Physiology | Lecture 12

Membrane potential of excitable tissues pt.3

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Refractory periods

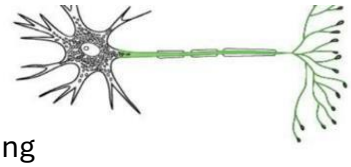
The refractory period is a phase during which a membrane temporarily stops responding to stimuli with an action potential. This period is primarily determined by the activity of sodium (Na^+) channels (firing stage) and is divided into two stages:

1. Absolute Refractory Period: During this phase, Na^+ channels are open, making it impossible for the membrane to respond to any stimulus, regardless of its strength.

• In cardiac muscle cells, the absolute refractory period is significantly longer than in other muscle types. This prevents premature contractions, ensuring the heart has enough time to relax before the next contraction.

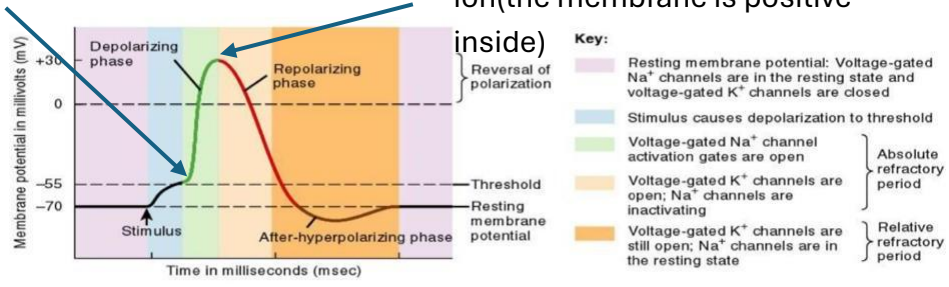
• Skeletal muscle cells, being voluntary, have the shortest refractory periods, allowing for rapid and repeated contractions.

2. Relative Refractory Period: During this phase, Na^+ channels are closed, but they can respond to a stimulus only if it is significantly stronger than usual. This stronger-than-normal stimulus is referred to as a suprathreshold stimulus, which typically occurs under controlled experimental conditions most of the stimuli in our bodies are subthreshold.



At the threshold we have the largest driving force for Na+

Here at the overshot we have the largest driving force for the potassium ion and the chloride ion(the membrane is positive inside)



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There is a difference between the conductance and the driving force

(at the firing stage you have maximum conductance for sodium ion and in the failing stage you have the maximum conductance for potassium ions)

Refractory periods

In addition to the role of voltage gated Na+ channels in establishing the relative refractory period, the presence of widely opened K+ channels during falling phase, which cause excess flow of positive charges to the outside, may also play a role by opposing stimulating signals

Since the refractory period is dependent on Na^+ channels, it's essential to understand their three functional states:

1. **Closed but capable of opening:**

• This occurs during the resting potential when the membrane is not in a refractory period.

• The channels can open normally in response to a typical stimulus.

2. **Open:**

• This occurs during the depolarization (firing) phase.

• The membrane cannot respond to any additional stimulus during this absolute refractory period, regardless of its strength.

3. **Closed and incapable of opening:**

• This happens during the falling phase and hyperpolarization.

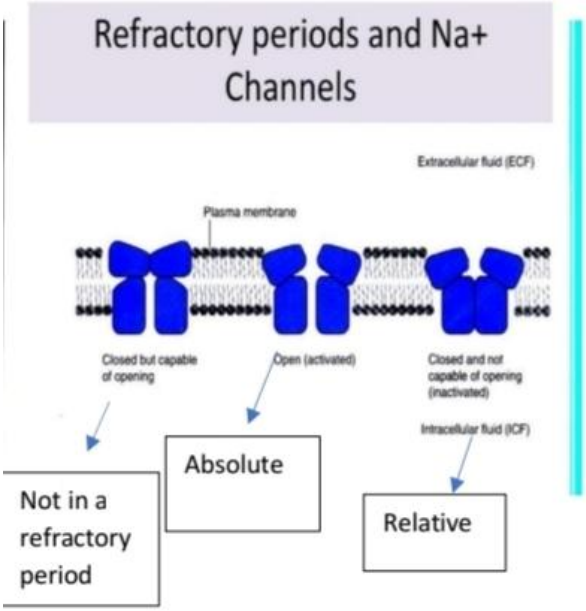
• The channels remain in this state until the membrane potential returns to its resting level.

• Once the resting state is restored, the Na^+ channels transition back to the "closed but capable of opening" state.

• A more negative membrane potential increases the number of Na^+ channels in this excitable state.

The absolute refractory period begins at the threshold and ensures that once an action potential is initiated, it completes fully before another can be triggered.

• The "all-or-none" principle states that a neuron either fires a full action potential or does not fire at all. If the stimulus reaches the threshold, a complete action potential is generated. If it does not, no action potential occurs



In addition to the role of voltage gated Na channels in establishing the relative refractory period, the presence of widely opened K+ channels during falling phase, which cause excess flow of positive charges to the outside, may also play a role by opposing stimulating signals

Importance of Sodium Channel Density in Excitability

The number of sodium (Na^+) channels in the "closed but capable of opening" state plays a crucial role in determining the excitability of a tissue. **Tissues with a more negative resting membrane potential are generally considered more excitable** because they have a higher density of these Na^+ channels.

