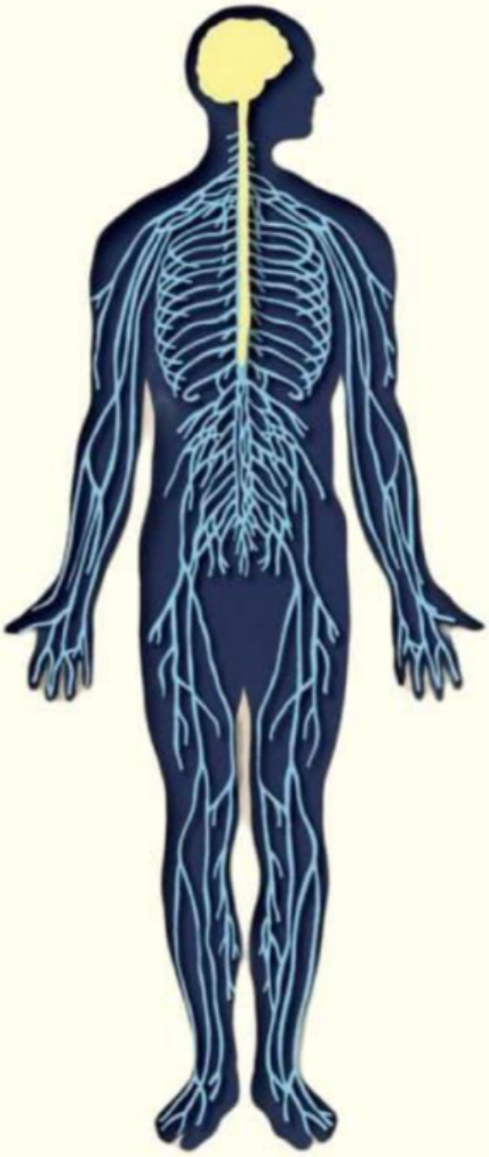
Wisdom
Dentistry 2023

SHEET NUMBER : 6,7



2023

PHYSIOLOGY

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Refractory periods

- ❖ It's a period where membranes stop responding by an action potential to stimuli and it depends on the activity of sodium channels.

There are two stages of it:

1) Absolute refractory periods: the channels are open making it impossible to respond to any kind of stimuli.

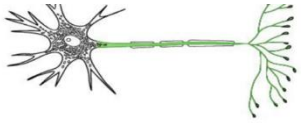
    *All channels are open.

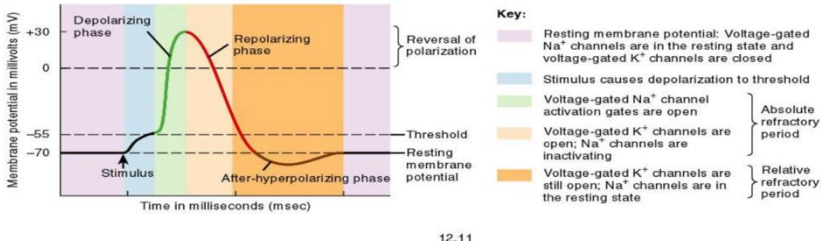
2)Relative refractory periods: they are closed and won't respond to stimuli except if the threshold stimulus was much stronger than usual called supra threshold stimulus occurs in the lab only.

*Some channels are open these channels won't respond.

In cardiac muscle cells the absolute refractory period is longer than other muscles to avoid another contraction before relaxation.

While the skeletal muscles have the shortest refractory periods because they are voluntary.





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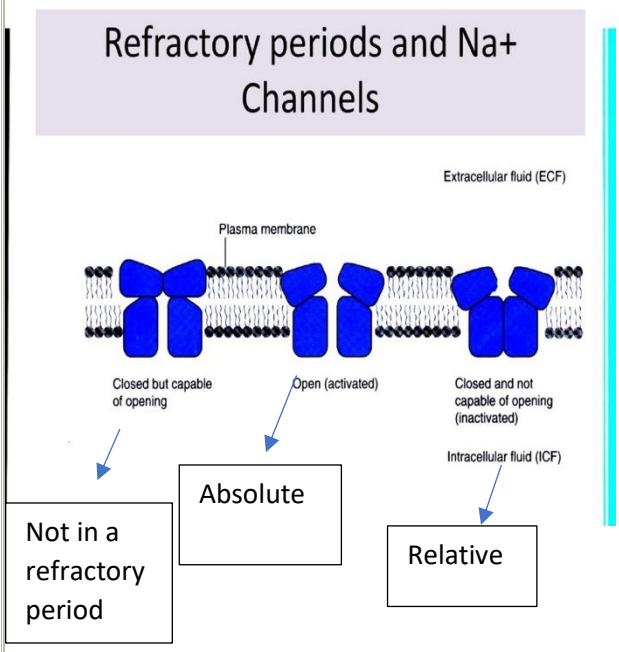
Sub threshold stimulus: a stimulus that is too small to produce an action potent in excitable cells.

Since this period depends on the Na+ channels we're going to talk about their three states:

1) Closed but capable of opening: during resting potential which is **not in a refractory period** and can open with usual stimuli.
2) Opened: during the firing phase any stimuli even the strongest one (absolute refractory period).
3) Closed and not capable of opening: during the falling phase and hyperpolarization they can go back to the first state when the potential is back to the resting state (relative refractory period) can be opened with supra-threshold stimulus only.



In addition to the role of voltage gated Nat 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

- What is the importance of having more sodium channels at the first state at the surface area that can define the threshold? Because the more negative tissue is considered as the more excitable tissues and at these tissues we have more of these sodium channels, neural cells for example have a resting potential of -80 while the threshold is -75 while skeletal cells have a resting potential of -70 and the threshold is -50 why are these channels closed at -70 in skeletal while being open in neural because we have less number of sodium channels at the state of closed and capable of opening in skeletal cells so we're not getting an action potential (so neural cells is said to be more excitable than muscle cells).

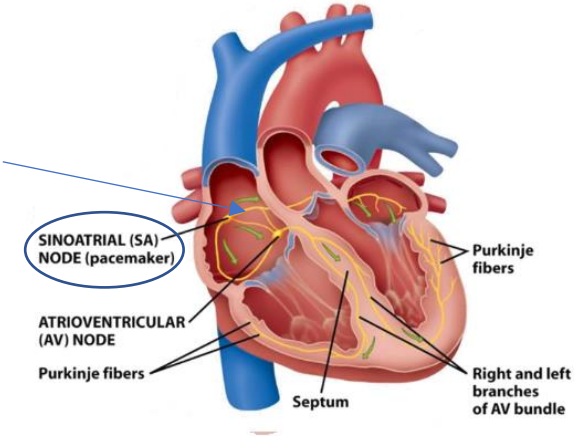
- But if we took two cells from the same type of tissue (similar resting potential and threshold) if one cell is less negative and closer to the threshold it's easier to stimulate it (the excitability for the similar cells can change according to each cell's membrane potential) so more negative potentials need stronger stimulus.

