PHYSIOLOGY

Lec: 16 (31/3)

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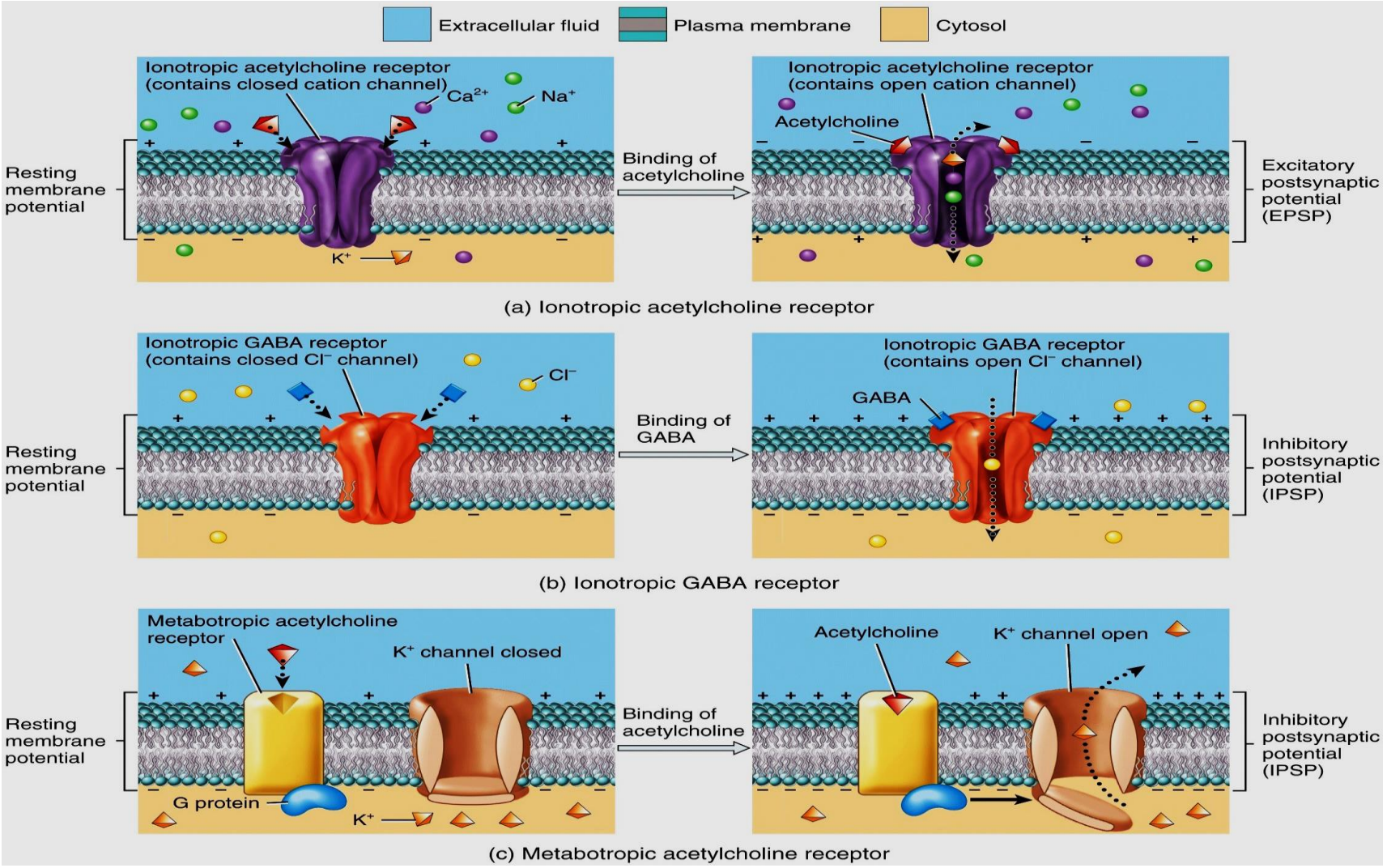
السلام عليكم و رحمة الله

بداية رمضان كريم علينا وعليكم جميعا يا رب، و تقبل الله صيامكم و قيامكم و طاعاتكم
بالنسبة لهذا التفريغ:
١- بعض الكلمات ما كانت واضحة بالريكورد ف بدي اعتذرعن أي خطا موجود مسبقا
٢- لما تدرس من التفريغ اسمع الريكورد بنفس الوقت، لأنه الدكتور كان بتنقل كثير بين
السالايدات و بالتالي ممكن تتخربط
٣- إذا الريكورد كان شغال و ما لقيتوا الكلام المكتوب بكون بدكم تنزلوا أو تطلعوا
بالسلايدات و تدوروا عليه، الله بيعينكم، لأنه زي ما حكيت فوق الدكتور كثير كان يتنقل بين
السلايدات
٤- يعطيكم العافية جميعا و ما تنسوا اهلنا في غزة من دعائكم

Ionotropic & Metabotropic Receptors

-Ionotropic: Transmitter-gated ion channels
-Neurotransmitter receptors that directly gate ion channels are often called ionotropic receptors,
Metabotropic receptors : activating a second messenger through G proteins coupled receptors that gates the channel and alters permeability



We have, in terms of the action of the neurotransmitters we have what's known as ionotropic receptors or ionotropic neurotransmitters, those neurotransmitters when they bind with their receptors, they go directly and work on The channels and they open the channels, they open it for Na, cl, K, maybe these three and these would either cause depolarization or hyper-polarization so we call them ionotropic neurotransmitters like for ex: (acytlecholine) that works on the synapse of The motor neurons and the skeletal muscles, that's one example.

Another example about the ionotropic is the GABA, it binds with the receptor and increases the permeability of Cl ions, in this case the Cl ions will enter the cell and cause hyper-polarization rather than depolarization, alternatively those neurotransmitters will bind with what's known as metabotropic neurotransmitters, what that means is the don't act directly on the channel, the usually act on what's known as G proteins coupled receptors and those receptors will induce several chemical reactions within the cells, and those chemical reactions will cause a change in the ovaling of the channel or they would do something else within the cell that will initiate the release of the ionic cells, that's the difference between them (ionotropic and metabotropic)
The thing that works on the ionotropic is faster than the metabotropic

The metabotropic neurotransmitter for example the acytlecholine … just to let you know, for one neurotransmitter there are different types of receptors, for example the acytlecholine we have (nicotinic, muscarinic which is divided into M1/2/3/4) the GABA we have (GABA A-receptor) for dopamine (D1/2/3/4), for the catacholamines which are the norepinephrine and epinephrine have (alpha and beta receptors and the alpha is divide into alpha1/2/…..) so having these varieties of different types of receptors and different receptors wether it's ionotropic or metabotropic make the neurotransmitters act differently at one site it could be excitatory and in another it could be inhibitory, for example the acytlecholine is excitatory in the muscle cells (skeletal) but in the haert at the SA node it becomes inhibitory, so the presence of different types of receptors, the presence of either ionotropic or metabotropic Receptors, enable these neurotransmitters to do different

- ما رح يحكي منها كثير لانه حيعطيها المحاضرة الجاية بالتفصيل

Metabotropic Receptors

The second messenger system by which a neurotransmitter can affect the activity of postsynaptic cell

