Physiology | Lecture 13

Generation of action potential at Neural cells

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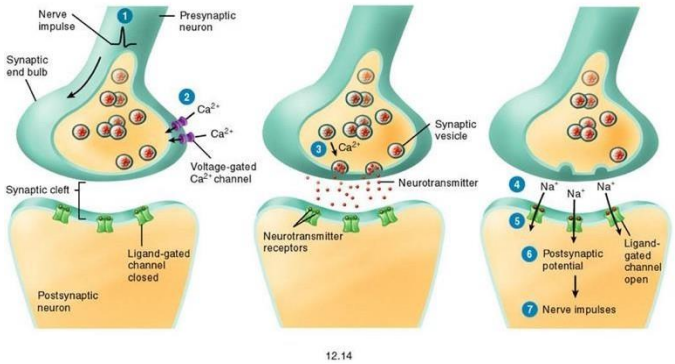
Action potential across a synapse

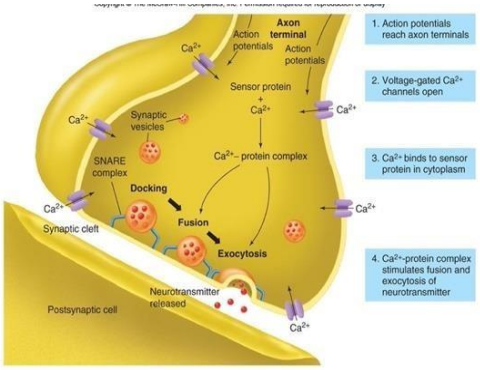
-As we previously mentioned action potentials travel toward terminals and synapses.



12.14

➡ 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**).



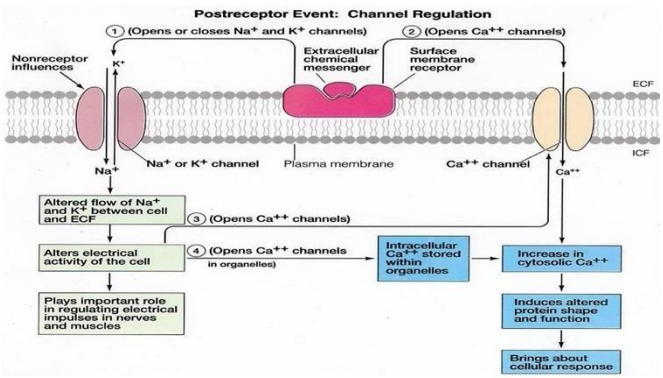
-BUT, how does an action potential cause neurotransmitters to be released?

➡ 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 types of channels which are activated determine the change in the potentioal.



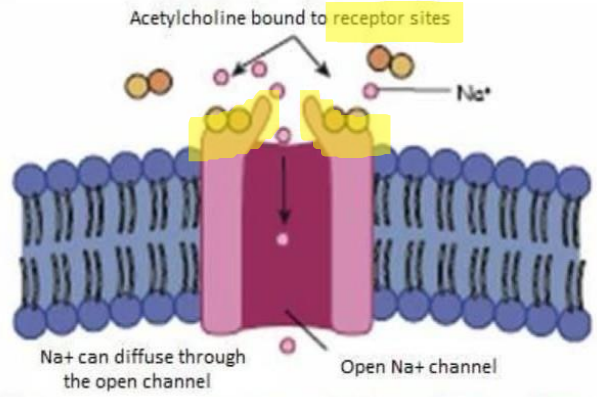
➡ THE activation of sodium channels will cause depolarization, inducing **Excitatory Postsynaptic Potential** (**EPSP**) "In other words less negative but not reaching the threshold."

➡ 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."