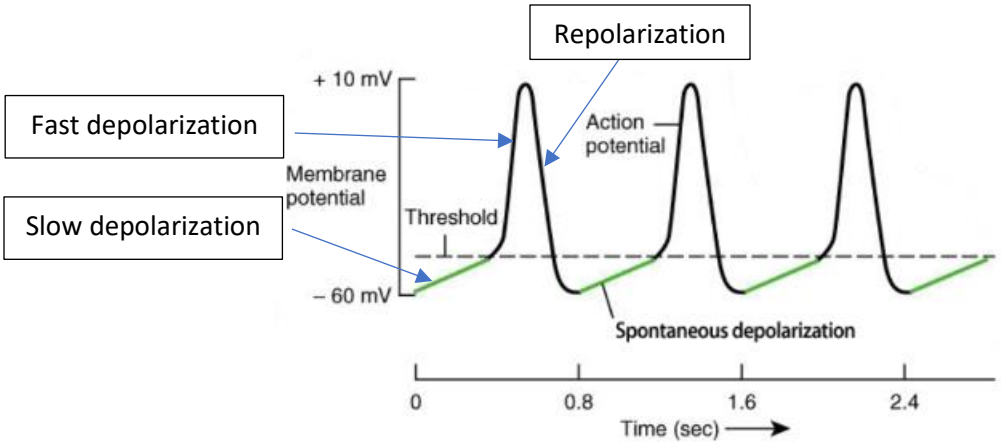
In tissues the more negative means more excitable while in similar cells the more negative needs a stronger stimulus.

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).

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





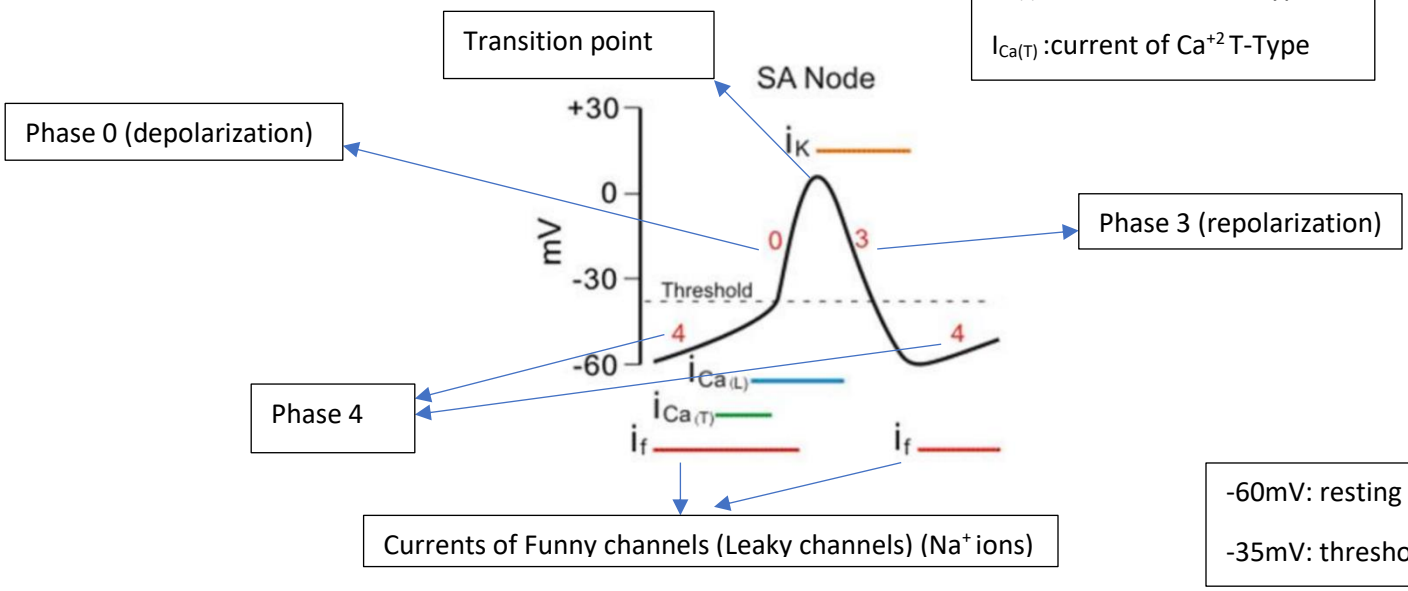
There are a lot of channels, and each channel will be activated at specific voltage point. Let's see an example for more understanding.

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



-60mV: resting point

-35mV: threshold

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)

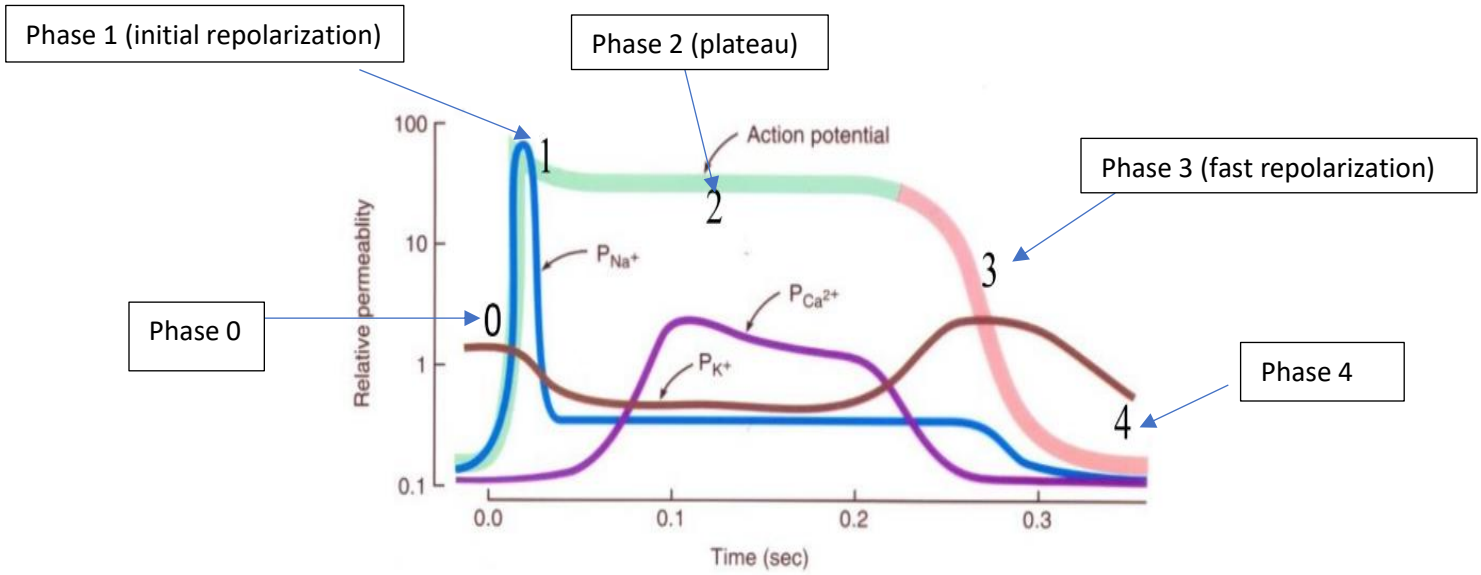
- The resting membrane potential will never reach -90mV due to the leakage of Na+ in phase 4.

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

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).