NTR complex are coupled to G protein coupled receptor

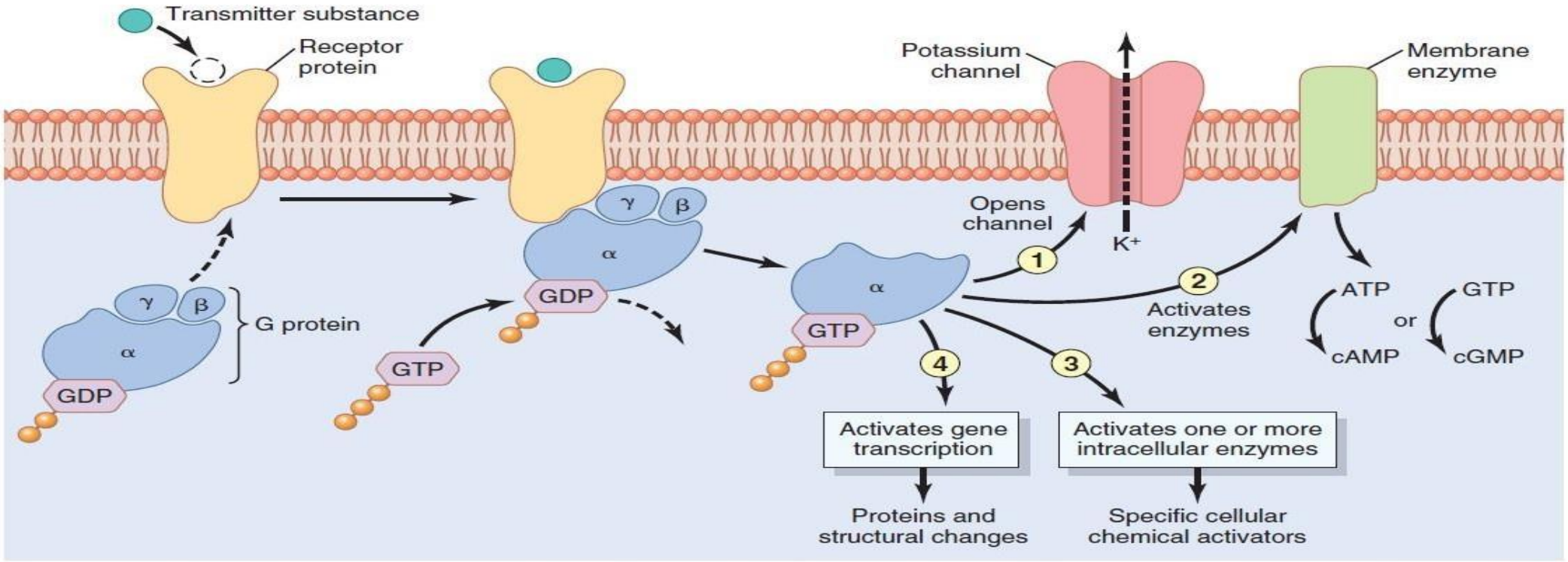


Figure The "second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first causing a transformational change in the receptor that releases the activated alpha (α) subunit of the G protein into the second neuron's cytoplasm. Four subsequent possible effects of the G protein are shown, including *1,* opening an ion channel in the membrane of the second neuron; *2,* activating an enzyme system in the neuron's membrane; *3,* activating an intracellular enzyme system; and/or *4,* causing gene transcription in the second neuron. Return of the G protein to the inactive state occurs when guanosine triphosphate *(GTP)* bound to the α subunit is hydrolyzed to guanosine diphosphate *(GDP)* and the β and γ subunits are reattached to the α subunit.

When we talk about sensory transduction, but this is the receptor and this is the neurotransmitter, this is the receptor protein that is within the cell membrane, usually this receptor is coupled with the G-protein couple receptor, so when the neurotransmitter binds somehow it causes structural changes within this receptor, and it releases this sub unit as this guy has 3 subunits and look as it's dense form in the sense of the neurotransmitter, it's not gonna be (…….) what the neutrons better bind with the receptor, what's gonna happen is that GTP would be .. you know somehow converted to GDP and then, once this happens it causes the release of this alpha subunit, now this alpha subunit does all the work, does all the action of the receptor with the G-protein, so as you could see here it could open a channel for the K ion, or it could do something else, it could activate enzymes and for example the activation of these enzymes in the membrane could convert ATP into cyclic AMP which is the second messenger, and this second messenger would later do the work, in the end we activate protein synthesis within the cell that would alter the cell membrane function or the cell function itself, also at the end, for it to go back to its normal state, the GTP comes and binds to the alpha subunit and is hydrolyzed to GDP, and then it would bind to it again and cause the inactivation, that's how they work, most of them are probably neurotransmitters work in groups with these G-proteins

Chemically gated channels

- The chemical-gated ion channels in the postsynaptic membrane are usually of two types:
  - 1) Cation channels (for Na+ but sometimes allow K+ and/or Ca2+ to pass)
  - 2) Anion channels that mainly allow Chloride to pass but allow minute quantities of other anions to pass as well.
- The neurotransmitter that opens cation channels are excitatory transmitter, whereas those that open anion channels are called inhibitory transmitters.
- Therefore, there are two types of synapses, depending on the permeability changes induced in the postsynaptic neuron by the neurotransmitter: excitatory synapses and inhibitory synapses

Membrane potential changes in excitatory and inhibitory synapses

- Activation of one excitatory synapse produces a small depolarization of the postsynaptic neuron. However, it can rarely depolarize the postsynaptic neuron sufficiently to bring it to threshold.
- Activation of one inhibitory synapse produces a small hyperpolarization of the postsynaptic neuron - having greater internal negativity. This small hyperpolarization moves the membrane potential even farther away from threshold

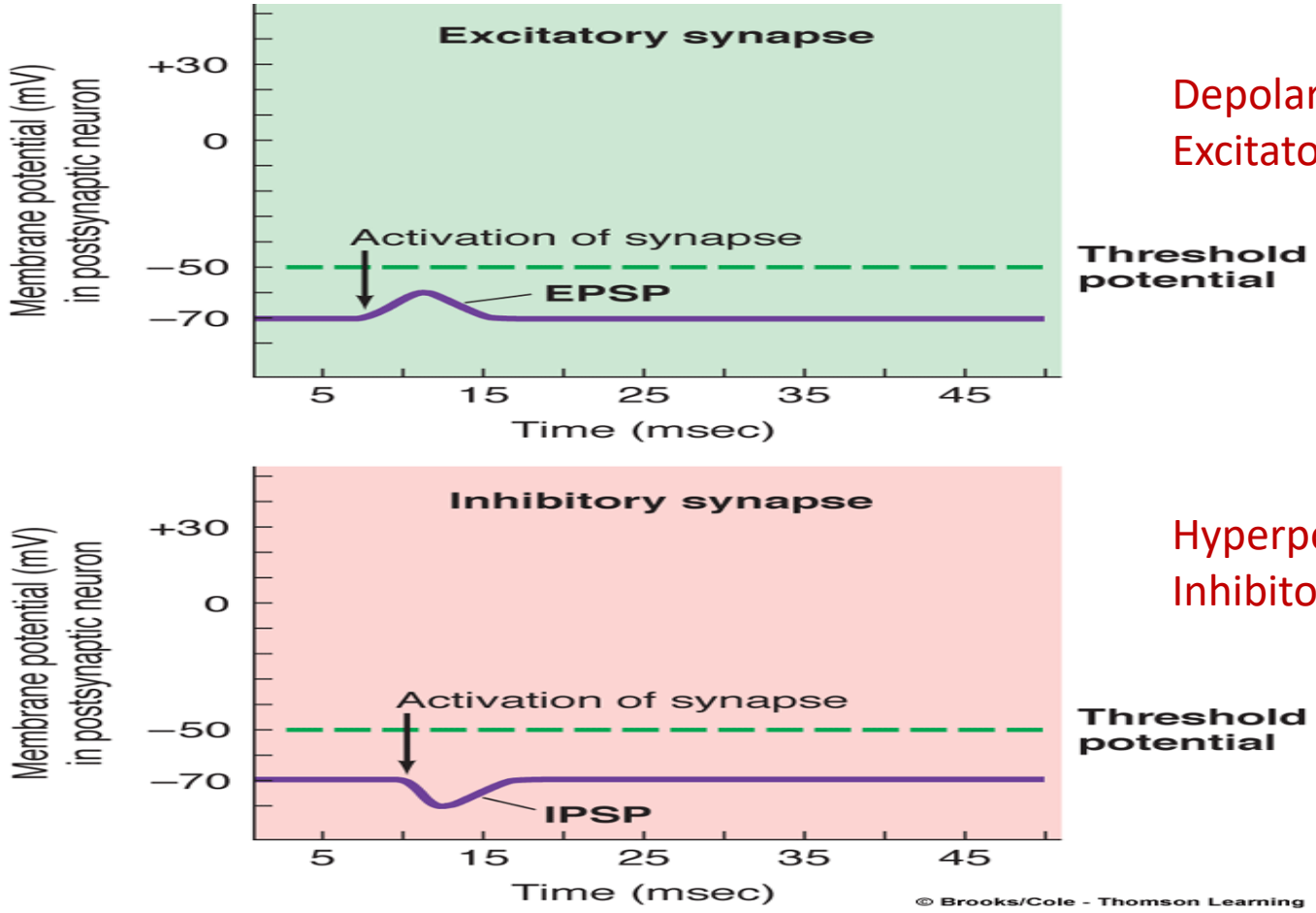
As a result of the action in the neurotransmitter wether is metabotropic or ionotropic, we get depolarization or hyper-polarization, so, the cell either will get close to the threshold and have an action potential, or it gets to be harder for the cell to be depolarized, or in other words to prevent the occurrence of the action potential.

