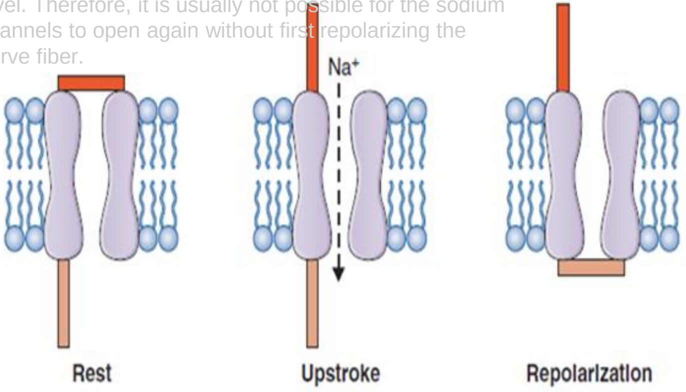
<u>2-Activated state:</u> "Threshold Depolarizing Stimulus" moves the MP from its resting value (**-90 mV**) to its threshold value (**-65 to -55 mV**)This will **<u>open the activation gate</u>**, (in this case BOTH the activation gate & inactivation gate are open) permeability to Na+ becomes increased 500 to 5000 times Na+ influx. Na+ flows into intracellular in large amounts.

<u>3-Inactivated state:</u> A few milliseconds after the **activated state**, the channel becomes **inactivated** by **closing inactivation gate**. The **activation gate** is still **open**. At the same time Voltage gated K+ channel will be open.

Dr.mohammed said : it's very important and many student get confused



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.



What Happens After Action Potential? → Refractory Period

Refractory period: few milliseconds

- Time during which the neuron can't be stimulated a second time
- Happens until recovery of resting potential

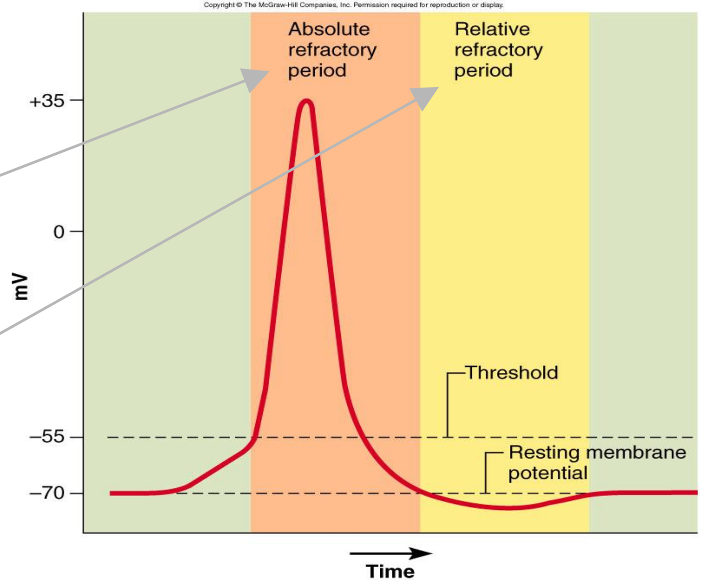
Two Stages

➢ **Absolute refractory period:**

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

➢ **Relative refractory period:**

Can trigger new action potential if stimulus (nonphysiological) is very strong.



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

Hyperpolarization

Hyperpolarization (Positive after-potential):

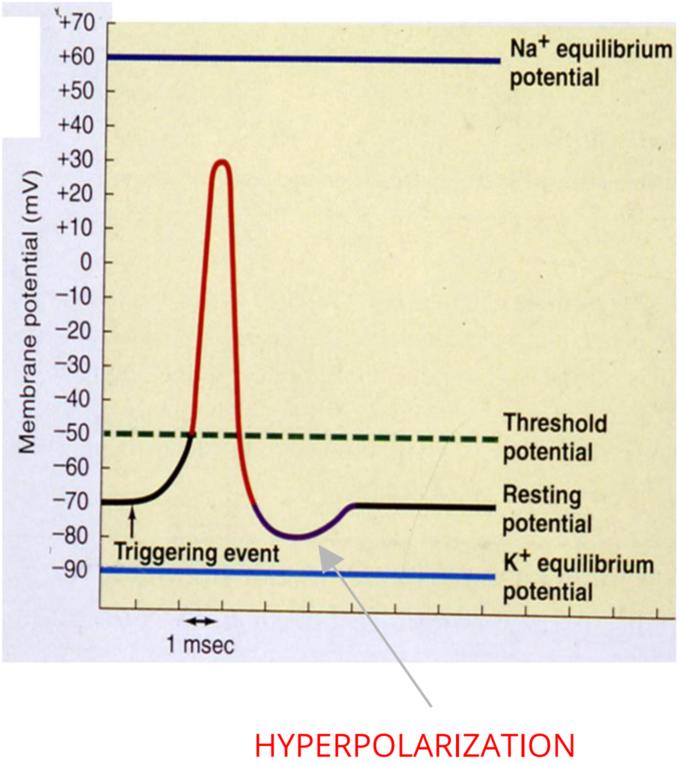
- **Hyperpolarization** is a change in a cell's membrane potential that makes it more negative inside and more positive outside,more than resting membrane potential. It inhibits action potentials by increasing the stimulus required to move the membrane potential to the action potential threshold.