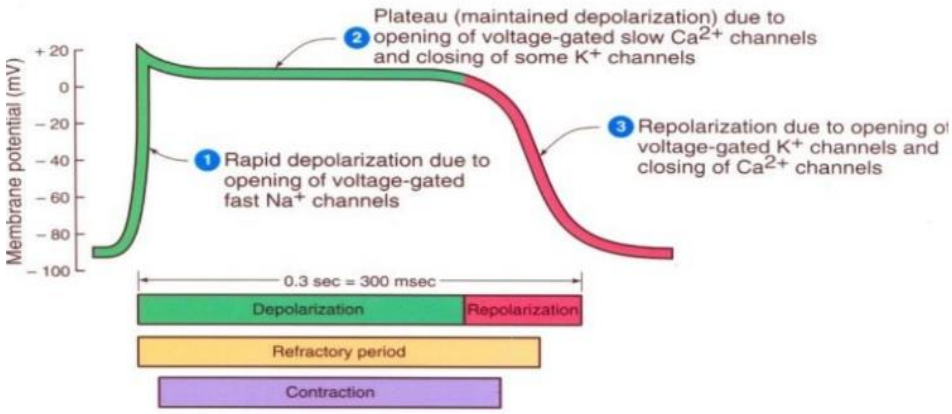
-our doctor didn't say the number of voltage difference at each phase.

- 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.

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

-Phase 4 (resting potential).



(a) Action potential, refractory period, and contraction

Look at this table.

	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 okasha

Neural cells (Neurons)

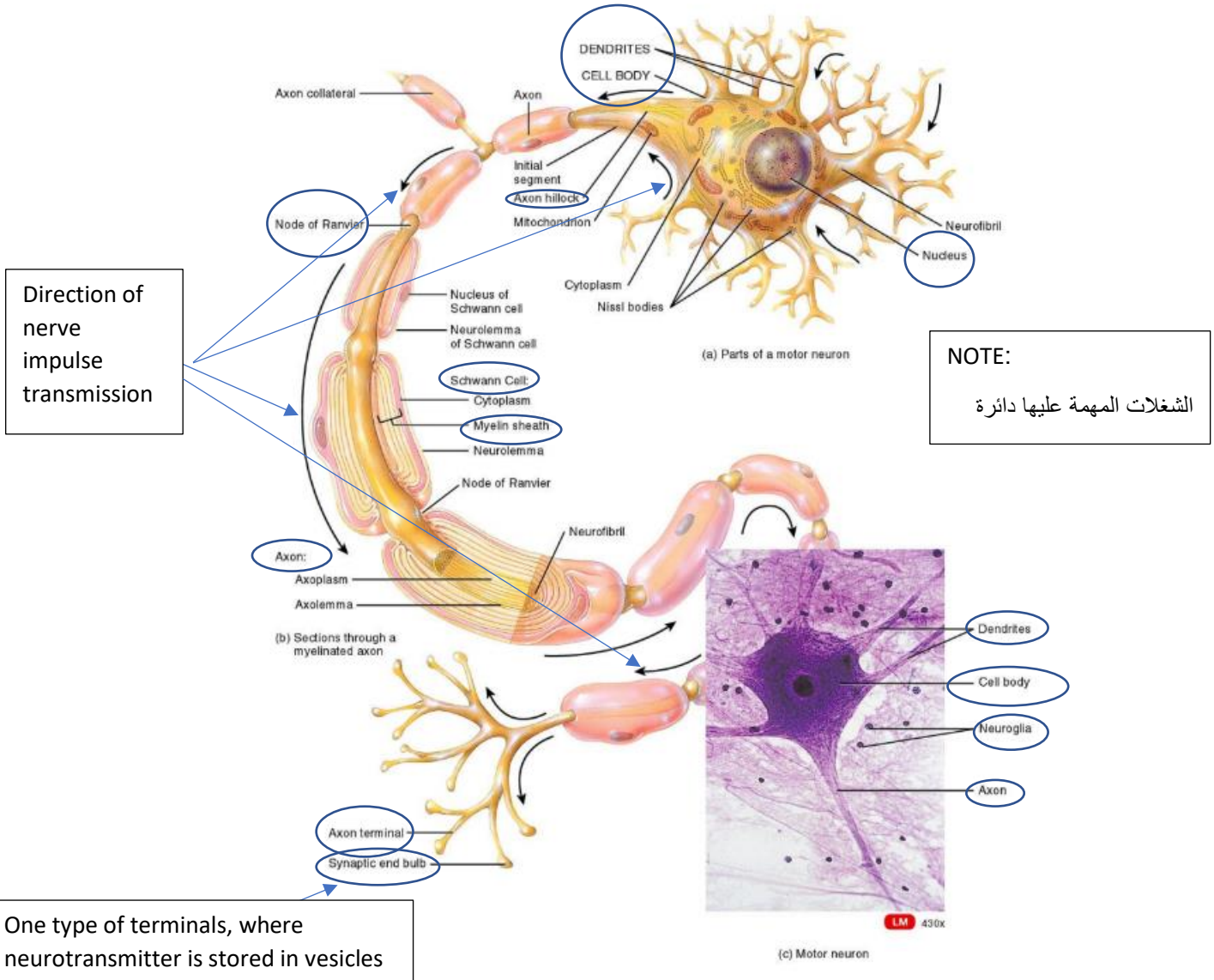
- Neural cells are very important in our body, it functions to generate Action potential and to have that action potential spreading towards termina, and the terminals are transmitting neurotransmitters, typically consist of 3 basics parts: cell body, dendrites, and axon (or nerve fiber).

We have two types of terminals.

-There are many types of neurons:

1-Motor neurons: generating action potential in **axon hillock** which is small part between the cell body and the axon.

2-Sensory neurons.



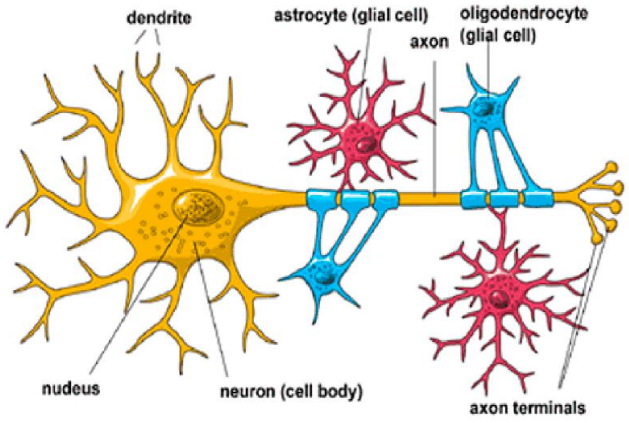
Direction of nerve impulse transmission

NOTE:

الشغلات المهمة عليها دائرة

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

-Around the neurons, there are linkage cells which are called **Supportive cells (NEUROGLIA),** 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.

2- Synthesize and release neurotrophic factors ⟶ maintain the survival and protection of neurons

3- Other specialized supportive cells are responsible for myelination of axons. In the CNS these cells are oligodendrogliocytes. 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 are used for transmission of impulse along myelinated nerve fiber.