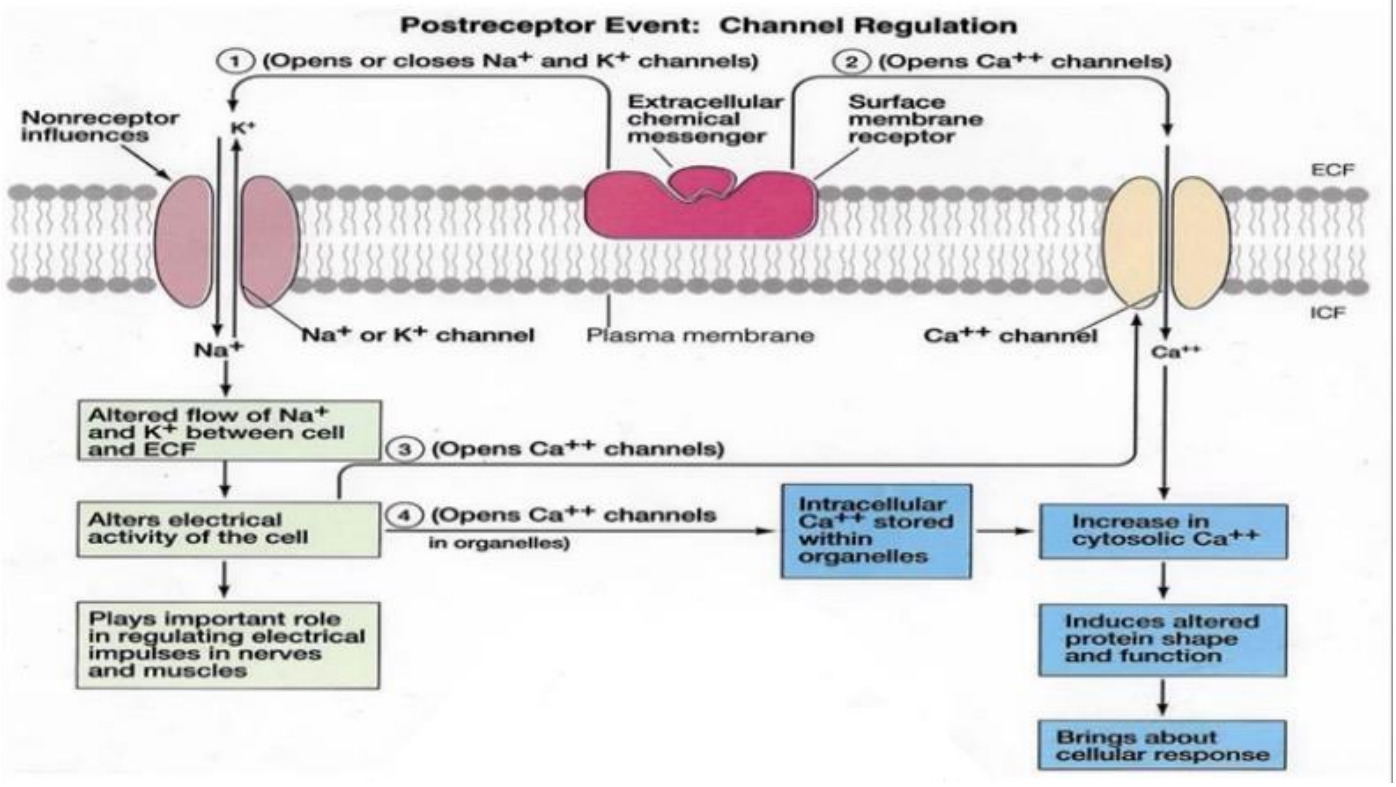
NOTE: increasing the concentration of the neurotransmitters will increase the chance of them binding to receptors.



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

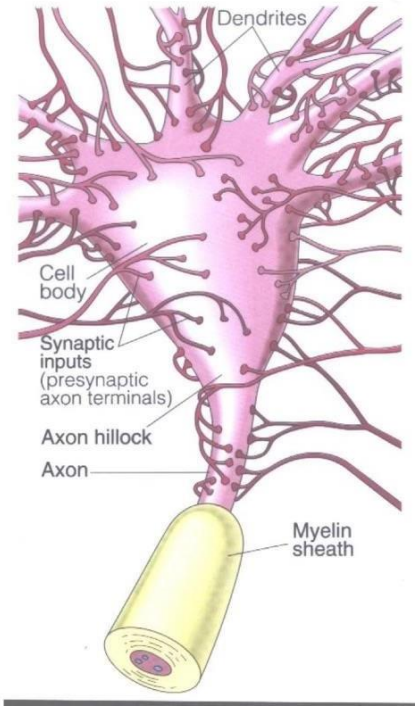
➡ Acetylcholine is an example of neurotransmitters which causes **EPSP** as it binds to the receptor sites on the sodium channels causing them to open.