-Thus we have two types of electrical changes:
1-excitatory postsynaptic potential
2-inhibitory postsynaptic potential

Electrical Events at Excitatory or Inhibitory synapses

Depolarization
EPSP

Hyperpolarization
IPSP

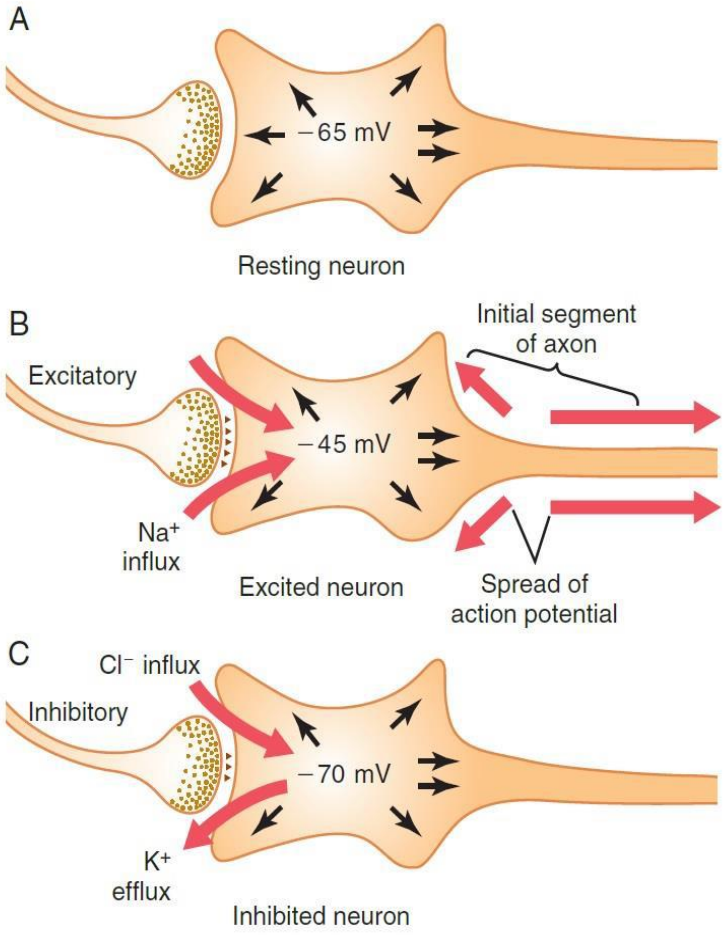


Depolarization
Excitatory synapse

Hyperpolarization
Inhibitory synapse

Excitatory Postsynaptic Potential –EPSP:

- Excitatory Postsynaptic Potential –EPSP
- This potential is generated when transmitter acts on the membrane excitatory receptor to increase the membrane's permeability to Na+.
- The rapid influx of positively charged Na+to the interior neutralizes part of the negativity of the resting membrane potential.
- In the figure the resting membrane potential has increased in the positive direction from -65 to -45 mV, to a less negative value. This less negative value (closure to the threshold) is called the excitatory postsynaptic potential (or EPSP).
- The mathematical value is EPSP= New membrane potential-RMP (resting membrane potential). The value is always positive (i.e. millivolts more positive than the resting value). It is +20 mV in this example.



1-We should know wether it’s inhibitory or excitatory

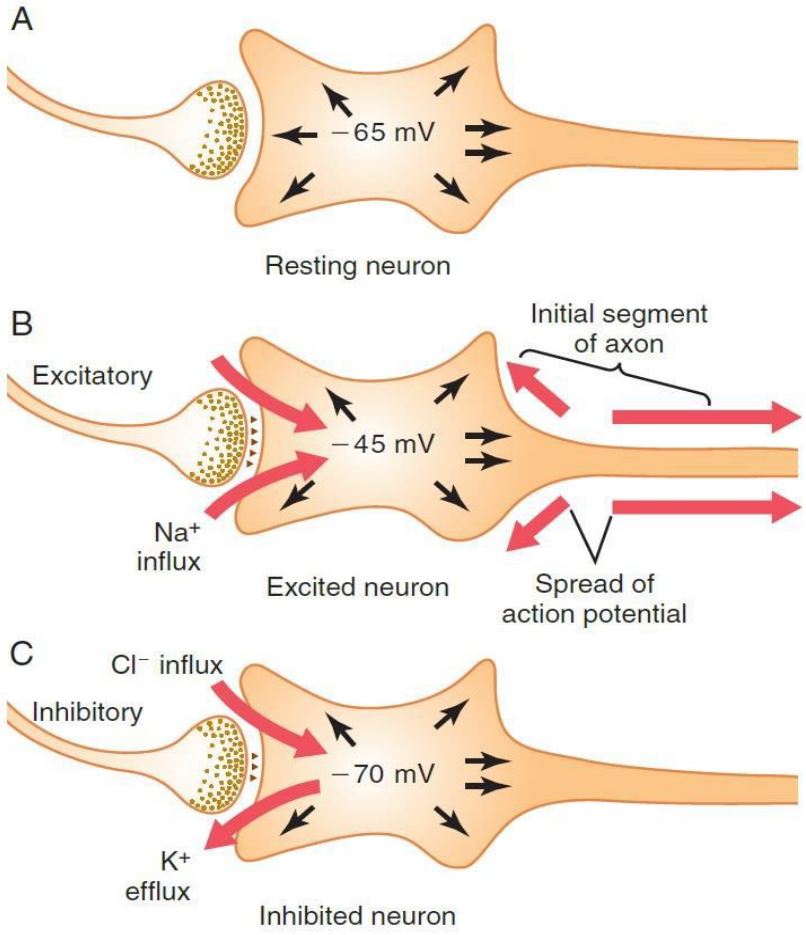
2-Which ion movements happen in the inhibitory or excitatory

3-The time duration, it could last about 20ms (the regular action potential is 2ms)

4-usually one EPSP is not gonna be sufficient for an action potential to happen in the post synaptic cell we should have more than one EPSP, more than one molecule of neurotransmitter, more than one nerve excited to cause an action potential in the post synaptic cell, cause our goal from the EPSP is to activate the Na channel in the axon vein or the initial segment that is found in the postsynaptic cell, because of that, the action potential that happened in the postsynaptic neuron what it’s gonna do is induce the EPSP, and if the amplitude of the EPSP sufficient to bring the postsynaptic cell to the threshold level, the postsynaptic cell will initiate an action potential, if the EPSP was at a sub threshold level (below the threshold) which is not enough, it will die out, and the cell won’t be excited. However when we need a signal, we make sure that the amount of neurotransmitter that will be released will be enough to bring the postsynaptic cell to the firing level

Excitatory Postsynaptic Potential –EPSP:

- Discharge of a single presynaptic terminal can only generate a small EPSP. In the spinal cord, discharge of as many as 40 to 80 terminals may be needed to bring large EPSP all the way up to -45 millivolts. This simultaneous discharge occurs by a process called **summation**.
- When the EPSP rises high enough in the positive direction, an action potential initiates in the initial segment of the axon where the axon leaves the neuronal soma (i.e. **axon hillock or** the trigger zone).
- The membrane of the hillock segment has seven times as great a concentration of voltage-gated sodium channels as does the soma and the dendrites and, therefore, can generate an action potential with much greater ease than can the soma.
- An EPSP between +10 and +20 mV will elicit an action potential in the axon initial segment



Usually if we have one presynaptic cell/neuron, the amount of EPSP won't be enough, so usually we have to excite more than one presynaptic neuron going to the postsynaptic cell, or the cell itself:

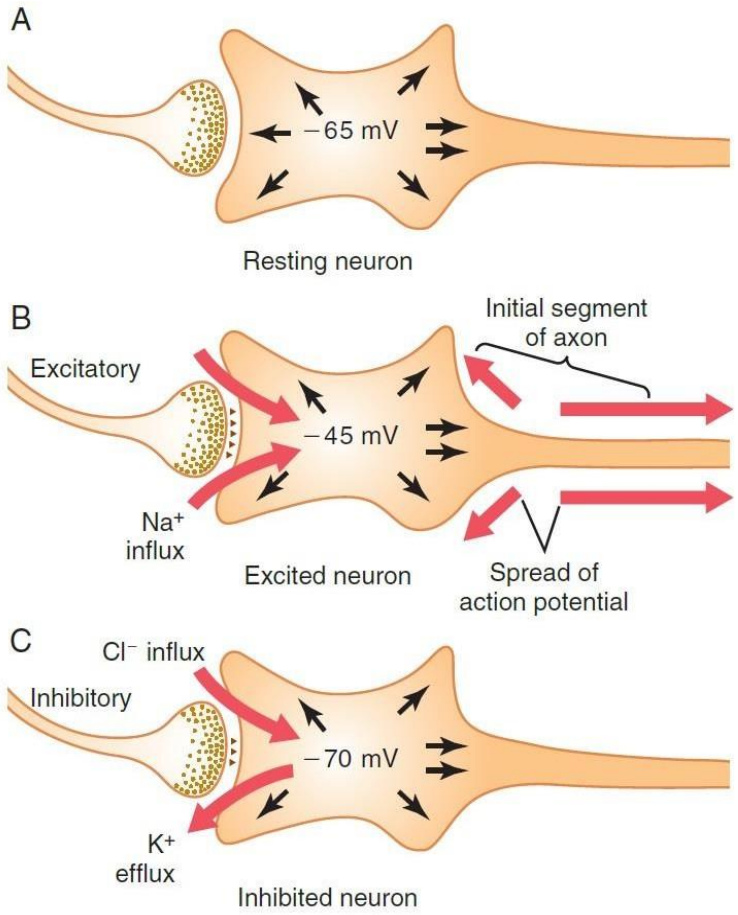
-the amount of action potentials that go to the presynaptic neuron is high (a lot of action potentials), so the amount of neurotransmitters increases, the increase either increases the amount of cells that secrete (تفرز) the neurotransmitters and have the same synapse with the postsynaptic cell,