• Neural cells, the most excitable, have a resting potential of -80 mV and a threshold of -75 mV.

• Skeletal muscle cells have a resting potential of -70 mV and a threshold of -50 mV.

• Cardiac muscle cells have a resting potential of -60 mV.

The reason neural cells are more excitable than skeletal muscle cells is that they have a greater number of Na^+ channels available to open at a given potential. In skeletal muscle cells, fewer Na^+ channels exist in this state, meaning that even at -70 mV, an action potential is not easily triggered.

Excitability in Similar Cells

When comparing two cells of the same tissue type (with similar resting membrane potentials and thresholds), excitability depends on how close the membrane potential is to the threshold.

• A less negative membrane potential (closer to the threshold) makes it easier to stimulate the cell, requiring a weaker stimulus.

• A more negative membrane potential (further from the threshold) makes the cell harder to stimulate, requiring a stronger stimulus.

Thus, while more negative tissues (such as neurons) are generally more excitable, within the same type of tissue, a more negative cell is less excitable and requires a stronger stimulus to generate an action potential.

Neurons are more excitable NOT because they are more negative only, but because:

- high Na^+ channel density (concentration outside)
- channels are fully ready (pre threshold)
- relatively closer to threshold

Final golden rule:

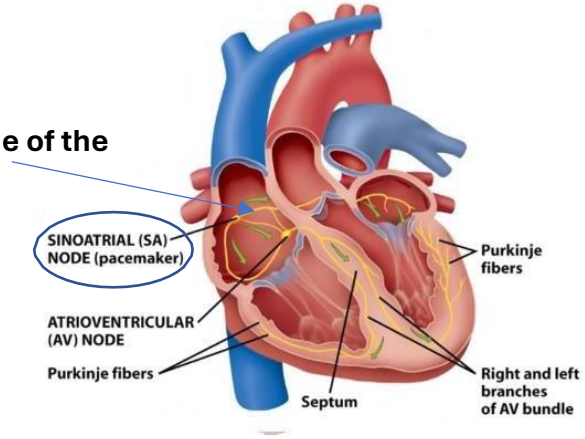
- **More negative alone → less excitable**
- **More negative + other factors → more excitable**

Involvement of other Ions in Action potential

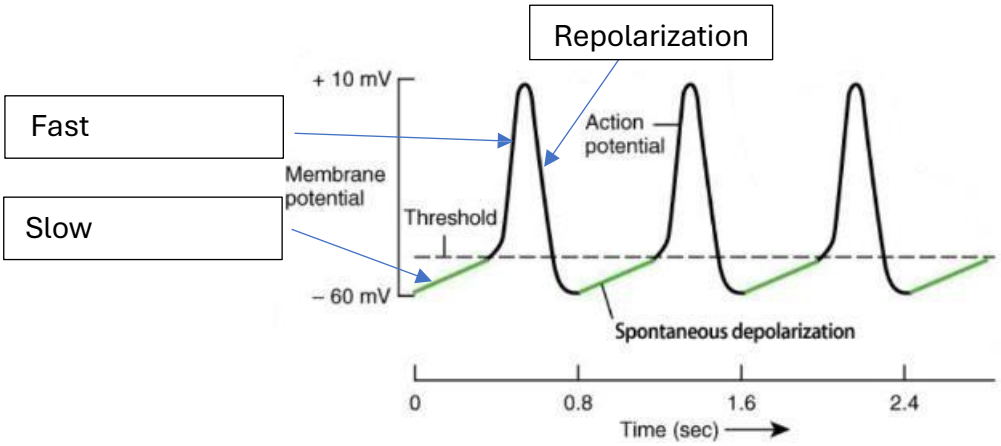
We have cells that have other ions involved in Action potential such as cardiac cells (Ca^{+2} ions participate in their action potential).

There are two excitable tissues

in muscular and nervous



this type of action potential takes place in conductive tissue (in yellow, conductive tissues in your heart that generate action potential in **automatic** way).