***NOTE:** there is a barrier between the blood and cerebrospinal fluid called blood brain barrier (BBB) that prevents substances pass from blood toward cerebrospinal fluid and allows to specific particles to pass.

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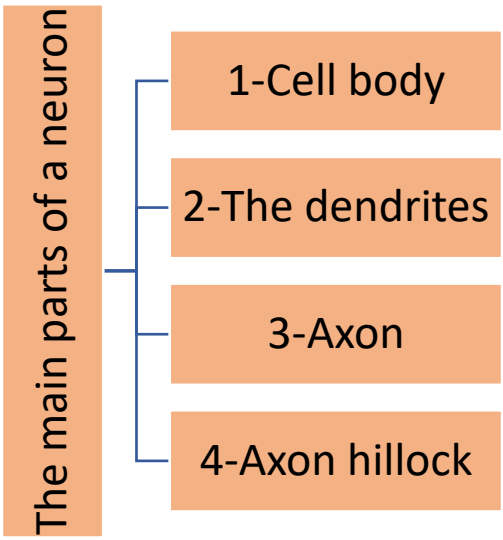
وما سعى ساعٍ الا استطاع

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 travels along the axon towards the other terminals they are **synapsing** with.

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

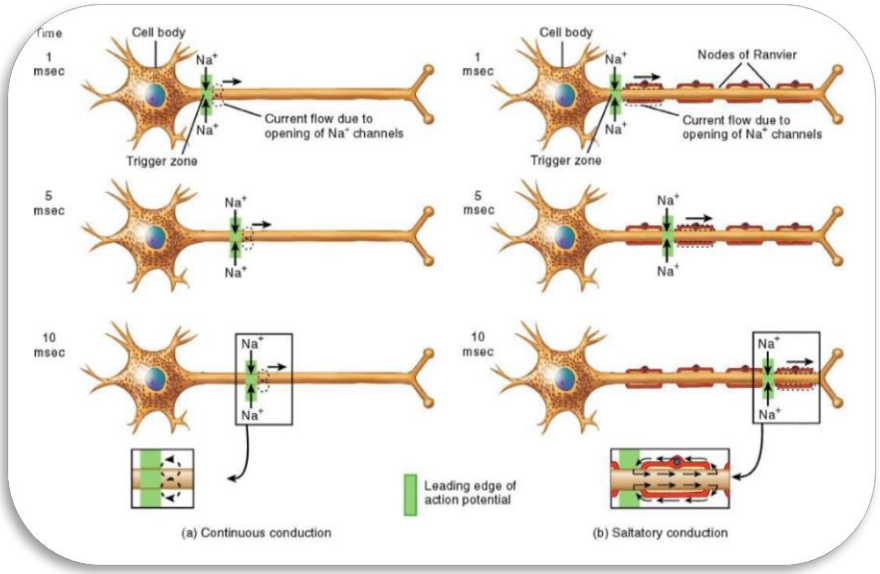
-**Note**: The term **TRIGGER ZONE** is **only** used for **motor neurons**.

Types of neurons-

-We have two types of neurons:

1-Myelinated neurons.

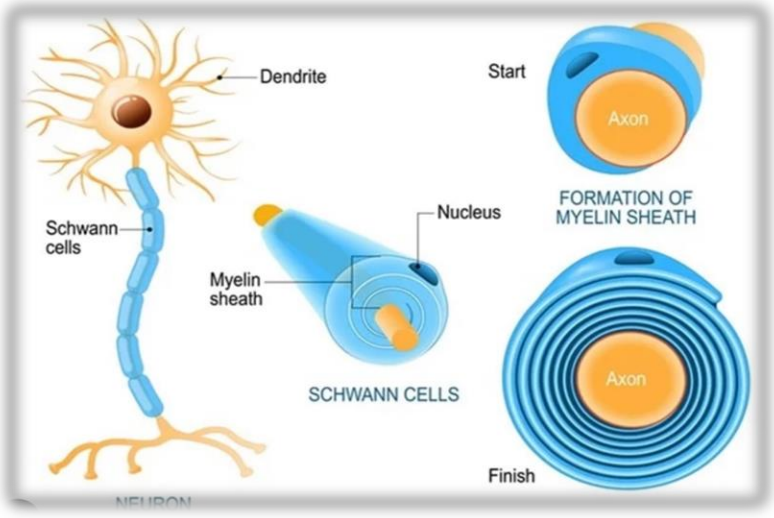
2-Un-myelinated neurons.



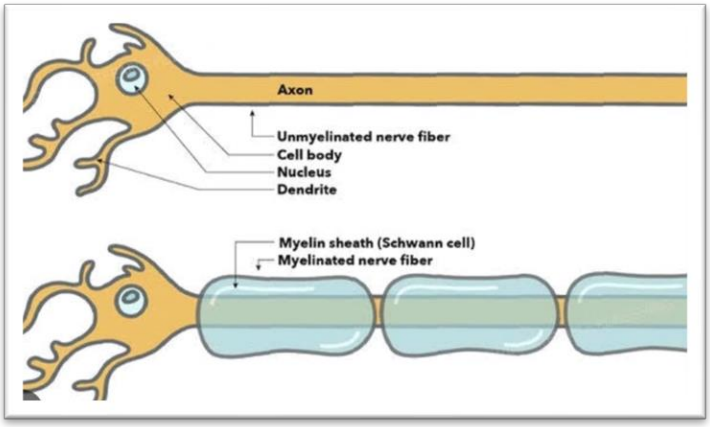
-Now you might ask what is myelin?

Myelin: is the sheath wrapped around some axons, it enables electrical impulses to transmit very quickly along the nerve cells and its made up of **sphingolipids.**

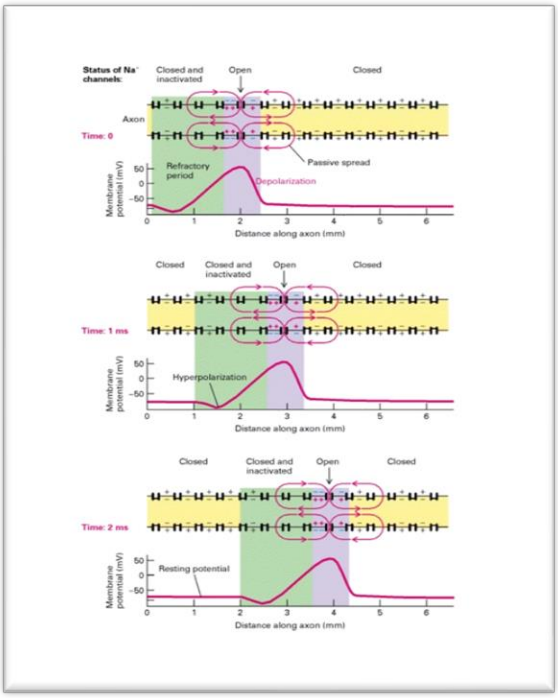
-The supportive cells called <u>SCHWANN CELLS</u> wrap around the axons secreting huge amounts of myelin hence, forming many layers around the axons and neurons (**these neurons are myelinated neurons**).



-The myelin sheaths themselves aren't able to conduct the 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 is 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**).

-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**) 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.

- Now why is the refractory period important?