-if we have one or two (cells that make neurotransmitters) we increase the number of excitation in the presynaptic cell for it to secrete more neurotransmitters and the amplitude becomes closer to the threshold, for example if the cell is -80mV, we need the EPSP amplitude to be -60mV for an action potential to happen in the postsynaptic cell

For example, this is the resting state, assume that we have a neurotransmitter here, by increasing the Na channel and permeability, Na will get through to the cell from the outside because the concentration of Na is higher, so when the Na get through the cell, the membrane potential is decreased from -65mV to -45mV, so there is a localized potential, localized excitatory potential, as we see here this localized potential is known as EPSP (Excitatory PostSynaptic Potential) it is called excitatory because the neurotransmitter causes depolarization or excitation of the post synaptic cell, hence the name (that's why it is called EPSP)

Inhibitory Postsynaptic Potential – IPSP:

- The inhibitory synapses open mainly chloride channels, allowing easy influx of chloride ions.
- Also opening potassium channels will allow positively charged K^+ to move to the exterior and will also make the interior membrane potential more negative.
- Thus, both Cl^- influx and K^+ efflux increase the degree of intracellular negativity (i.e.
  - hyperpolarization) → inhibitory postsynaptic potential (IPSP).
- In the diagram the value of the IPSP is -5mV. This means 5 millivolts more negative than normal, which inhibits transmission of the nerve signal through the synapse.



so if this change occurred in the postsynaptic cell like this, if we have an inhibitory neurotransmitter we could either cause an influx in Cl, which is a negative ion, that will break the membrane potential more to the negative side, if it was here (resting neuron picture) -65mV it will be here -70, -75mV (inhibited neuron) depending on how many Cl ions, or alternatively the K ion is gonna move out, so wether we get sodium in or potassium out the end result will be hyper-polarization, and this hyper-polarization is again a localized potential it's getting away from the threshold, and cuz it's inhibitory and happened in the post synaptic cell, it is called IPSP (Inhibitory PostSynaptic

So, one of them tends to excite the cell (EPSP) and the other one tends

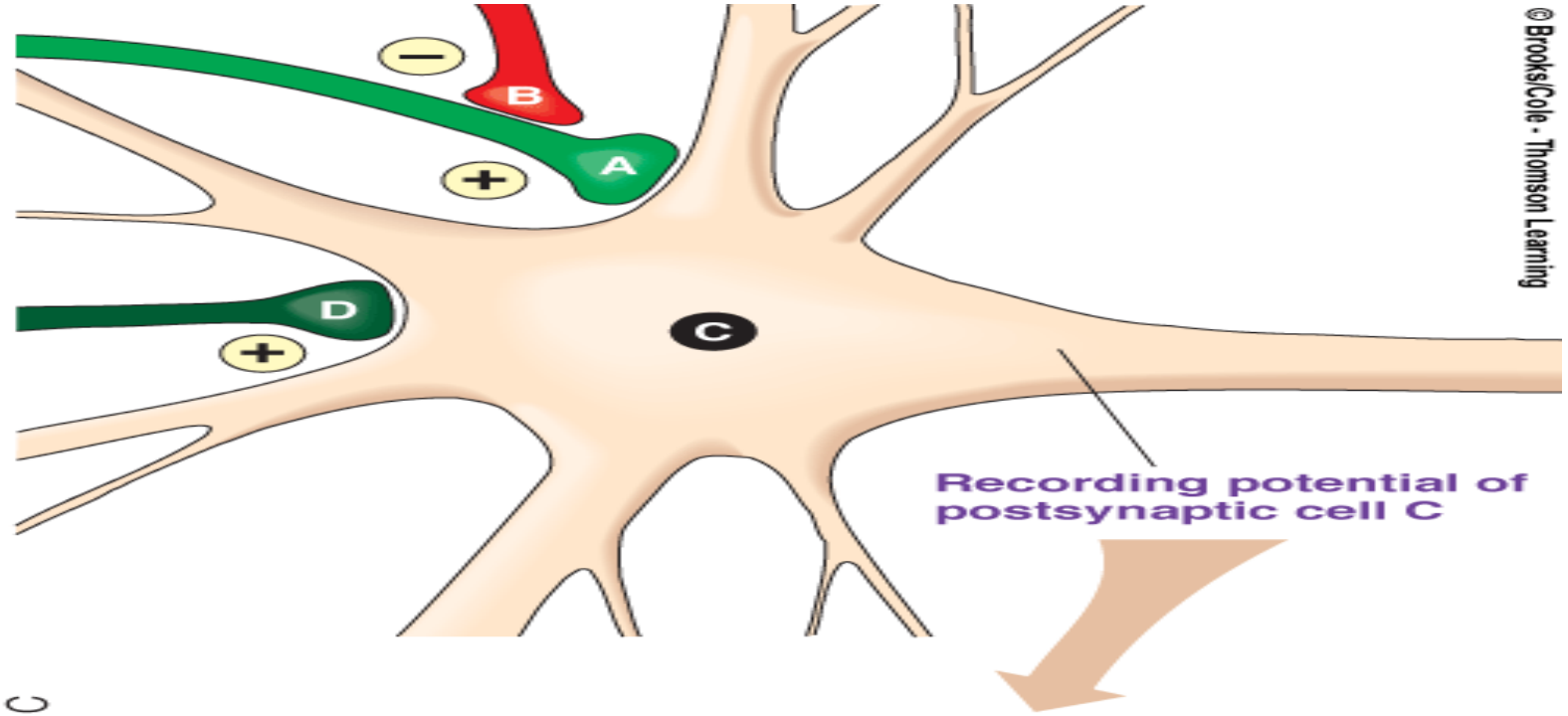
The synaps transmission or those synaptic potentials are not like action potential, the don't propagate for long distances so they are localized and then they're amplitude will be dependent on the amount of neurotransmitter, the more the neurotransmitters the more the amplitude or the action potential is increased.

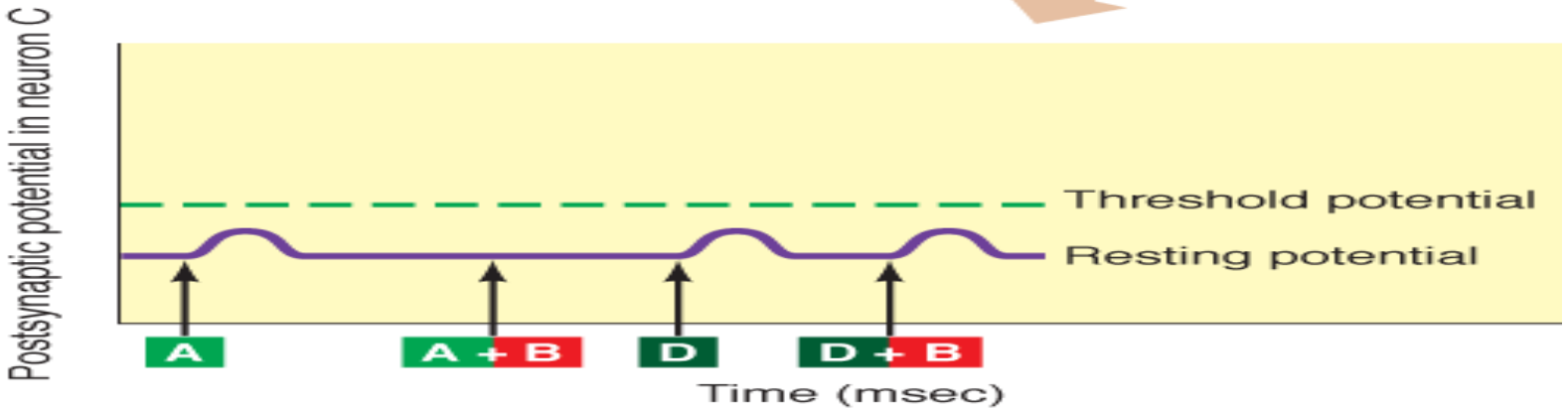
-The main characteristics of the synaptic potentials are:

1-they are localized potentials and are not propagated like an action potential

2-They are graded, which means that they're amplitude is gonna vary depending on the amount of neurotransmitters released by the synaptic