- 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, so the RMP is resumed and the membrane is ready for another stimulus

- While hyperpolarized, the neuron is in a refractory period.

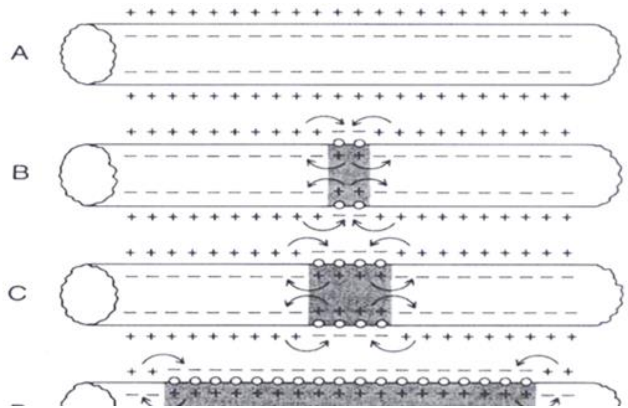
- Hyperpolarization occurs after Repolarization for a brief period because K+ migrate"leave" the cell in amounts a bit more than normal

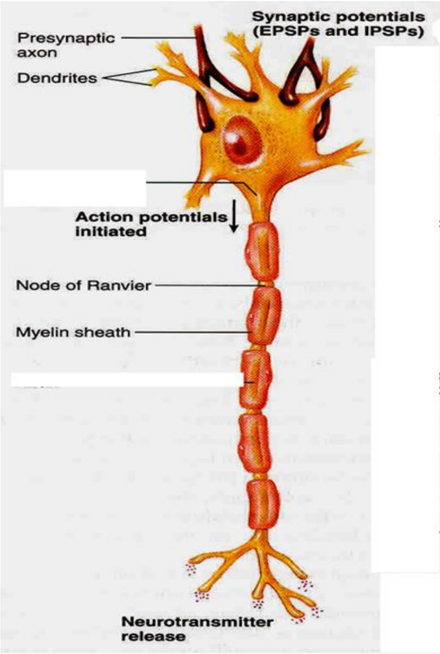


(Direction of AP Propagation (Conduction

-Under Artificial condition of electrical stimulation in the laboratory, the AP propagates in both directions. until the entire membrane has become depolarized

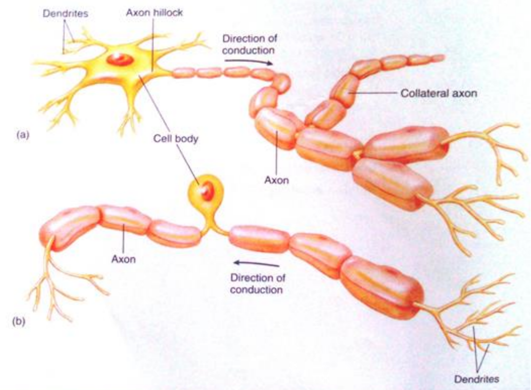
-But normally AP starts in axon hillock & propagates distally in one directions





Propagation of action potential:

Myelinated nerve fibers: Saltatory conduction (jumping) value:		**Non-myelinated nerves**	
a. ↑velocity of conduction of nerve impulses.	b. Conserve energy for axon because only nodes depolarize.	(local circuits) =point to point	Depolarization pass by local circuits



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

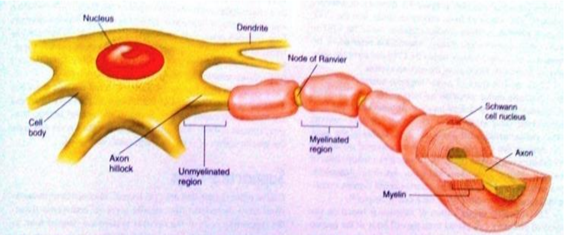


Figure 7.2 Parts of a neuron. The axon of this neuron is wrapped by Schwann cells, which form a myelin sheath.

Saltatory :they can flow with ease through the nodes of Ranvier.
Therefore, action potentials occur only at the nodes
ما يكون فيه أكشن بوتنشال إلا بأطراف المايلين شيت

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 (more than the length of a football field in 1 second) in large myelinated fibers.