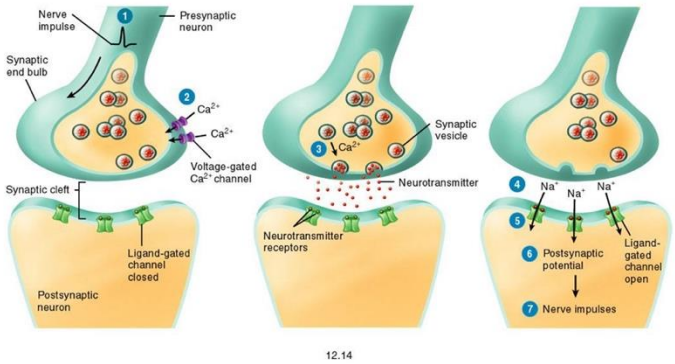
The refractory period ensures that the action potential will only propagate in one direction, resulting in the depolarization of the next region while the previous region gets hyperpolarized.

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.

Action potential across a synapse

-As we previously mentioned action potentials travel toward terminals and synapses.



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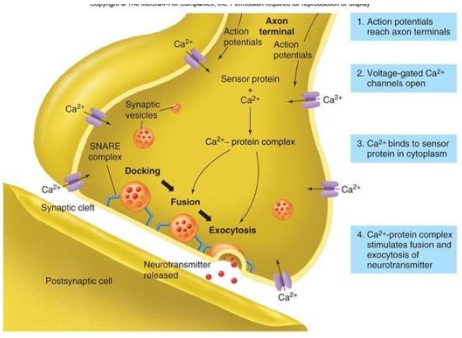
➡NOW once the action potentials reach the terminals neurotransmitters are released into the **synaptic cleft** "which is a small gap between the axon terminal of the presynaptic neuron and the membrane of the postsynaptic cell".

➡This is due to the terminal synapsing with a second neuron resulting in the formation of a synapse (**as shown in fig. 12.14**).



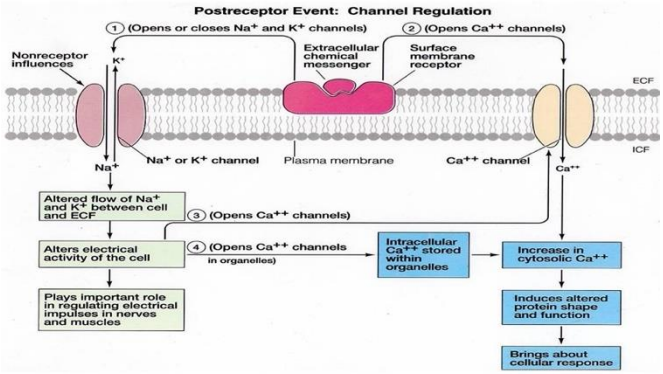
-BUT, how does an action potential cause neurotransmitters to be released?

➡When the action potential reaches the terminal of the presynaptic neuron, it activates the calcium voltage-gated channels present, causing them to open allowing calcium ions to enter the terminal increasing **Ca^{+2}** concentration inside the cell.

➡The calcium ions will bind to a sensor protein in the cytoplasm, stimulating the fusion of the neurotransmitters containing vesicles to the plasma membrane, resulting in the exocytosis of the neurotransmitters into the synaptic cleft.

➡ Now, the released neurotransmitters bind to their specific receptors present on the postsynaptic membrane "which are attached to either sodium or potassium channels, which will activate them".

➡ THE activation of sodium channels will cause depolarization, inducing **Excitatory Postsynaptic Potential** (**EPSP**) "In other words less negative but not reaching the threshold".

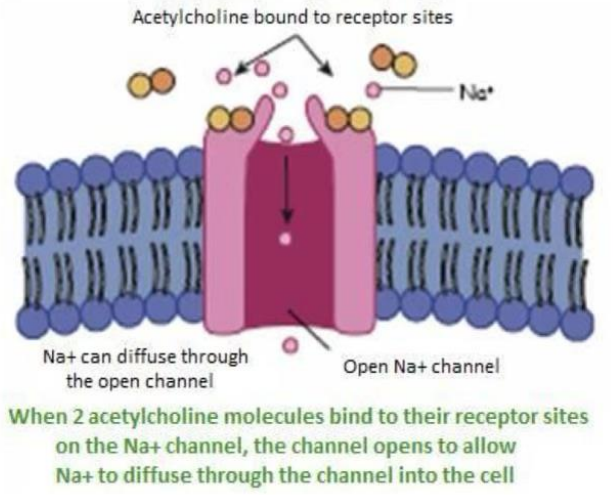


➡ While the activation of potassium channels will cause hyper polarization, inducing **Inhibitory Postsynaptic Potential** (**IPSP**) "In other words more negative but not reaching the threshold".

★ Doc example: "how do the calcium ions activate the release of neurotransmitters?

Answer: Simply imagine that these vesicles are negatively charged and the membrane on the inside is also negatively charged, this will cause repulsion hence the increase in calcium ions (**which are positively charged**) concentration will allow the vesicles to bind and release neurotransmitters."

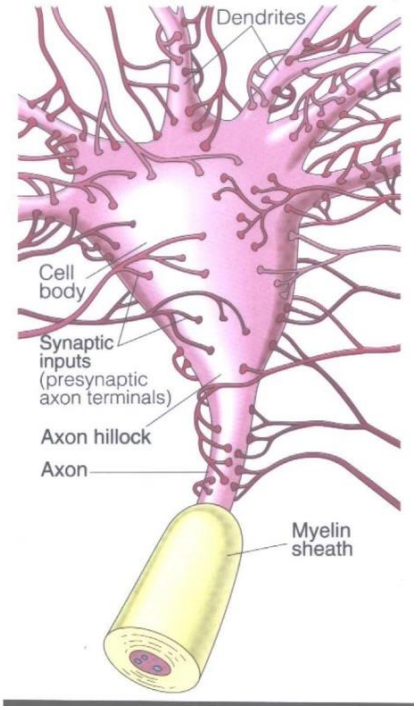
NOTE: increasing the concentration of the neurotransmitters will increase the chance of them binding to receptors.



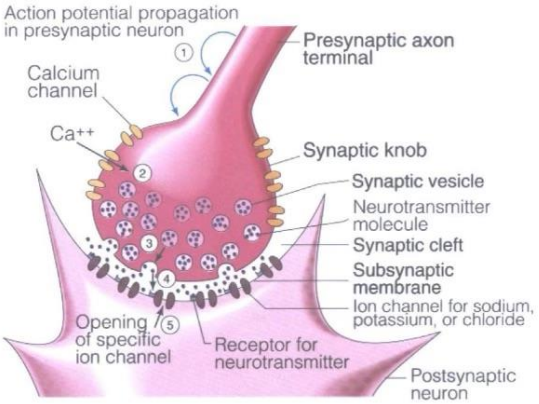
When 2 acetylcholine molecules bind to their receptor sites on the Na+ channel, the channel opens to allow Na+ to diffuse through the channel into the cell

➡ Acetylcholine is an example of neurotransmitters which causes **EPSP** as it binds to the receptor sites on the sodium channels causing them to open.