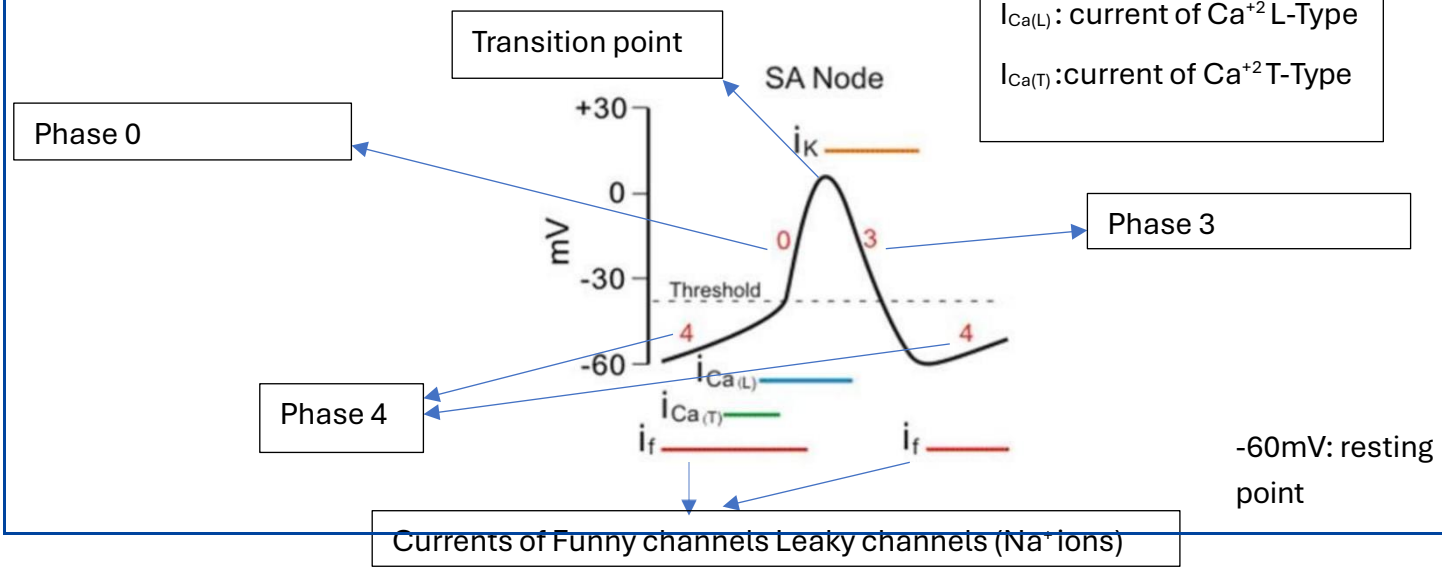
There are a lot of channels, and each channel will be activated at specific voltage point. Let's see an example for more understanding.

SA NODE (pacemaker of the heart)

I_k: current of K^+

$I_{Ca(L)}$: current of Ca^{+2} L-Type

$I_{Ca(T)}$: current of Ca^{+2} T-Type



Did you see the picture? Let's explain now the whole process then we will explain each phase.

-The SA node cells have a resting membrane potential of around -60 mV, which is maintained by the movement of ions through ion channels in the cell membrane (leaky channels) , When the SA node receives a signal, it causes the membrane potential to depolarize rapidly around -50 mV (by increasing of Na^+ conductance). now, a type of calcium channels called Transient type of calcium channel ($I_{ca(T)}$) will be activated, so we will get Ca^{+2} current from outside to inside making less negative inside. When we reach -40mV, we reach Threshold. Second type of calcium channels will be activated (L-Type calcium channels), and we will start fast depolarization causing inside to be less negative (it is called phase 0). Now, the calcium current will pass through the membrane reaching the transition point which is around +20mV in this example. At this point, K^+ channels will be activated, so K^+ ions will move from inside toward outside making the membrane more negative inside ,which is called repolarization. Until we reach -60Mv, we will be at resting point again (by F currents), And the process occurs.

Now, let's talk about each phase of this process:

- Phase 4(resting membrane potential): During this phase, the membrane potential of the SA nodal cells slowly depolarizes from a negative value (around -60 mV) towards the threshold potential (around -40 mV)

*In this phase we will see two types of channels: 1-Na^+ channel 2-T-Type Ca^{+2}

- Phase 0 (depolarization): During this phase, the membrane potential of the cell undergoes a rapid change from its resting negative value to a positive value. And in this phase, T-Type channels are slow, and they will be closed.

*Here we will see L-Type channels.

So, are there phases 1 and 2?

No, we will talk about them in next example.

- Phase 3 (repolarization): phase 3 is triggered by the outward movement of potassium ions (K+) through voltage-gated potassium channels, which open in response to the depolarization of the cell membrane. The rapid efflux of K+ ions results in a rapid repolarization of the membrane potential, causing it to return to its resting negative value. (inactivation of Ca^{+2} channels)

Generation of Action potential every 0.8 seconds, or 75 action potentials per minute at the SA node (Pacemaker of the heart)

- The resting membrane potential will never reach - 90mV due to the leakage of Na+ in phase