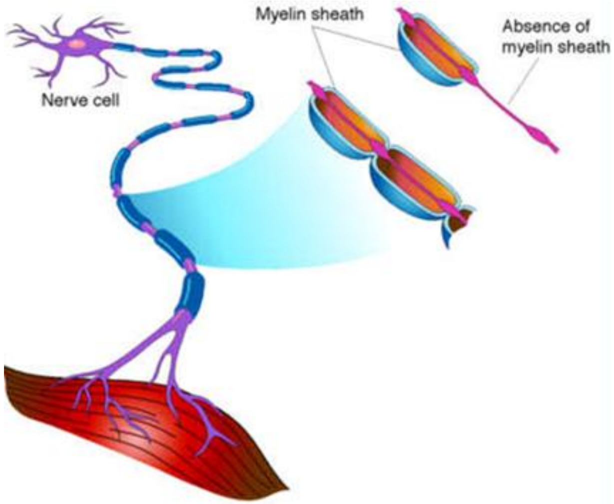
What else influences speed of action potential?

Axon diameter

The larger the diameter, the faster the speed of transmission and the less resistance to current flow

What happens if myelination is lost?

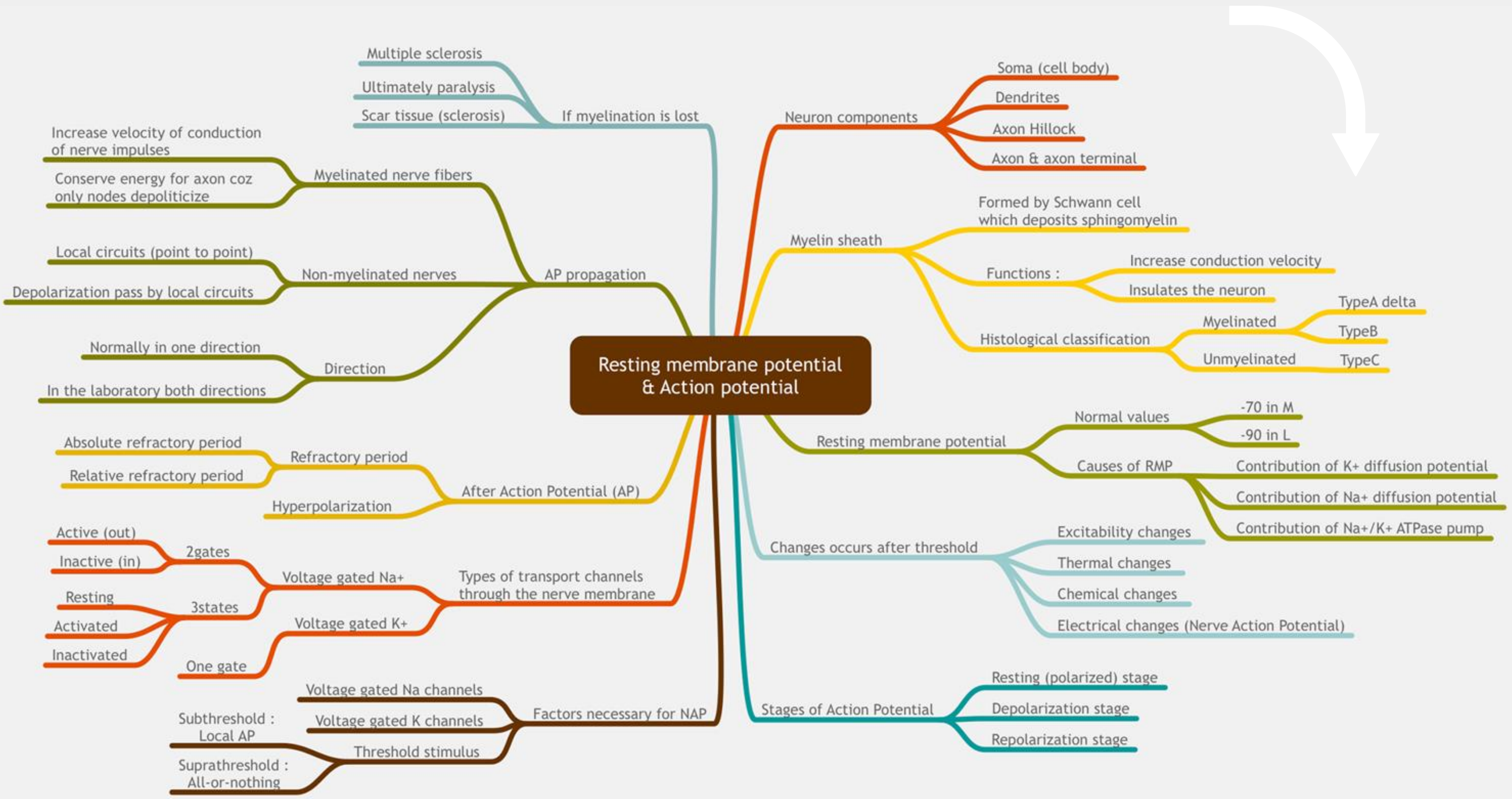
- Multiple sclerosis
  - Autoimmune disease
  - Usually young adults
  - Blindness, problems controlling muscles
- Ultimately paralysis
  - Immune system attacks myelin sheaths and nerve fibers
- Scar tissue (sclerosis) replaces some damaged cells