Synaptic structure and function

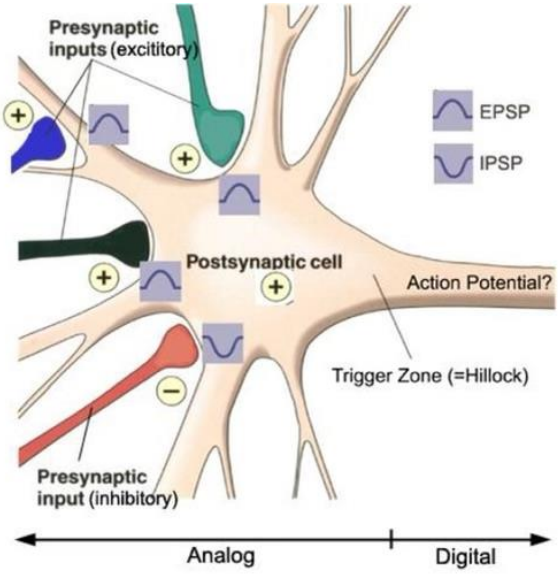


As shown here, most of the synapse are with the cell body, however you can still find some of them at the base of the dendrites

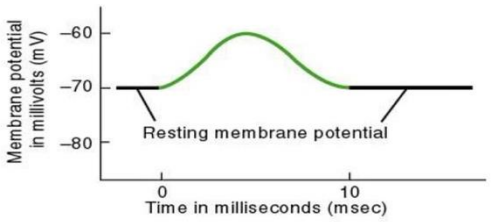


- Not all synapses will be able to cause **EPSP** and **IPSP**, some will cause **EPSP** while others will cause **IPSP**.

- The generation of action potentials depends on the summation of all potentials that reach the trigger zone "where a higher concentration of voltage-gated sodium channels is present" if the summation reaches the threshold only then an action potential is generated.



-**NOTE**: The activation of chloride channels is considered inhibitory to the postsynaptic neuron as many excitatory potentials inhibit the depolarization process. "Cause the threshold won't be reached."



(b) Depolarizing graded potential

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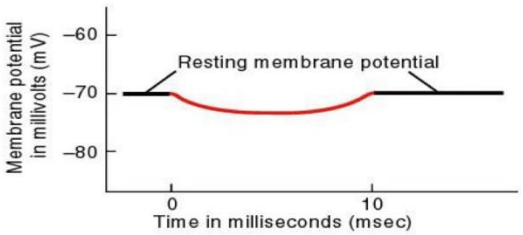
EPSP



(a) Hyperpolarizing graded potential

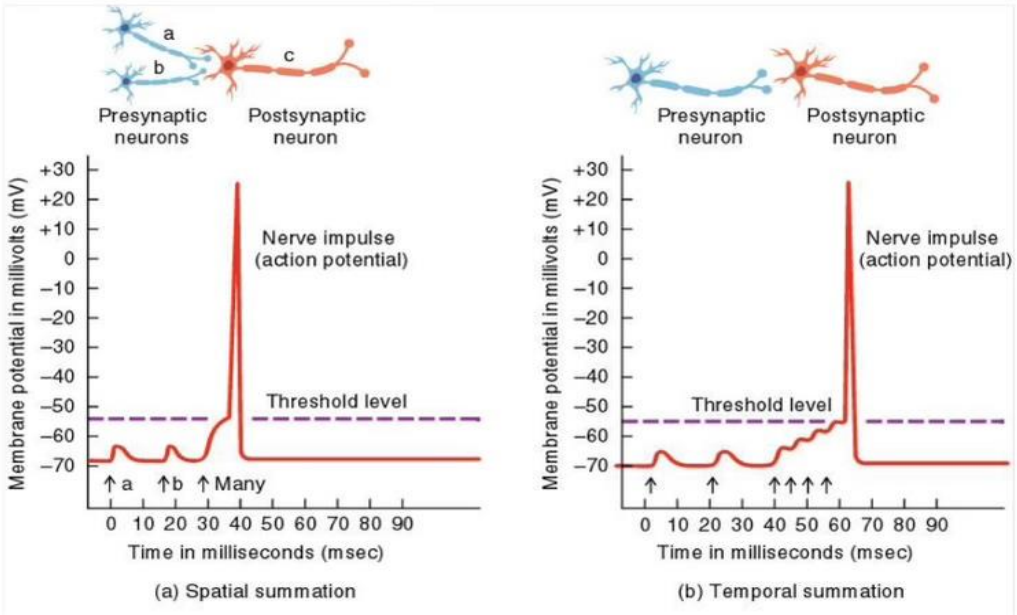
IPSP

-Summation of postsynaptic potentials

-There are two types of summation:

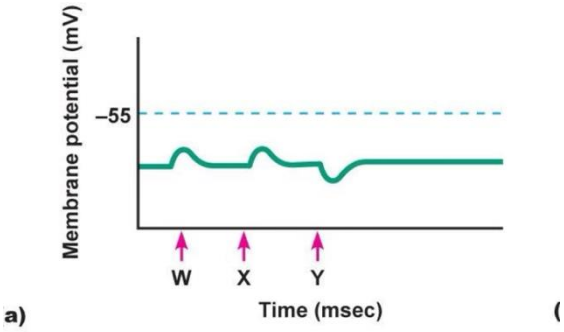
1)**Spatial summation**: The presynaptic neurons A&B can generate a small potential on their own, but together they generate a bigger potential that's enough to cross the threshold (**this is shown in figure a**).

2)**Temporal summation**: The presynaptic neuron will be affected by many stimuli generating many small potentials which together are enough to reach the threshold (**this is shown in figure b**).

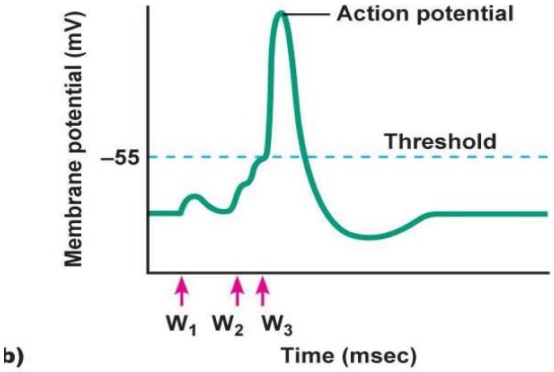


In spatial summation the neurons work at the same time while in temporal summation the neuron generates the potentials at different times.

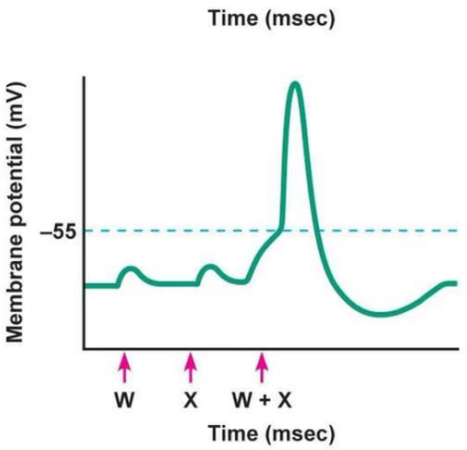
The duration of the generated action potential is less than that of the excitatory potential.