Presynaptic inhibition





Neuron D

Neuron A

Neuron B

N D+B

N A+B

This is a postsynaptic cell, it receives input from D and from A,

-If you simulate A alone (a signal arrived only for A), the amplitude of the EPSP will be low, thus no action potential will happen in the postsynaptic cell, cuz the neurotransmitter isn't enough, the amplitude of the EPSP isn't enough

-Now if you stimulate D alone, the amplitude of the EPSP did not bring the postsynaptic cell to the threshold

-if you stimulate A and B there will be no EPSP cause this neuron makes presynaptic inhibition to the neuron A, thus the EPSP won't have a neurotransmitter, or the signal here will be inhibited by the signal from stimulating neuron B. So this better (.....) where a neuron makes an axo-axonic synapse and inhibits the release of the neurotransmitter here is known as presynaptic inhibition, so if we stimulated a postsynaptic cell and at the same time we stimulated a presynaptic cell that's makeing an axo-axonic synapse, the two will cancel out each other and there will be no change in the membrane potential

-Usually our cells have a poll of neurons, some excitatory and some inhibitory ....., but at the end what determines wether the postsynaptic cell will be excited or not is the winner, who's the excitation and who's the inhibition,and usually we have a balance between excitation and inhibition, if we had a problem in the balance of excitation and inhibition, we will have hyper-excitability of the neurons, for example if the neurotransmitter gap is decreased which is an inhibitory neurotransmitter, the (.....) goes wild, and some will start having seizures, also some manifestations but mainly motor-manifestations along with other things that happen with the epilepsy patients, one of the theories of the patients that have epilepsy is that they have a disturbance in the excitation and inhibition, we lose inhibition one way or the other, so the brain cells go wild, they become or hyper-excitable, and people will exhibit what's known as seizures, the manifestations which occurs (happens) during an epileptic attack, the start jerking (تشنجات و تحركات سريعة و حركات لا إرادية) and loss of consciousness etc....

Presynaptic Inhibition

- It is an inhibitory input act on the presynaptic terminal before the signal ever reaches the synapse to make it less likely to communicate with postsynaptic neurons.
- Presynaptic inhibition is caused by release of an inhibitory substance, like GABA, acts on GABA receptors onto the outsides of the presynaptic nerve fibrils before their own endings terminate on the postsynaptic neuron.
- GABA receptors activation causes a chloride influx, which hyperpolarizes the cell that will cancel much of the excitatory effect of Na^+ that also enter the terminal fibrils when an action potential arrives.
- Presynaptic inhibition occurs in many of the sensory pathways in the nervous system.
- Mediated by axoaxonic synapse

Properties of synaptic potential

- Graded potential : amplitude of EPSP or IPSP depends on neurotransmitter released
- Exhibit summation: Temporal and spatial summation
- Decremental ie decrease amplitude as signals moves a away from site of stimulation
- none propagated localized potential

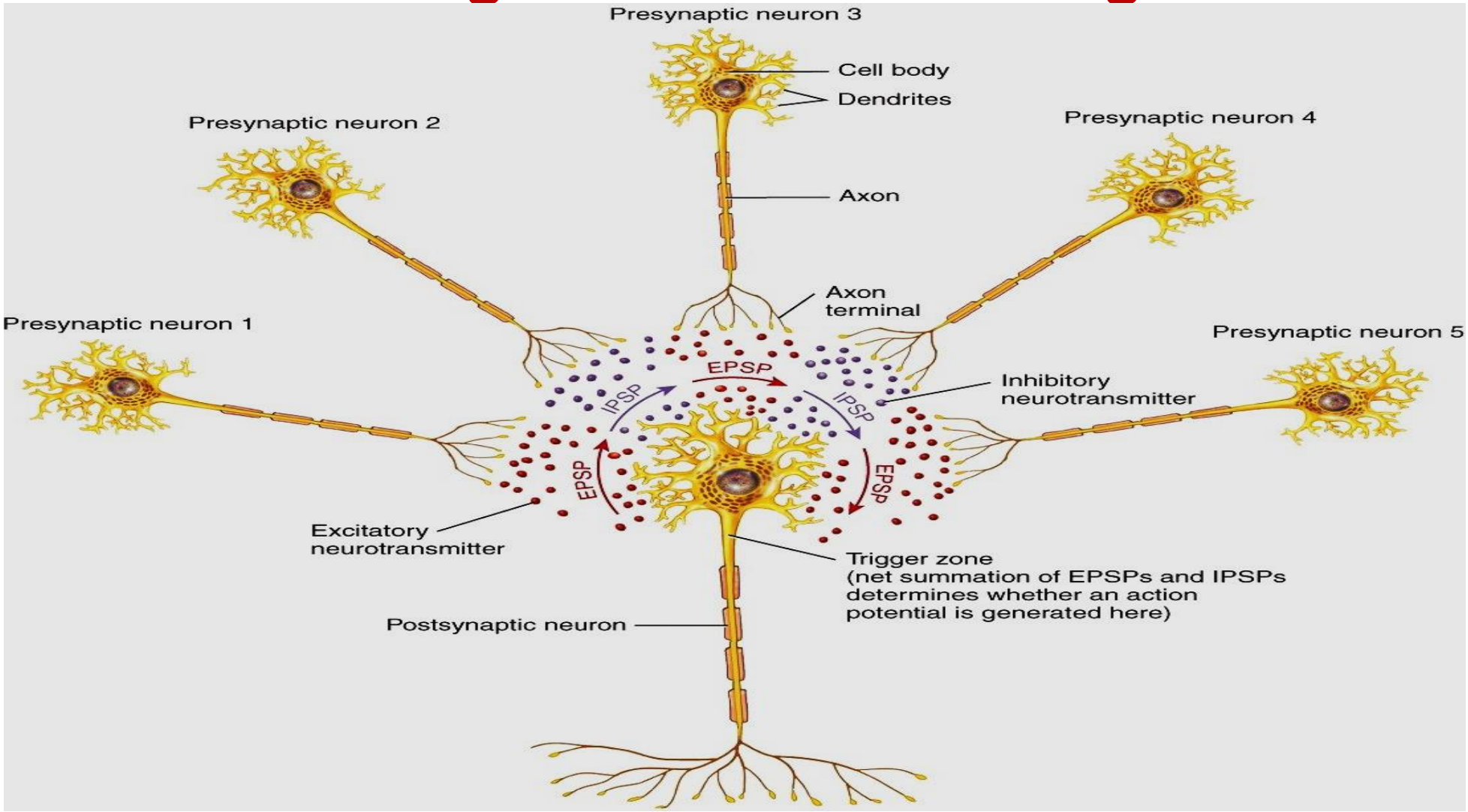
They exhibit 2 types of summation, this also occurs in the sensory system, temporal and spatial:

-Temporal: with time, meaning you increase the frequency of firing of the presynaptic neuron, instead of having 10 action potentials per second, they'll become 20.

-spatial: with space, we have a postsynaptic cell, and it has 10 incoming presynaptic inputs and they secrete the same neurotransmitters

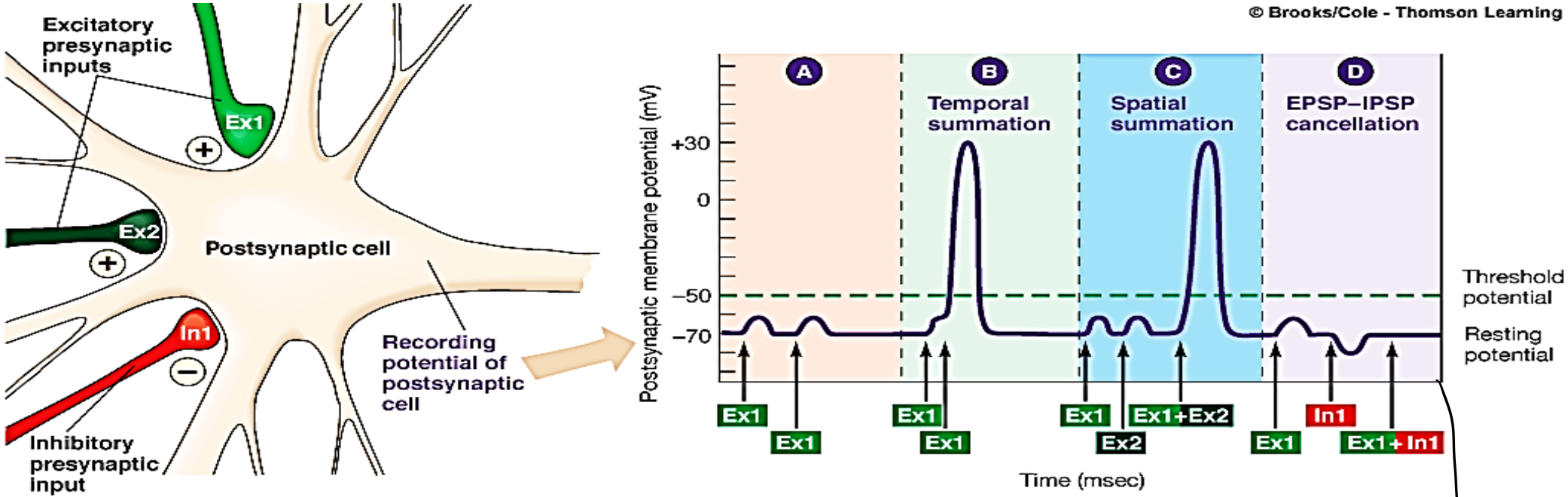
-Decremental: assume that you record the synaptic potential right at the cell body, at the dendrite, if you move away from the dendrite the amplitude will start to decline (not the same as the action potential which maintains its level when getting away from the dendrite) the more we get away from the site of recording the EPSP for example, the lower the amplitude gets, (the definition in the slide) the further we are from the point of the synaptic contact and a depolarization happened and a hyper-polarization, the lower the amplitude gets