Quiz

1. A typical neuron has a resting membrane potential of about:
   (A) +70 mV (B) +70 V
   (C) −70 mV (D) −70 V
2. The following ion(s) is/are involved in the neuronal action potential:
   (A) Sodium (Na+) (B) Potassium (K+)
   (C) Calcium (Ca2+) (D) Both A&B
3. At the peak of the action potential, the membrane potential is:
   (A) exactly at the Na+ equilibrium potential (VNa)
   (B) close to but more positive than the Na+ equilibrium potential (VNa)
   (C) close to but less positive than the Na+ equilibrium potential (VNa)
   (D) exactly at 0 mV
4. At what membrane voltage do neuronal voltage-gated Na+ channels become activated?
   (A) −70 (B) −50
   (C) 0 mV (D) +50 mV
5. The hyperpolarization phase of the action potential is due to:
   (A) the opening of voltage-gated Cl− channels
   (B) the prolonged opening of voltage-gated K+ channels
   (C) the closure of resting Na+ channels
   (D) due to the closure of Cl− channels

Answers :
1 : C
2 : D
3 : C
4 : B
5 : B



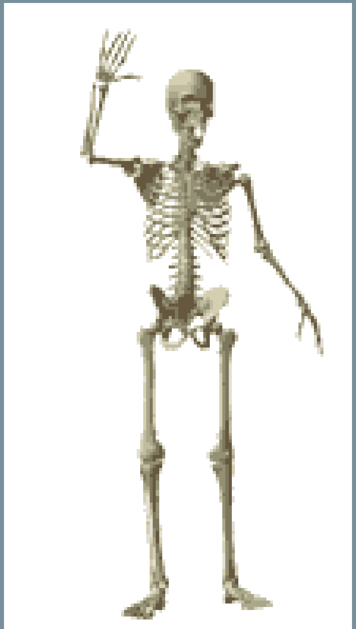
Resting membrane potential & Action potential
Neuron components
Soma (cell body)
Dendrites
Axon Hillock
Axon & axon terminal
Myelin sheath
Formed by Schwann cell which deposits sphingomyelin
Functions :
Increase conduction velocity
Insulates the neuron
Histological classification
Myelinated
TypeA delta
TypeB
Unmyelinated
TypeC
Resting membrane potential
Normal values
-70 in M
-90 in L
Causes of RMP
Contribution of K+ diffusion potential
Contribution of Na+ diffusion potential
Contribution of Na+/K+ ATPase pump
Changes occurs after threshold
Excitability changes
Thermal changes
Chemical changes
Electrical changes (Nerve Action Potential)
Stages of Action Potential
Resting (polarized) stage
Depolarization stage
Repolarization stage
If myelination is lost
Multiple sclerosis
Ultimately paralysis
Scar tissue (sclerosis)
AP propagation
Myelinated nerve fibers
Increase velocity of conduction of nerve impulses
Conserve energy for axon coz only nodes depoliticize
Non-myelinated nerves
Local circuits (point to point)
Depolarization pass by local circuits
Direction
Normally in one direction
In the laboratory both directions
After Action Potential (AP)
Refractory period
Absolute refractory period
Relative refractory period
Hyperpolarization
Types of transport channels through the nerve membrane
Voltage gated Na+
2gates
Active (out)
Inactive (in)
3states
Resting
Activated
Inactivated
Voltage gated K+
One gate
Factors necessary for NAP
Voltage gated Na channels
Voltage gated K channels
Threshold stimulus
Subthreshold : Local AP
Suprathreshold : All-or-nothing

Female's team:

1. Ahad Algrain
2. Hadeel
3. Maha Alnahdi
4. Majd AlBarrak
5. Rahaf Alshammari
6. Rinad Alghoraiby
7. Munira Alhadlg
8. Sarah Alblaihed
9. Renad Almogren

Male's team:

1. Mohammed Alhassan
2. Abduljabbar Alyamani
3. Abdullah Alzaid
4. Abdulrahman altalasy
5. Fahad alhussain
6. Mohammad aljumaah
7. Hesham alshaya



Team Leaders:

Abdulhakim AlOnaiq
Alanoud Salman

contact us at:

physiologyteam437@gmail.com

@physio437

editing file:
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