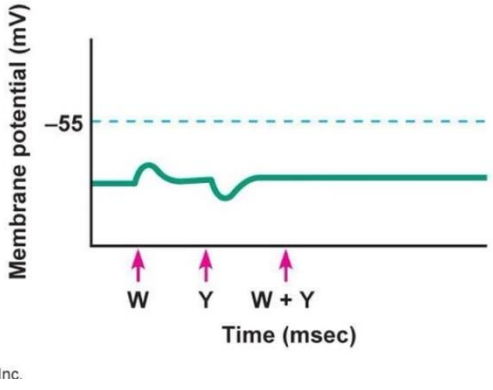
One stimulus causes depolarization while the other causes hyper-polarization hence they cancel each other out.



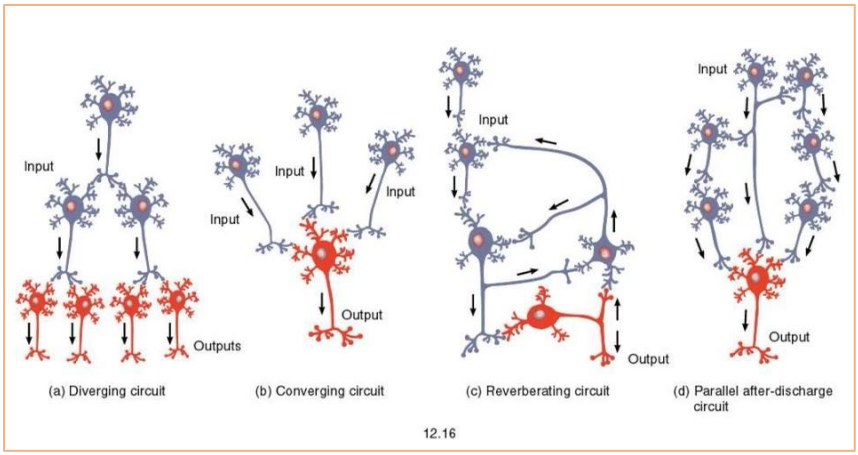
Many stimuli are generating Action potential “in other words **Temporal summation**”



These 2 are spatial summation



-Synaptic organization



- Neurons are organized in various methods in our nervous system:

1)Diverging circuit: this is basically when one presynaptic neuron has many terminals synapsing with different types of neurons.

2)Converging circuit: is when many presynaptic neurons with only **SOME** terminals from each neuron synapsing with one post synaptic neuron.

3)Reverberating circuit

4)Parallel after-discharge circuit

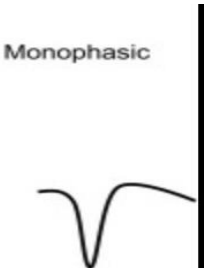
The doc said that only the first two are important, the last two wont be discussed.

-Monophasic VS Biphasic action potentials

- Monophasic action potential is recorded by placing one electrode inside while the other one stays outside, the recording acquired could be either positive or negative "**<u>can't be both</u>**".

- Biphasic action potential is recorded by placing the two electrodes outside, the recording acquired can be **positive** "during the first wave/depolarization" and **negative** "during the second wave /repolarization."

Now, how can we record an action potential by placing the two electrodes outside (Biphasic action potential)?



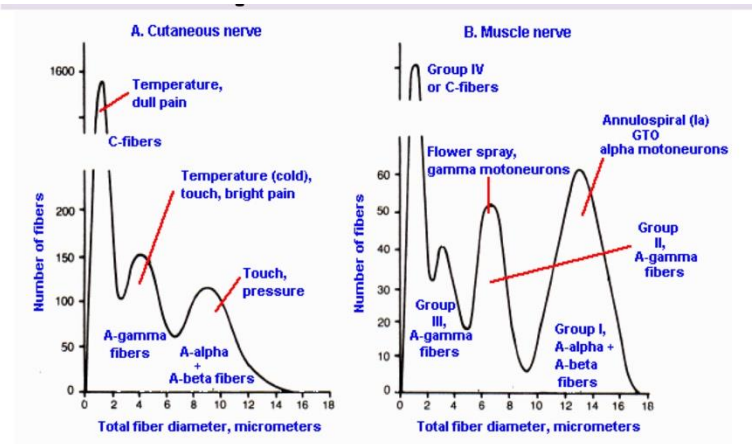
-When we place the 2 electrodes outside while the membrane is at resting potential the difference in voltage will be **zero**.

-However, once we start generating an action potential and one area is being depolarized while the other is still undergoing resting potential, we will be able to record the action potential at that exact moment due to the difference in voltage "this is known as the first wave/depolarization."

-NOW, when the whole membrane becomes depolarized the voltage difference will return to **zero**.

-However, when repolarizing starts to occur in certain areas we will be able to detect the voltage difference again "this sis known as the second wave/repolarization" until the membrane goes back to its resting potential.

Compound action potential



-Compound action potential is the recording of the sum of all recorded action potentials generated by all the nerve fibers "**<u>axons</u>**" at a certain point.

-If the length of the region on which the electrodes are placed on **INCREASES** we will have longer

splits in the records, this is caused by the difference in conducting velocities between nerve fibers.

- -This type of recordings helps us check the integrity of nerve fibers in a nerve.

NOTE: classifications of nerves will be discussed later on, however note that **ALPHA FIBERES** are the **FASTEST** in signal transmission.

Some important notes:

- What's the difference between conductance, permeability and driving force:

Conductance: measures the movement of charge across the membrane.

يعني قياس حركة الأيونات التي تنتقل فعليًا خلال الغشاء في هذه اللحظة

Permeability: measures the capability of ions to flow across the membrane regardless of whether they are moving across the membrane.

قياس سماحية الغشاء لنقل الأيونات خلاله بغض النظر عن انتقالها حاليًا أو لا

Driving force: gradients in the chemical potential, the electrical potential and the hydrostatic pressure which could result in a diffusion.

يعني هي القوى التي تعمل على نقل المواد خلال الغشاء مثل فرق التركيز فهنا تعمل القوة على نقل المواد من التركيز الأعلى للأدنى

- At what point of the action potential is the driving force for Na^+ and K^+ maximum:
  For **Na^+** is when the cell is the most hyperpolarized
  For **K^+** is when we're at the tip of the action potential
- The driving forces for sodium and potassium:
  Na^+: chemical gradient and electrical one because of the positive charge for Na^+ & the negative charge inside the cell
  K^+: chemical driving force pushes it out of the cell.

THE END OF SHEET

Please check on the professor's handout,
Very Important ..

University of Jordan
Faculty of Medicine
Department of Physiology & Biochemistry

Introduction Med, 2023/2024

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Membrane physiology and the basis of excitability

Ref: Guyton, 14th ed. 63-76, Jordan and 13th ed. pp: 61-71. 12th ed. pp: **57-69**,

MEMBRANE POTENTIALS AND ACTION POTENTIALS:

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 can

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, oligodendrogliocytes 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 oligodendrogliocytes. 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.