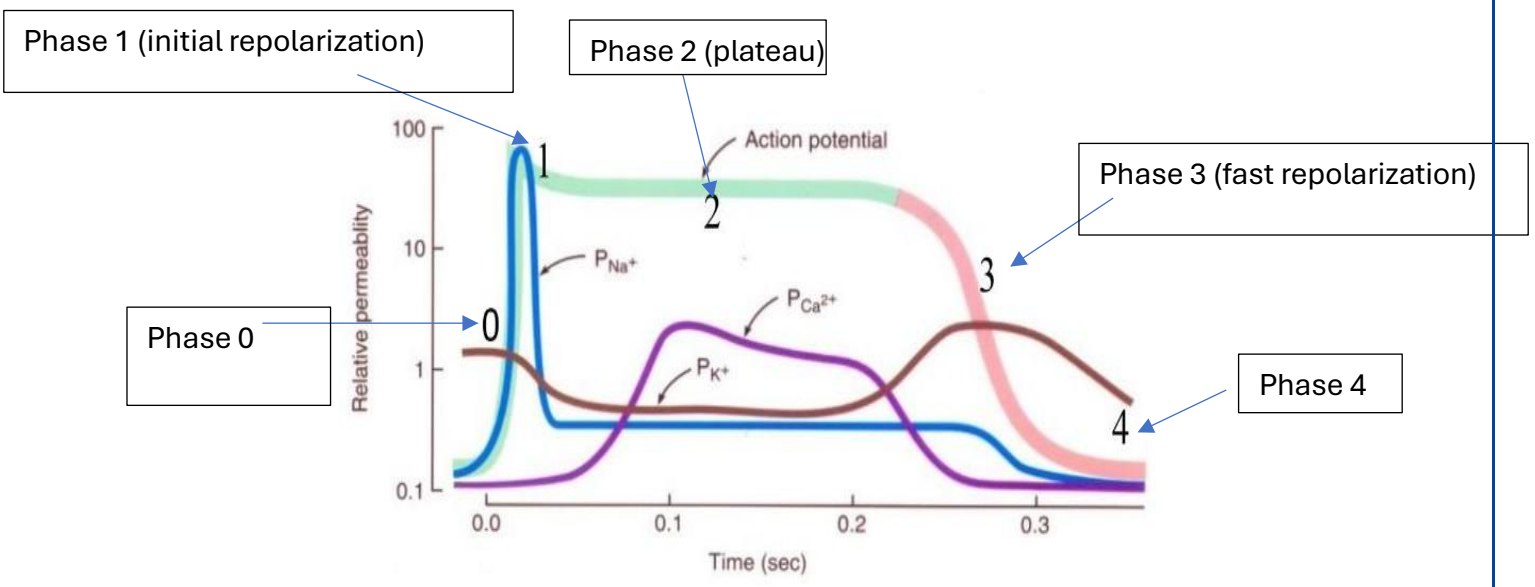
*IMPORTANT VEDIO:
https://www.youtube.com/watch?v=Gkm5NGq9ErI&feature=youtu.be

If the pacemaker isn't functioning that doesn't mean the heart will stop ,the structure downward will take the action but instead of creating 75 cycles per minute it will create much lower rate which indicates a heart disease .

Cardiac muscle action potential

It is important to contraction, relaxing and protection.

its resting point around -90mv.



I think you've already understood each phase, so we will not explain each phase in detail again. We will just determine the difference between cardiac muscle and SA Node.

- Phase 0: instead of Ca^{+2} voltage gated channels (SA node), there will be Na^{+} voltage gated channels (cardiac muscle).

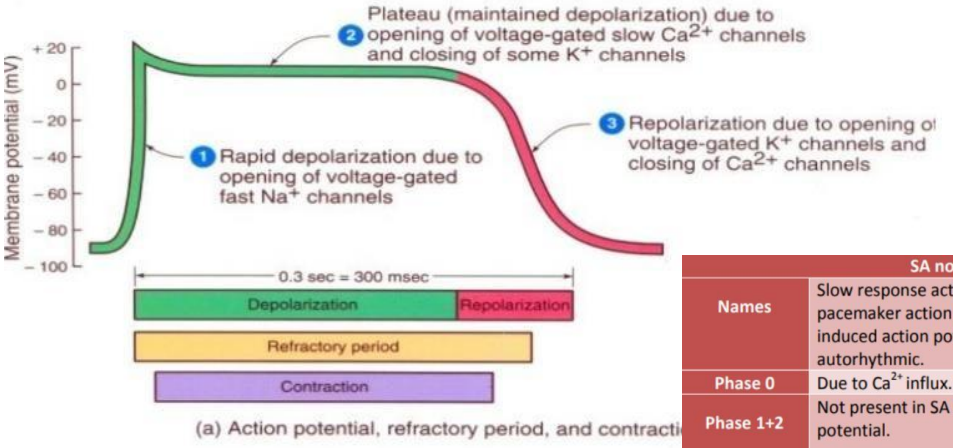
-our doctor didn't say the number of voltage difference at each phase.

- Phase 1 (initial repolarization): the first step of repolarization due to the K^+ Current from inside to outside. In this phase, Na^+ will be closed (inactivation).

-Phase 2 (plateau): slow voltage gated Ca^{+2} channels open so the calcium moves according to its electrochemical gradient from outside to inside and closing some of the K^+ channels
It works as some kind of protection to the heart as you know the heart during absolute refractory period doesn't respond to any stimuli but if(theoretically speaking) it has responded the heart may remain contracted and doesn't fulfill its role, which is totally different from the mechanism of skeletal muscles

-Phase 3 (repolarization): Ca^{+2} channels are closed and K^+ channels will be activated.

-Phase 4 (resting potential).