Summation of Postsynaptic Potentials and integration of neuronal signals



We have a bunch of synapses here, and let's say that they're all excitatory, they release the same neurotransmitter, if we stimulate all of them at one time, all the presynaptic terminal, 3 EPSP's and at the same time there's a potential that some of these neurons are inhibitory, meaning that the cell can have both excitatory and inhibitory, and wether the postsynaptic cell will be excited or not, is determined by who will win, if the excitatory is more the cell will get excited, if they're the same they'll cancel out each other,

Summation of Postsynaptic Potentials



Panel A If an excitatory presynaptic input (Ex1) is stimulated a second time after the first EPSP in the postsynaptic cell has died off, a second EPSP of the same magnitude will occur.

Panel B If, however, Ex1 is stimulated a second time before the first EPSP has died off, the second EPSP will add onto, or sum with, the first EPSP, resulting in *temporal summation*, which may bring the postsynaptic cell to threshold.

Panel C The postsynaptic cell may also be brought to threshold by *spatial summation* of EPSPs that are initiated by simultaneous activation of two (Ex1 and Ex2) or more excitatory presynaptic inputs.

Panel D Simultaneous activation of an excitatory (Ex1) and inhibitory (In1) presynaptic input does not change the postsynaptic potential, because the resultant EPSP and IPSP cancel each other out.

every Part has a paragraph with its own colour

Temporal summation

-If we increase the frequency of stimulation of presynaptic neuron going to the postsynaptic cell, the EPSP will be added up providing that the time between them is short, even before the ending of the first EPSP, if we stimulate another EPSP, they will add to each other and they will reach the firing level, this method of summation of EPSP's is called temporal (time) meaning that we increase the frequency, and if it's enough to add the 1st to the 2nd to the 3rd, we can bring the postsynaptic cell to the firing level

Spatial summation

-Timing, if we stimulate 1 alone, we get this EPSP (in the picture the small wave) which didn't get the postsynaptic cell to the firing level, if we stimulate neuron 2 again, we will not achieve firing level too. However, if we stimulate 1 and 2 together at the same time, the EPSP's will add up together and we bring the postsynaptic cell to the firing level

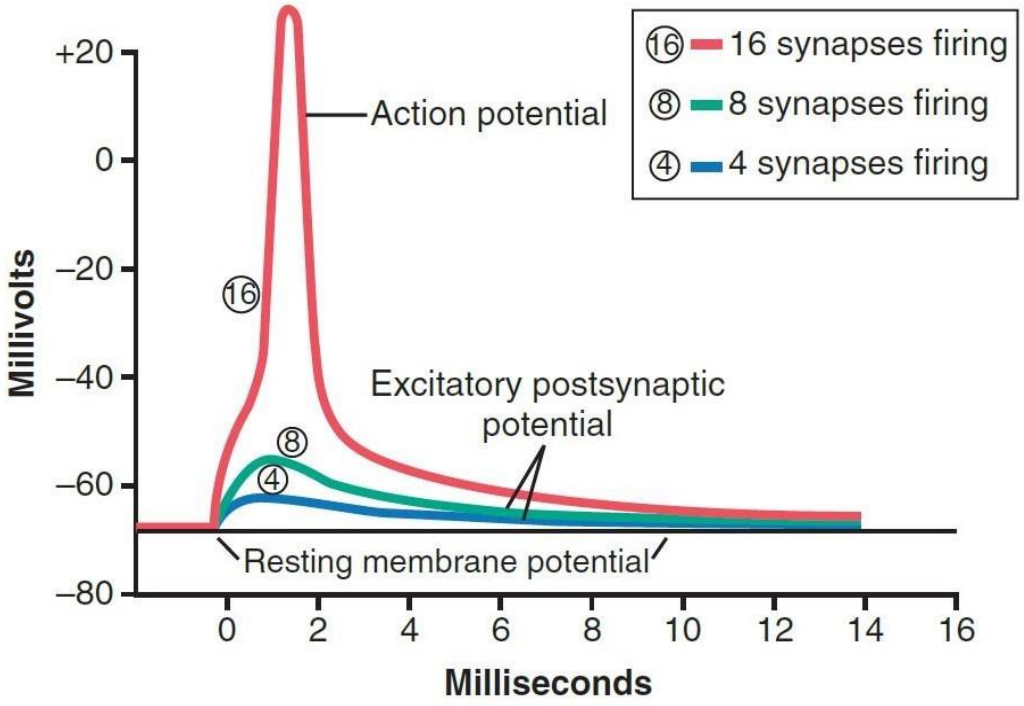
EPSP-IPSP cancellation

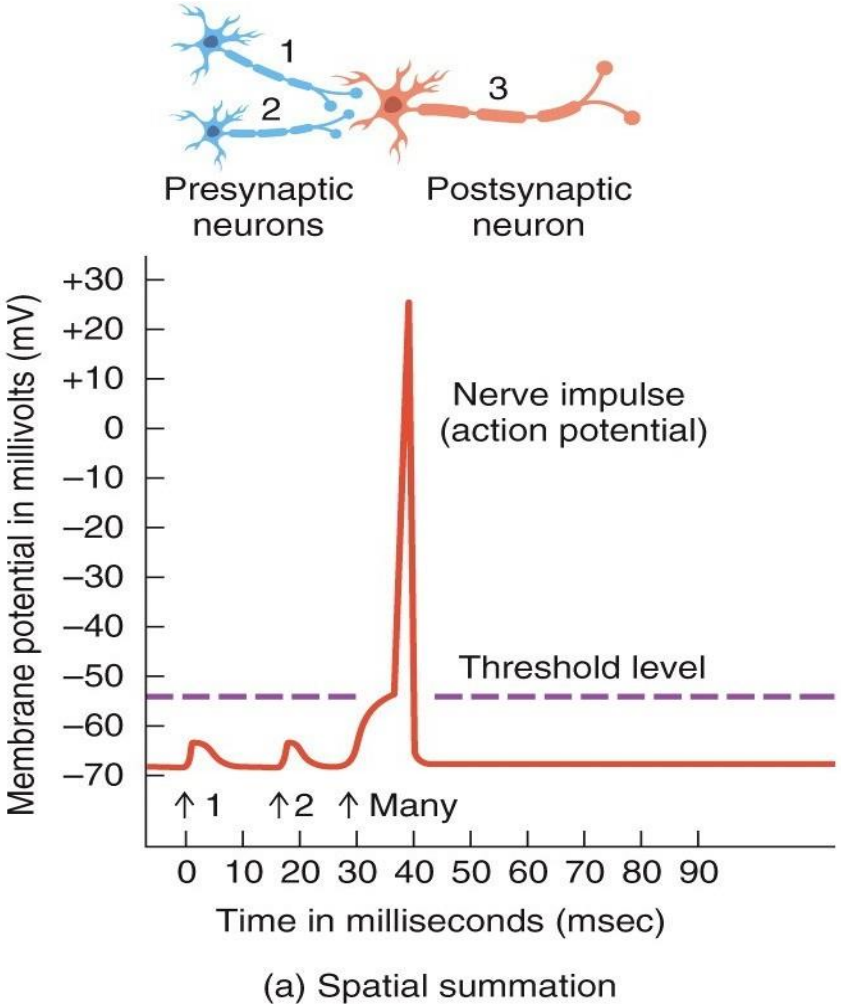
-if we stimulate for example the excitatory one and at the same time the inhibitory one, we get an EPSP here (small bulge up) and an IPSP here (small hole) and there will be no change in the membrane potential, cuz the inhibition will cancel the excitation

So the main goal for EPSP and the temporal and spatial summations is to make sure there is a sufficient amount of neurotransmitters, so the amplitude or the EPSP is enough to bring the postsynaptic cell to the firing level, and of course the action potential is gonna be initiated in the initial segment or axotonic, cuz the Na gated channels are high in concentration or amount

Spatial Summation

is the summation of EPSPs originating simultaneously from several different presynaptic inputs (that is, from different points in "space").