Chemical gated Channels

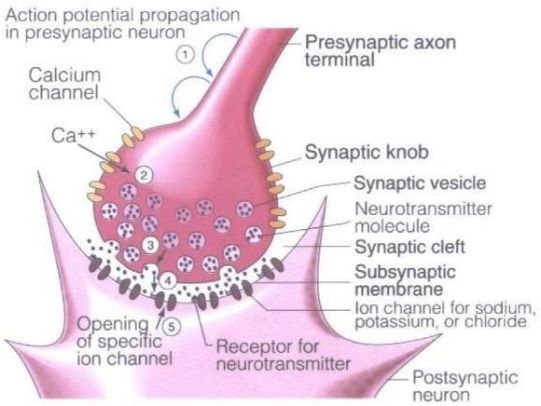


Receptors can influence ion channels either directly as ligand-gated channels (as the photo in the previous page for acetylcholine, look at the highlighted sites), or indirectly through G-proteins and second messenger pathways, which can modulate voltage-gated Na^+ and K^+ channels.

Synaptic structure and function

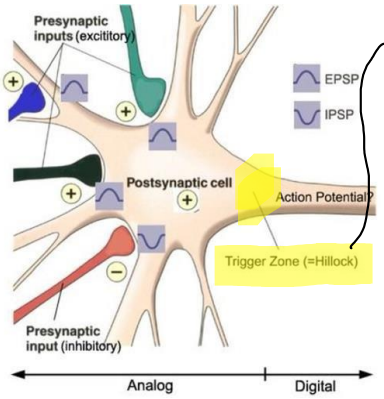


As shown here, most of the synapse are with the cell body, however you can still find some of them at the base of the dendrites



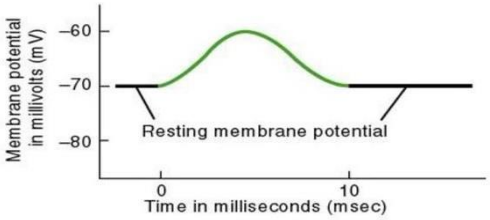
- Not all synapses will be able to cause **EPSP** and **IPSP**, some will cause **EPSP** while others will cause **IPSP**, depending on the type of activated channels.

- The generation of action potentials depends on the **<u>summation</u>** 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.



This is the place where the action potential is generated because of the presence of voltage gated channels. However, there is low concentration of voltage gated channels in soma and dendrites. There is a high concentration of chemical channels instade.

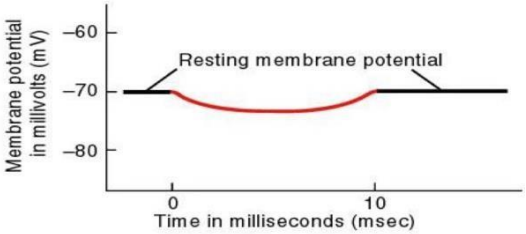
-**NOTE**: The activation of chloride channels is considered inhibitory to the postsynaptic neuron as many excitatory potentials inhibit the depolarization process. "Cause the threshold won't be reached."