(a) Action potential, refractory period, and contracti

	SA node	Contractile cardiac AP
Names	Slow response action potential, pacemaker action potential, self-induced action potential, autorhythmic.	Fast response action potential, Non-pacemaker action potential.
Phase 0	Due to Ca^{2+} influx.	Due to Na^+ influx. (rapid)
Phase 1+2	Not present in SA node action potential.	Phase 1: initial repolarization by K^+ efflux. Phase 2: transient increase in Ca^{2+} influx.
Phase 3	Due to K^+ efflux.	Due to K^+ efflux and decrease in Ca^{2+} influx.
Phase 4	Due to Na^+ influx. (leaky)	Due to equal efflux and influx currents.
Plateau	No presence of plateau.	Presence of plateau in Phase 2.
Resting membrane potential	The cells of the conduction system have no actual resting potential as the membrane potential does not stay the same due to leaky sodium channels. We also call it pacemaker potential and it equals -60mV.	The resting membrane potential equals -90mV.

From Abdelhadi

Neural cells (Neurons)

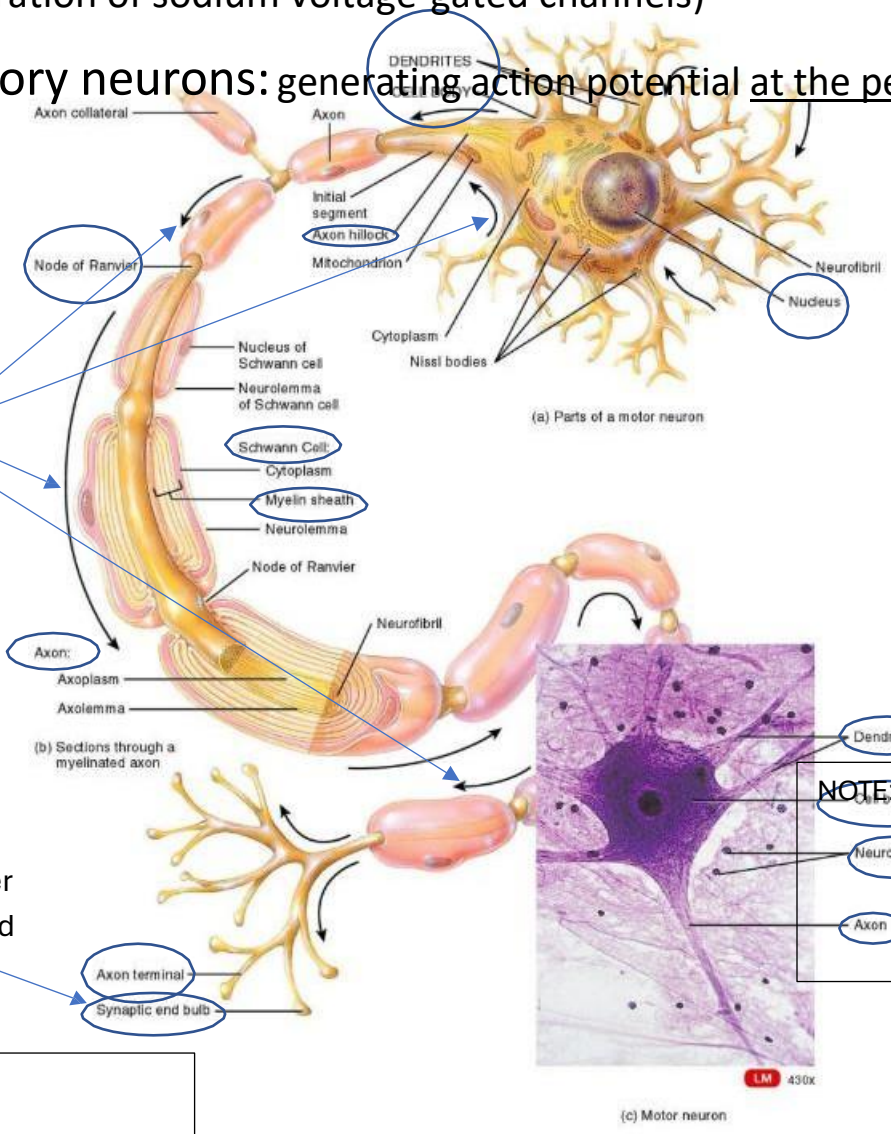
- Neural cells are very important in our body, it functions to generate Action potential and to have that action potential spreading towards termina, and the terminals are transmitting neurotransmitters, typically consist of 3 basics parts: cell body, dendrites, and axon (or nerve fiber).

We have two types of terminals.

-There are many types of neurons:

1-Motor neurons: generating action potential in **axon hillock,** which is the initial segment of the axon. (higher concentration of sodium voltage-gated channels)

2-Sensory neurons: generating action potential at the periphery.