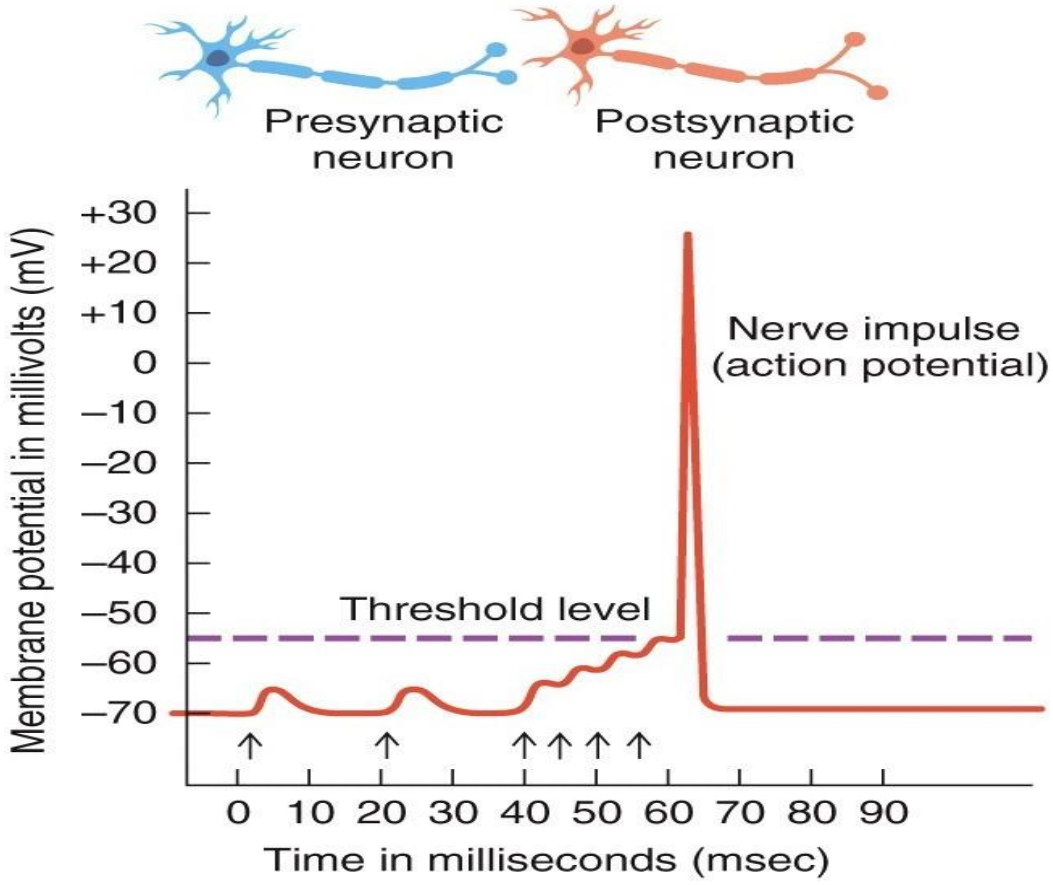




(a) Spatial summation

Temporal Summation

- The released transmitter substance opens the membrane channels for at most a millisecond or so. However, the changed postsynaptic potential lasts up to 15 milliseconds after the synaptic membrane channels have already closed.
- Therefore, if a presynaptic neuron fires quickly twice in row, causing two EPSPs, the second EPSP may arrive before the first one has dissipated, bumping the membrane potential toward threshold.
- The summing of several EPSPs occurring very close together in time because of successive firing of a single presynaptic neuron is known as temporal summation (tempus means "time").



(b) Temporal summation

Properties of chemical synaptic transmission

1. One way transmission
2. If an IPSP and an EPSP act on a neuron at the same time, these two effects can either completely or partially nullify each other. The summation of the membrane's EPSPs and IPSPs will determine the final membrane potential.
3. Synaptic potentials are localized graded and decremental neuronal potentials
4. EPSP and IPSP exhibit spatial and temporal summation
5. Repetitive neuronal stimulation at a rapid rate can develop **fatigue** of synaptic transmission. The mechanism of fatigue is mainly exhaustion or partial exhaustion of the stores of transmitter substance in the presynaptic terminals. The development of fatigue is a protective mechanism against excess neuronal activity.
6. **Alkalosis** greatly increases neuronal excitability (hyperventilation, which blows off CO_2 and elevates the pH, may precipitate an epileptic attack).
7. **Acidosis** greatly depresses neuronal activity. In very severe diabetic or uremic acidosis coma develops.
5. **Caffeine**, **theophylline** (found in coffee, tea, and cocoa) increase neuronal excitability, presumably by reducing the threshold for excitation of neurons.
5. Most **anesthetics** increase the neuronal membrane threshold for excitation and thereby decrease synaptic transmission at many points in the nervous system.

Neurotransmitters and chemical synapses

- N**eurotransmitters**
  - Chemicals synthesized, packed and released by presynaptic neurons
  - Diffuse across the synaptic cleft
  - and interact with postsynaptic neurons membrane receptors
  - Neurotransmitters either excite the neuron or inhibit or or modify its sensitivity of the postsynaptic neuron
  - Inhibition or excitations is determined by the neurotransmitter , its receptors and permeability changes in postsynaptic cell induced by neurotransmitter receptor interaction

-A lot of the neurological things, particularly those associated with behavioral diseases, are related to the neurotransmitters

-EX 1: schizophrenia (انفصام الشخصية) is related to dopamine which is an important neurotransmitter in the nervous system the people with schizophrenia often have problems with dopamine levels

EX 2: depression and other are related things are related to catecholamines in general, which include norepinephrine etc...

EX 3: epilepsy is related to the disturbance in the GABA level

EX 4: Parkinson’s disease is caused by a decrease in dopamine in a nuclei called basal ganglia

The Neurotransmitters

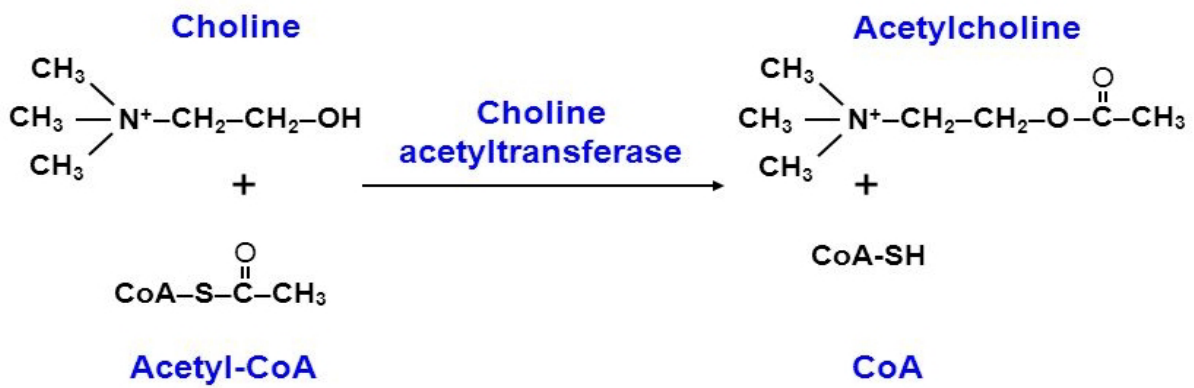
- More than 50 chemical substances function as synaptic transmitters.
- These chemical substances can be grouped into; Small- molecule (rapidly acting transmitters) and Neuropeptide (slowly acting transmitters or growth factors).
- The small-molecule, rapidly acting transmitters cause most acute responses of the nervous system, such as **transmission** of sensory signals to the brain and of motor signals back to the muscles.
- The neuropeptides usually cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, long-term opening or closure of certain ion channels, and possibly even long-term changes in numbers of synapses or sizes of synapses (Synaptic plasticity).

Small-Molecule, Rapidly Acting Transmitters:

- These types of transmitters are **synthesized in the cytosol** of the presynaptic terminal and are absorbed by means of active transport into the many transmitter vesicles in the terminal.
- Most often the effect of these transmitters is to increase or decrease conductance through ion channels.
- Small molecule transmitters are **continually recycled** and used over and over again. Acetylcholine, Norepinephrine, and Nitric oxide are examples of such transmitters.
- **Acetylcholine (Ach)**, in most instances, has an excitatory effect; however, it is known to have inhibitory effects at some peripheral parasympathetic nerve endings (as in the heart).
- **Norepinephrine (NE)** is synthesized within the vesicle from dopamine ithe enzyme dopamine β hydroxylase is present in the vesicle. NE in many areas within the CNS, activates excitatory receptors, but in a few areas, it activates inhibitory receptors instead.