(b) Depolarizing graded potential

12.10

EPSP



(a) Hyperpolarizing graded potential

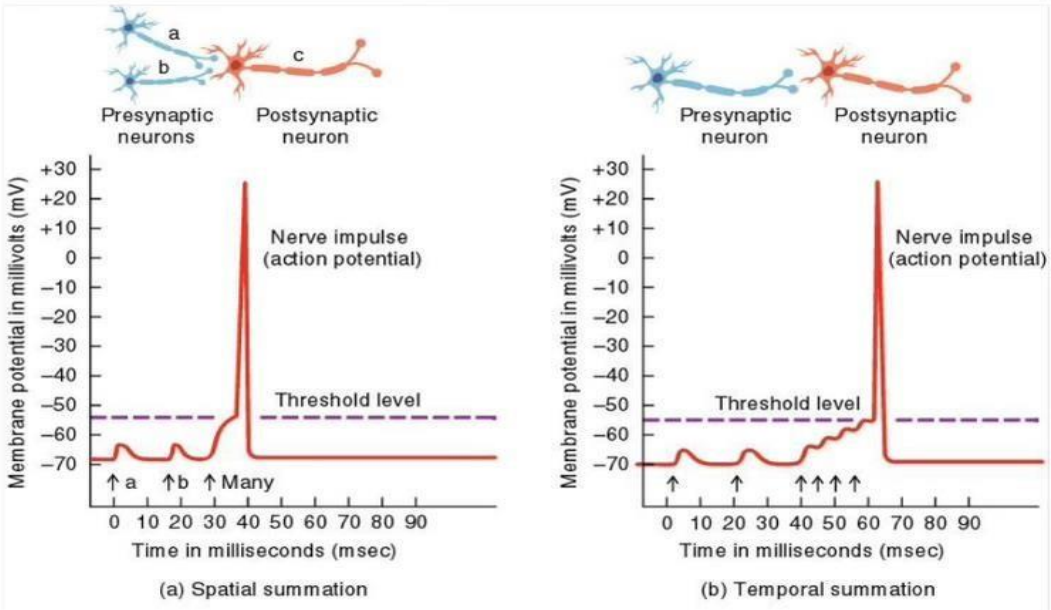
IPSP

-Summation of postsynaptic potentials

-There are two types of summation:

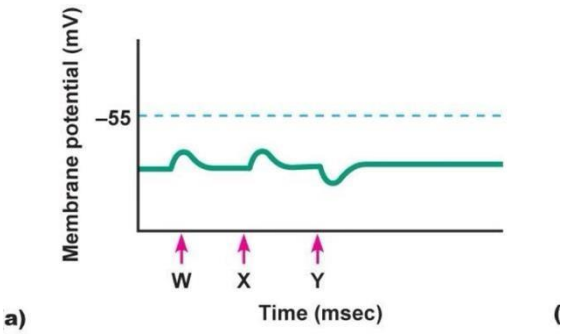
1)**Spatial summation**: The presynaptic neurons A&B can generate a small potential on their own, but together they generate a bigger potential that's enough to cross the threshold (**this is shown in figure a**).

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**).

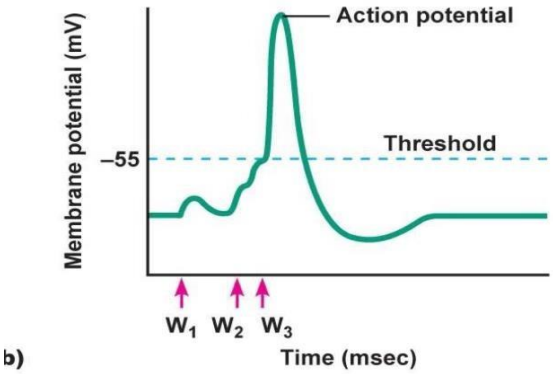


In spatial summation the neurons work at the same time while in temporal summation the neuron generates the potentials at different times.

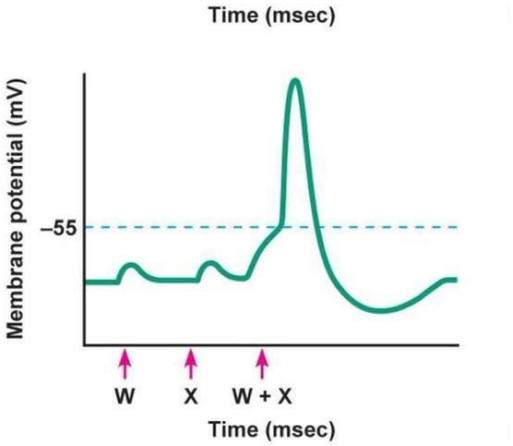
The duration of the generated action potential is less than that of the excitatory potential. We can see that in the previous photo.