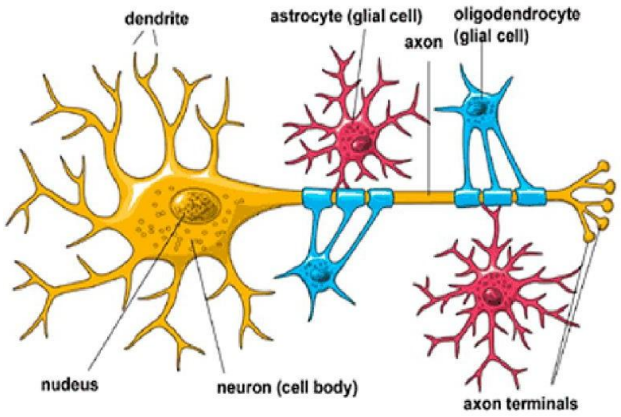
Direction of nerve impulse transmission

One type of terminals where neurotransmitter is stored in vesicles and ready for the release

NOTE:

الشغلات المهمة عليها دائرة

-Around the neurons, there are linkage cells which are called **Supportive cells (Neuroglial cells),** to support the function of neurons.



Some functions of supportive cells:

1- Keeping clear media around neurons (ECM) which is called cerebrospinal fluid (this fluid is circulating between neural cells to provide them nutrients).

- How can they clear the media? by uptaking of K+ and neurotransmitters from the interstitial fluid around the neurons.

Why do we need this media (CSF) to be clear? To get optimal functions of the neurons

2- Synthesize and release **neurotrophic factors** → keep the survival of neurons for all our lives (relatively long duration) because neurons are non-dividing cells, so they need to be alive for all our lives. (neurons capture these factors via its dendrites)

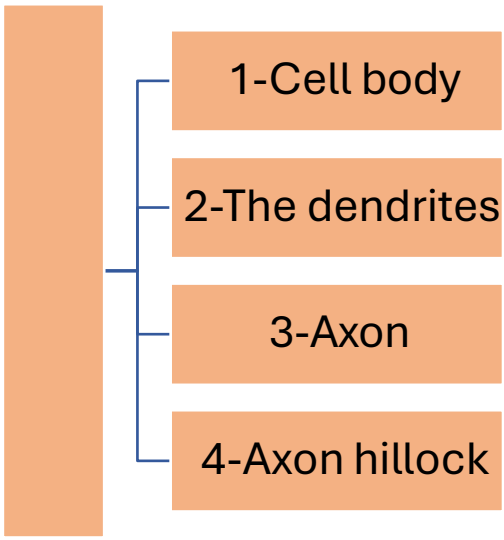
3- Other specialized supportive cells are responsible for myelination of axons. In the CNS these cells are oligodendrocytes. In the peripheral nervous system, these cells are known as Schwan cells. These cells wrap axon segments and secrete myelin sheath (a protein lipid complex that insulates nerve fiber). There are gaps in myelin sheaths known as nodes of Ranvier, which appear at intervals along axon. These gaps (nodes of Ranvier) are used for transmission of impulse along myelinated nerve fiber.

***NOTE:** There is a barrier between the blood and the structures of the brain called brain blood barrier (BBB) that prevents substances from passing from blood toward the structures of the brain and allows specific particles to pass.

4- Some of these supportive cells function in phagocytosis of pathogens that penetrate the BBB (this rarely occurs) those cells are called microglial cells.

Conduction of impulses

A little recap:



-Now the ends of each axon are called the axon terminals, these can be connected to other cells such as muscle cells and other neurons.

-The **axon hillock** (**also known as the trigger zone**) is the small part between the **axon** and the **cell body** and it's the site of action potential generation in **motor neurons**.

-While sensory neurons generate action potential at the terminals which travel along the axon towards the CNS to be processed.

-**SYNAPSE**: is the connection between a terminal of a neuron and the membrane of another.

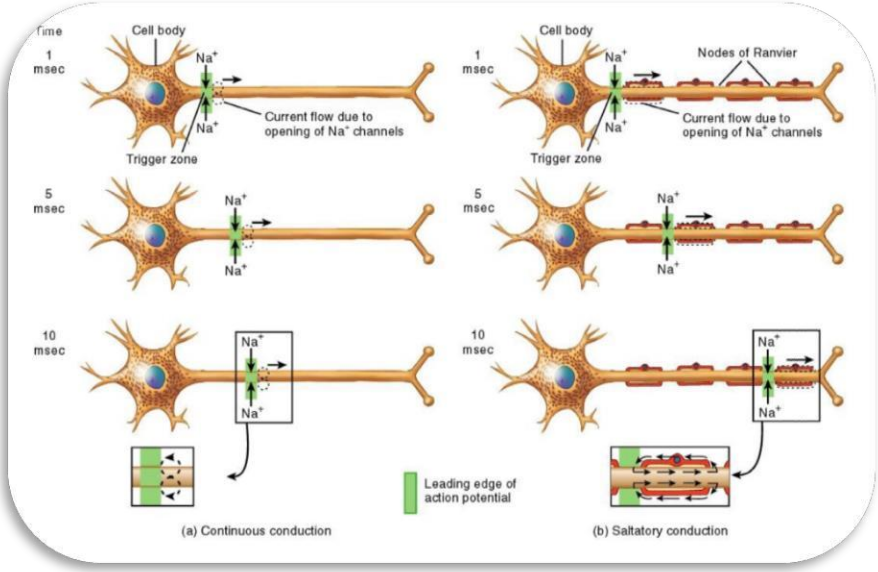
-**Note**: The term **TRIGGER ZONE** is **only** used for **motor neurons**.