TANSMISSION OF ACTION POTENTIAL ALONG NERVE FIBERS:

Once an action potential is generated at the axon hillock, no more triggering events are needed to activate the whole nerve fiber (axon). The generated impulse is conducted along the nerve fiber by one of the followings 2 methods of propagation:

1. Continuous conduction (conduction by local current flow): occurs in unmyelinated fibers. Local currents flow between the active area, which is at the peak of action potential and the inactive area, which is still in resting potential. This flow will cause activation of Na+ channels in the inactive area and reduce

the membrane potential to the threshold, which triggers an action potential in this area (that was previously inactive).
This process is repeated all along the nerve fiber until the impulse has reached nerve terminals.

2. Saltatory conduction: In myelinated fibers, the impulse skips the myelinated regions in the axon and jumps from one node of Ranvier to the adjacent node. This process ensures faster propagation of an action potential along the myelinated axons (50 times faster than in unmyelinated fibers of the same size). The conduction also involves current flow between two adjacent nodes of Ranvier, which results in activation of Na+ channels in the adjacent node, which is still in resting potential. The process is repeated until the impulse activates the axon terminals.

Note: current flow in both types of conduction is from the **positively charged to the negatively charged regions at both sides of the membrane**, and the membrane has high resistance to the passage of current flow across it (**no** current flow can pass through the membrane).

Not only myelination can influence the velocity of conduction, but also the diameter of nerve fibers. Larger fibers conduct impulse with higher velocity.
Nerve fibers have been classified in (A, which includes as subtypes (α, β, γ, δ) fibers, B, C). The diameter and the velocity of conduction is the highest in Aα, and is the lowest in C fibers.

The importance of refractory periods in conduction:

The presence of refractory periods during action potential is very important in the conduction of impulse. The refractory periods ensure the **one-way (unidirectional)** propagation of action potential. Once an area has developed an action potential, the previous region is still under refractory period (unresponsive area). This area will not develop another action potential. But the following area that is at resting potential is capable to initiate an action potential.

SYNAPSES AND INTEGRATION OF RESPONSES:

Synapses:

Neuron may terminate at one of three structures: a neuron, a muscle, or a gland. The junction between 2 neurons is known as a synapse. The first neuron ends with end bulb (**synaptic knob**), where neurotransmitters are stored in vesicles and ready for the release. The membrane of the synaptic knob is known as **presynaptic membrane**. When secretory vesicles fuse with the presynaptic membrane, they release their content into a small space between two membranes known as the **synaptic cleft**. The released transmitters act on the second neurons by binding to their receptors at the second membrane, which is called **postsynaptic membrane** (**subsynaptic membrane**).

Synapses operate in one direction. Transmit signals from one neuron to an adjacent neuron. When the impulse from the presynaptic neuron reaches the synaptic knob, this will cause activation of voltage dependent Ca++ channels. This will result in Ca++ diffusion into the synaptic knob. The increase in Ca++ concentration inside the axon terminal will trigger the release of neurotransmitter from vesicles into synaptic cleft by a process of exocytosis. Inactivation of synaptic knob by inhibitory inputs that may synapse with the membrane at the nerve terminal may induce inhibition of the release of transmitter. This inhibition that appears at this site reduces the effectiveness of transmission in the synapse. This type of inhibition is known as presynaptic inhibition.

Once released, neurotransmitter binds to its receptor at the postsynaptic membrane. According to transmitter – receptor combination, this will induce either a decrease in membrane potential (depolarization) or increase in membrane potential (hyperpolarization). When there is a decrease in membrane potential, the developed postsynaptic potential is called **EPSPs** (**E**xcitatory **P**ost **S**ynaptic **P**otentials), while the increase in membrane potential is called **IPSPs** (**I**nhibitory **P**ost **S**ynaptic **P**otentials).

After inducing the appropriate response at the postsynaptic membrane, the transmitter is inactivated or removed, leaving the postsynaptic membrane ready to receive additional messages from the same presynaptic membrane. The inactivation of transmitter takes place by postsynaptic membrane bound enzymes. An example of these enzymes is *acetylcholine esterase*, which destroys acetylcholine (Ach) into acetyl and choline molecules, which then transported back to the synaptic knob, where they combine again to form new Ach molecules. Some types of transmitters are transported back, without inactivation, into

synaptic knob. Conditions that alter the activity of destroying enzyme, uptake of transmitter by nerve terminal, or induce release of high concentration of transmitter (presynaptic facilitation) alter the activity of synapse by prolonging the activation of receptors at the postsynaptic (subsynaptic) membrane. In addition to that, some drugs may combine with receptor and prevents binding of transmitter to its receptor. These drugs are known as **blockers**. An example of these is hexamethonium, which can bind to acetylcholine (Ach) receptor at postsynaptic membrane and prevents Ach from binding. This will inhibit transmission induced by Ach neurons.

The EPSPs are not action potentials. They are small depolarization (subthreshold potential) that can be induced by activation of few Na+ channels.

The IPSPs are usually induced by activation of K+ channels. Which result in efflux of K+ and change in the membrane potential to more negative potential. Some transmitters activate Cl- channels, the activation of these channels will not induce hyperpolarization (during rest, neural cell is near the E_{cl}, and the opening of Cl- channels will not induce inward diffusion of Cl-). But this activation is inhibitory on neural activity. This inhibition is achieved by holding the membrane at its resting potential and preventing depolarization.

The time it takes for a signal from the first neuron to induce changes in membrane potential in the second neuron is known as **synaptic delay**.

Integration of responses at postsynaptic membrane:

Usually, the complexity of neural network connections permit synapsing of many axonal terminals from different neurons to one neural cell body (called **convergence**), and branching of one nerve fiber to many terminals that synapse to different neurons (**divergence**). This complexity results in converting the signal from one neuron to many postsynaptic neurons in the case of divergence, and many inputs from presynaptic neurons can be received by a single postsynaptic neuron in the case of convergence.

As mentioned before, one stimulus may induce depolarization or hyperpolarization at the postsynaptic membrane. The induced depolarization is not an action potential, but it is a subthreshold potential. The action potential will develop only when the threshold is achieved. In a neural network, to have subthreshold potentials eliciting an action potential, **summation** (two depolarizations can sum to elicit a higher

depolarization) must take place between responses at the postsynaptic membrane.

Two types of summation are known at the postsynaptic membrane. **Spatial summation** appears when 2 or more responses from 2 or more different neurons have appeared simultaneously (at the same time) at the same site of postsynaptic membrane, which result in summing of these responses into a final response. This summation can take place between 2 or more IPSPs to elicit more hyperpolarization, two or more EPSPs to elicit more depolarization in the membrane, or between excitatory and inhibitory potentials which results in cancellation of potentials and induce postsynaptic inhibition.

The second type of summation is called **temporal summation**. Appears when 2 or more postsynaptic potentials, which were elicited by **one** presynaptic neuron at different times, sum to induce more depolarization in the membrane potential. In this case, the repetitive excitation of postsynaptic membrane from a single input induces a higher depolarization that may elicit an action potential at the postsynaptic membrane.

Recordings of action potential:

Recording of **monophasic action potential** is by placing one electrode inside the cell and the other electrode outside the cell. While a different configuration of an action potential can be obtained by placing the two electrodes outside the cell membrane. The later recording is known as **biphasic action potential**. Two waves are obtained in the recording of biphasic action potential, the first represents depolarization, and the second is in the reverse direction of the first and represents repolarization.