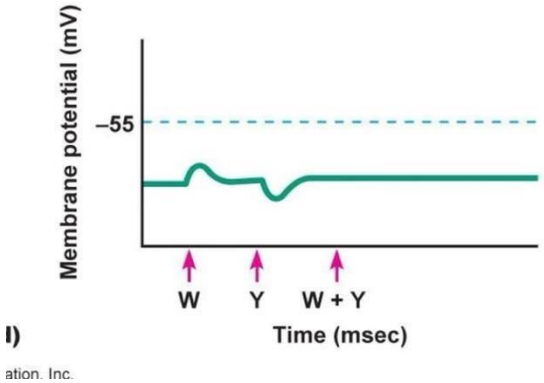
One stimulus causes depolarization while the other causes hyper-polarization hence they cancel each other out.



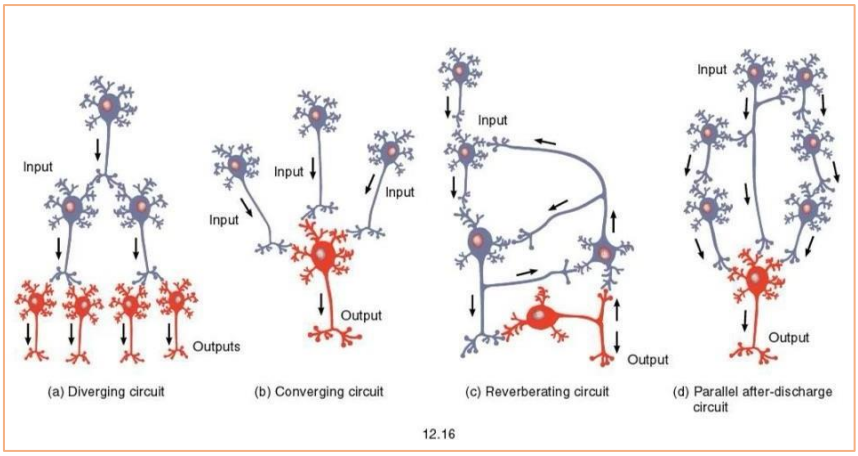
Many stimuli are generating Action potential “in other words **Temporal summation**”



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

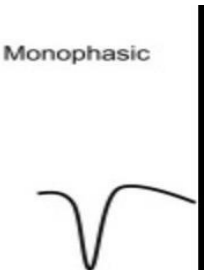
The doc said that only the first two are important, the last two wont be discussed.

-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.

Recording Electrical Activity in Nerves

What do we measure in nerves?

We measure the electrical activity called the Action potential, which is a change in membrane voltage caused by the movement of ions (Na^+ and K^+), not electrons.

How is the measurement done?

The measurement is done using two electrodes (+) and (−) **connected to a high-resistance device.** (this means All measurements are taken relative to a zero reference point.)

Usually we put the positive one outside and connect the negative one to high resistance (recording it to zero)

This allows the device to record the voltage difference without affecting the signal.

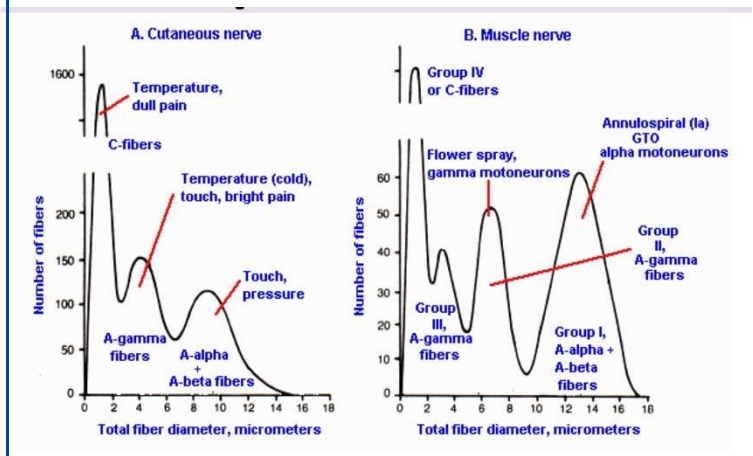
What is a nerve?

A nerve is a bundle of nerve fibers (axons).
Each fiber has a different conduction velocity, so signals do not arrive at the same time.

What happens when we stimulate a nerve?

When a nerve is stimulated:
All the fibers inside it generate action potentials
However, they do not all travel at the same speed
→ Fast fibers arrive first
→ Slower fibers arrive later

Compound action potential



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

It uses the same predicable for biphasic action potential.