Types of neurons-

-We have two types of neurons:

1-Myelinated neurons.

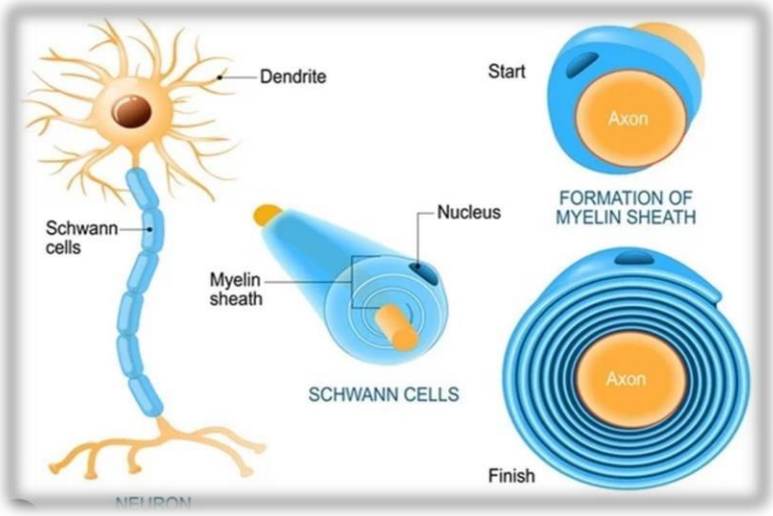
2-Un-myelinated neurons.



-Now you might ask what is myelin?

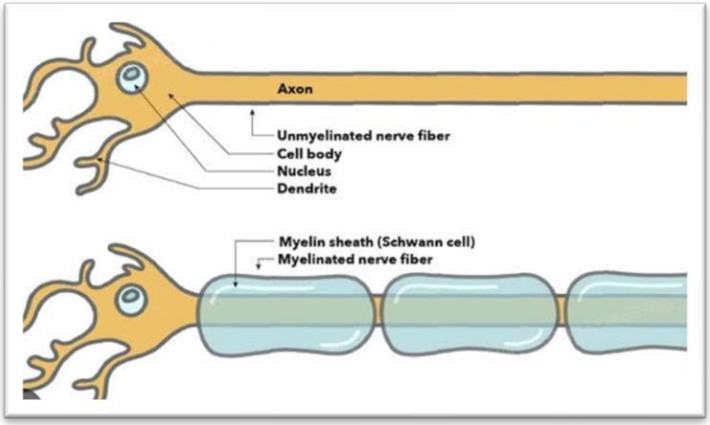
(**Myelin**: is the sheath wrapped around some axons, it enables electrical impulses to transmit very quickly along the nerve cells and it's made up of **Sphingolipids**).

-The supportive cells called SCHWANN CELLS wrap around the axons secreting huge amounts of myelin hence, forming many layers around the axons and neurons (**these neurons are myelinated neurons**).

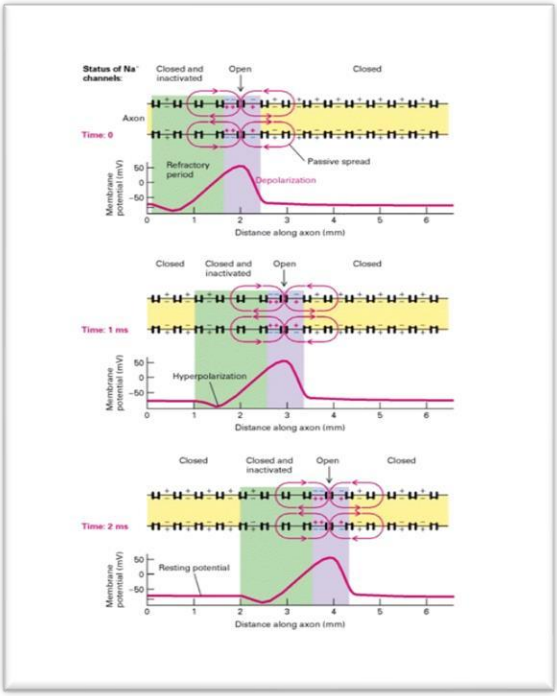


-The myelin sheaths themselves aren't able to conduct electrical impulses, so how are the electrical impulses transmitted in myelinated neurons?

Myelinated neurons contain un-myelinated gaps between their myelin sheaths called **NODES OF RANVIER** at which the current will skip to and from this is called **SALTATORY CONDUCTION**. This enables the electrical impulses to move faster across the nerve fiber.



-The transmission in un-myelinated neurons is much simpler and slower as the propagation of electrical impulses continues along the whole length of the nerve fiber.



-Now what actually causes this propagation?