-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.

It appears as multiple waves because fibers conduct at different speeds.

Fast fibers arrive first, while slower fibers such as C fibers appear later.

Early peaks → fast fibers

Later peaks → slower fibers such as C 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 خلالها 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.

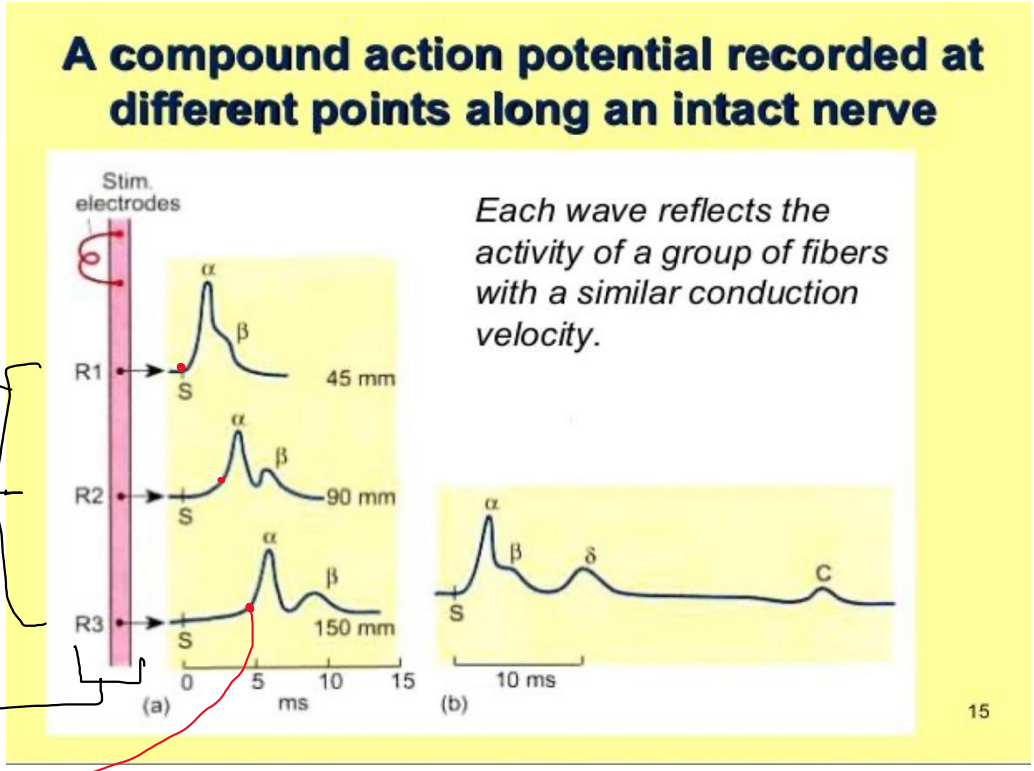
يعني هي القوى التي تعمل على نقل المواد خلال الغشاء مثل فرق التركيز فهنا تعمل القوة على نقل المواد من التركيز الأعلى للأدنى

- 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

recording points (electrodes) placed at different positions along the same nerve.
R1 → close to the stimulation point
R2 → a bit farther
R3 → even farther
We use them to have different recordings for the same event
Near recording site → single, sharp wave (minimal dispersion)
Intermediate distance → wave starts broadening and partially separating
Far recording site → clear separation of components due to different conduction velocities



This is a nerve

These red points are the start of the wave
Notice that we need more time in R3 because it is the furthest. So it has the lowest velocity

The time measured and shown on the right has clinical significance, as it is used to assess the functional efficiency of a nerve. By analyzing this value, we can determine whether the nerve is functioning properly or if there is an underlying problem. It also helps in identifying whether the issue is related to the alpha fibers or the beta fibers

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 chann pass three states during action potential. During resting potential, N 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

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.

Additional Resources

رسالة من الفريق العلمي:

دائماً فكروا بقوة الله، لاتفكروا بقوة الظروف.

For any feedback, scan or click the code.

Versions	Slide #	Before	After
V0 → V1			
V1 → V2			