The propagation is simply caused by the action potential, which is caused by the depolarization of the sodium and potassium channels (**as previously explained**).

The diameter of the axon is directly proportional to the conduction velocity of the action potential because the resistance of the current inside the axon is lower.

The saltatory conduction is 50 time faster than continuous conduction.

-Refractory period

-When a region has already experienced an action potential it will start going through **THE REFRACTORY PERIOD**.

-What happens during the refractory period?

The **sodium channels** are inactivated (**closed and not capable for opening**) while the **potassium channels** are activated (**opened**). This limits the rate at which action potentials can be generated as the next region is undergoing resting potential.

For clarity: We are talking here about the relative refractory because the segment should reach the overshoot (positive inside to make a current of cations) in order to transmit the action potential to the one after, so when it transmit the action potential and the segment after reach the overshoot (it has the ability to transmit the action potential), the previous one will be after the over shoot so absolutely it will not be in the absolute refractory period, so that's why it is written that the sodium channels are closed.

- Now why is the refractory period important?

The refractory period ensures that the action potential will only propagate in one direction, resulting in the depolarization of the next region while the previous region gets hyperpolarized.

If the action potential starts from the middle of the axon, it will be propagated in two directions, but when it reaches the soma, it will decrease until it disappears, so it will only be propagated in the other direction.

NOTE: this occurs in all types of neurons “unmyelinated and myelinated” however, in myelinated it **only occurs in nodes of Ranvier** and not Schwann cells.

-**Now to sum it all up: action potential is unidirectional**

Refractory periods of an action potential:

During an action potential, the cell is not able to respond to another stimulus. From the firing stage to the end of the first third of falling phase the cell will not respond at all even by a stronger stimulus. In this stage the cell is said to be in **absolute refractory period**. From the beginning of the second phase until the resting membrane potential is achieved, the cell cannot respond to the usual stimulus, but a stronger stimulus c change the membrane potential. In this period, the cell is in **relative refractory period**.

The periods depend on the activity of Na+ channels. These channels pass three states during action potential. During resting potential, Na+ channels are **closed but capable for opening** when stimulated. During the raising phase (firing), almost all Na+ channels are **opened**. And any other stimulus (even stronger one) will not cause activation of more Na+ channels. During this period, the membrane is in absolute refractory period.

In the third state, when voltage dependent Na+ channels become closed after the membrane potential has reached positive values. At this state, Na+ channels are not capable for opening. During all the falling phase of an action potential, these channels remain **closed and not capable for opening**. They can pass to the first state (closed and capable for opening) when the membrane potential returns to its normal level or to a more negative potential than resting potential. During this period, the membrane is in relative refractory period. This means that a stronger (suprathreshold) stimulus may activate the closed channels that are not capable for opening by normal stimulation. In addition to the role of voltage gated Na+ channels in establishing the relative refractory period, the presence of widely opened K+ channels during falling phase, which cause excess flow of positive charges to the outside, may also play a role by opposing stimulating signals.

Na+ -K+ pump and action potential:

This pump has **no** role in the electrical activity that are taking place during action potential. But it plays an important role in restoring ionic composition that has been altered during action potential. This role is important in maintaining the ionic composition of the intra- and the extra-cellular fluids.

Nerve Cells (Neurons)

The nervous system is formed of neurons and supportive cells. A neuron, typically consists of 3 basics parts: cell body, dendrites, and axon (or nerve fiber). Dendrites are short projections from the cell body, which receive inputs from neighboring neurons. Axon is a long tubular like structure which projects from cone-shaped elevation in the cell body known as axon hillock (means small hill). The impulse begins at the junction between axon hillock and the initial segment of axon. Axon ends

into fine processes called axon terminals. Some of these terminals end with a bulb-shape structure called synaptic end bulb (synaptic knob), where neurotransmitter is stored in vesicles and ready for the release.

Many classifications for neurons are known, according to shape,

function, neurotransmitter they release, myelination, location…etc.

Supportive cells and function (NEUROGLIA):

Many types of supportive cells around neurons have been described (at least 6). Microglia, Astrtocytes, oligodendrocytes have been shown around neurons from the CNS. And glial cells which are similar to astrocytes from the CNS have been described in the neural network of the GI tract.

These cells perform the following functions:

*Maintenance of neural environment.

-uptake of K+ and neurotransmitters from the interstitial fluid around the neurons.

*Synthesize and release neurotrophic factors maintain the survival and protection of neurons

* Other specialized supportive cells are responsible for myelination of axons. In the CNS these cells are oligodendrocytes. In

the peripheral nervous system, these cells are known as Schwan cells. These cells wrap around axon segments and secrete myelin sheath (a protein lipid complex that insulates nerve fiber). There are gaps in myelin sheaths known as nodes of Ranvier, which appear at intervals along axon. These gaps are used for transmission of impulse along myelinated nerve fiber.

Test yourself

https://forms.gle/7SLeDammLntU4rAm9

Additional Resources:

For any feedback, scan or click the code.

Versions	Slide #	Before	After
V0 → V1			
V1 → V2			