-Small-molecule neurotransmitters:
They are usually synthesized in the presynaptic terminal, their enzymes could be synthesized in the cell body and they move from the cell body at times via exoplasmic transport, they're synthesized and then bagged into vesicles and to the presynaptic neurons, most of these or in a lot of cases neurotransmitters act on channels, whether they're ionotropic or metabotropic eventually, they mediate their actions by acting on these channels

1-Acetylcholine: is found in the CNS (central nervous system) and in the PNS (peripheral nervous system) particularly in the autonomic part (parasympathetic) usually in the CNS it's excitatory, but in the PNS it's inhibitory in one site and excitatory in others, for example it decreases the heart rate which means it inhibits the SA node cells, whereas it increase the intestinal motility.
It's synthesized from acetyl coA + choline, and there is an enzyme called SA choline transferase it's responsible for the combination of acetyl coA and choline and the one responsible for degradation is called acetylcholinesterase



2-Norepinephrine: which belongs to a class called catecholamines, this class has norepinephrine, epinephrine, and dopamine, they have the same concept, which is that they all come from an amino acid thyrosine and there are a series of enzymes that convert one to another, the norepinephrine, it's essential enzymes is β hydroxylase, it could be excitatory and it could be inhibitory, it's present in the CNS and the PNS

Small-Molecule, Rapidly Acting Transmitters

- **Dopamine**, **Glycine**, and **GABA** (gamma-aminobutyric acid) are inhibitory transmitters. GABA is the primary inhibitory neurotransmitter of the CNS. It functions as a CNS depressant.
- **Glutamate** is secreted by the presynaptic terminals in many of the sensory pathways. Glutamate is the principle excitatory neurotransmitter of the CNS.
- **Serotonin** (or 5-hydroxytryptamine) acts as an inhibitor of pain pathways in the spinal cord, and an inhibitor action in the higher regions of the nervous system. Serotonin is involved in mood control, appetite control, and nausea. Perhaps it even causes sleep.
- **Nitric oxide** is a gas and is not preformed and stored in vesicles in the presynaptic terminal as are other transmitters. Instead, it is synthesized almost instantly as needed and then diffuses out of the presynaptic terminals over a period of seconds rather than being released in vesicular packets. It diffuses into the nearby postsynaptic neurons and changes intracellular metabolic functions that modify postsynaptic neuronal excitability.

3-Dopamine: another catecholamine, it's usually inhibitory, and it has been associated with schizophrenia, Parkinson's.
There 2 amino acids that should be known here,which are also known to be inhibitory neurotransmitters, glycine, it's an inhibitory amino acid and is present in the spinal cord, whereas GABA is centrally inhibitory neurotransmitter it's one of the main inhibitory neurotransmitter in the CNS, ex: when we have hyper-excitability due to loss of dopamine of a GABA (.....) neurons in the nervous system

4-Serotonin: which also a derivative of amino acids, its striped from tryptophan, it's usually an Inhibitory, and it might be involved in the inhibition of pain transmission, it's involved in the control of mood and behavior, similar to other catecholamines

5-Nitric oxide: it's believed to ba a neurotransmitter, the exact function of it is not really known, but it seems to act as an excitatory neurotransmitter, it may be important cause it acts as a neurotransmitter on smooth muscles of the blood vessels, and it causes vasodilation (dialation of the blood vessels), it's more important in this effect rather than its central effect, but that doesn't mean that it doesn't effect central neurons, it does, but one of the confirmed effects that it does is vasodilation, it makes the smooth muscles relax which allows the blood vessels to dialate (تتوسع)

The Neuropeptides:

- They are synthesized as integral parts of large-protein molecules by ribosomes **in the neuronal cell body**.
- The Golgi apparatus packages the neuropeptide into minute transmitter vesicles that are released into the cytoplasm. Then the transmitter vesicles are transported all the way to the tips of the nerve fibers by axonal streaming of the axon cytoplasm (**axoplasmic flow**), traveling at the slow rate of only a few centimeters per day.
- Much smaller quantities of neuropeptides than of the small-molecule transmitters are usually released at the neuronal terminals in response to action potentials.
- Neuropeptides are generally a thousand or more times as potent as the small-molecule transmitters and they often cause much more prolonged actions.

-Neuropeptides: they’re probably synthesized in the cell body as they move to the axon by axoplasmic transport, and those are very voltent but they take a longer time to work, they don’t act like the small-molecule neurotransmitter, they actually take a bit longer to work, and there are so many of them

Small molecules rapidly acting neurotransmitters

Table 46-1 Small-Molecule, Rapidly Acting Transmitters

Class I
Acetylcholine
Class II: The Amines
Norepinephrine
Epinephrine
Dopamine
Serotonin
Melatonin
Histamine
Class III: Amino Acids
Gamma-aminobutyric acid
Glycine
Glutamate
Aspartate
Class IV
ATP
Arachidonic acid
Nitric oxide
Carbon monoxide

inhibitory

or glutamic acid. is also an excitatory neurotransmitter

Neuropeptides, Slowly Acting Transmitters, or Growth Factors

Hypothalamic-Releasing Hormones
Thyrotropin-releasing hormone
Luteinizing hormone–releasing hormone
Somatostatin (growth hormone inhibitory factor)
Pituitary Peptides
Adrenocorticotropic hormone
β-Endorphin and encathrins (those are related to behavior and pain transmission
α–Melanocyte-stimulating hormone
Prolactin
Luteinizing hormone
Thyrotropin
Growth hormone
Vasopressin
Oxytocin

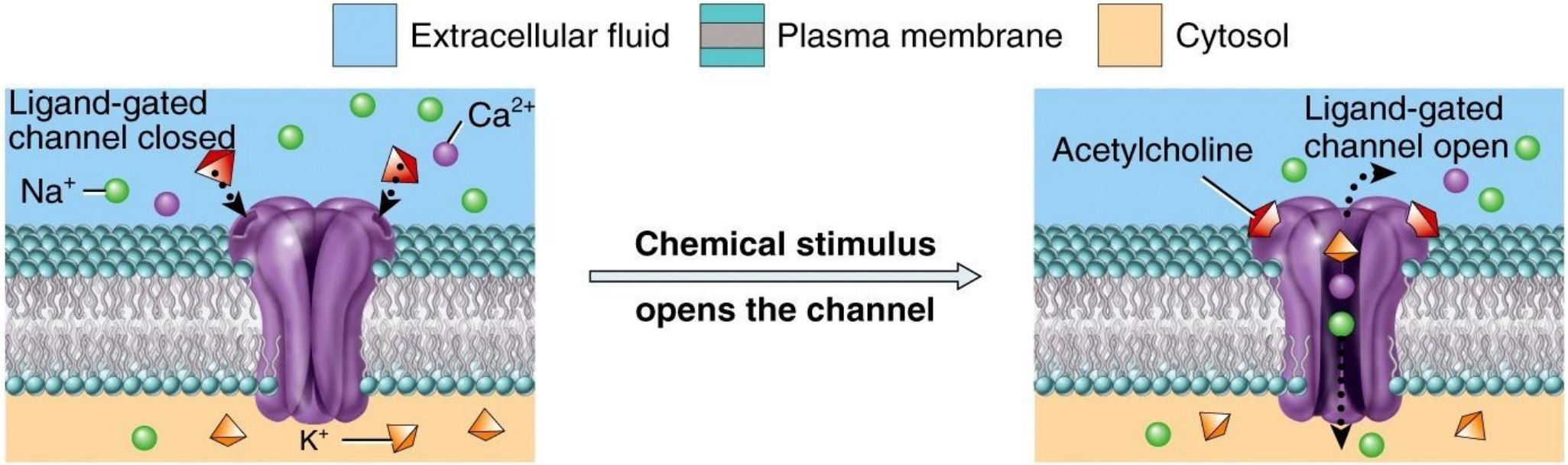
Peptides That Act on Gut and Brain
Leucine enkephalin
Methionine enkephalin
Substance P → brain and is related to pain transmission
Gastrin
Cholecystokinin
Vasoactive intestinal polypeptide
Nerve growth factor
Brain-derived neurotropic factor
Neurotensin
Insulin
Glucagon
Peptides from Other Tissues
Angiotensin II
Bradykinin
Carnosine
Sleep peptides
Calcitonin

Later we will confirm wether they’re peptide or small neurotransmitters, cholinergic, GABAergic, dopaminergic, norenergic glutamenergic,
(-ergic) means it releases something,
So we want to know if they’re small molecules and what they do after that,

Neuronal Graded Potentials

We said that we have local potential or graded potential and active potential, we should know the difference between them, so, local potentials they don’t propagate, and the amplitude decreases as you move away from the site of recording, like the synaptic potential, and the all or none will propagate the action potential

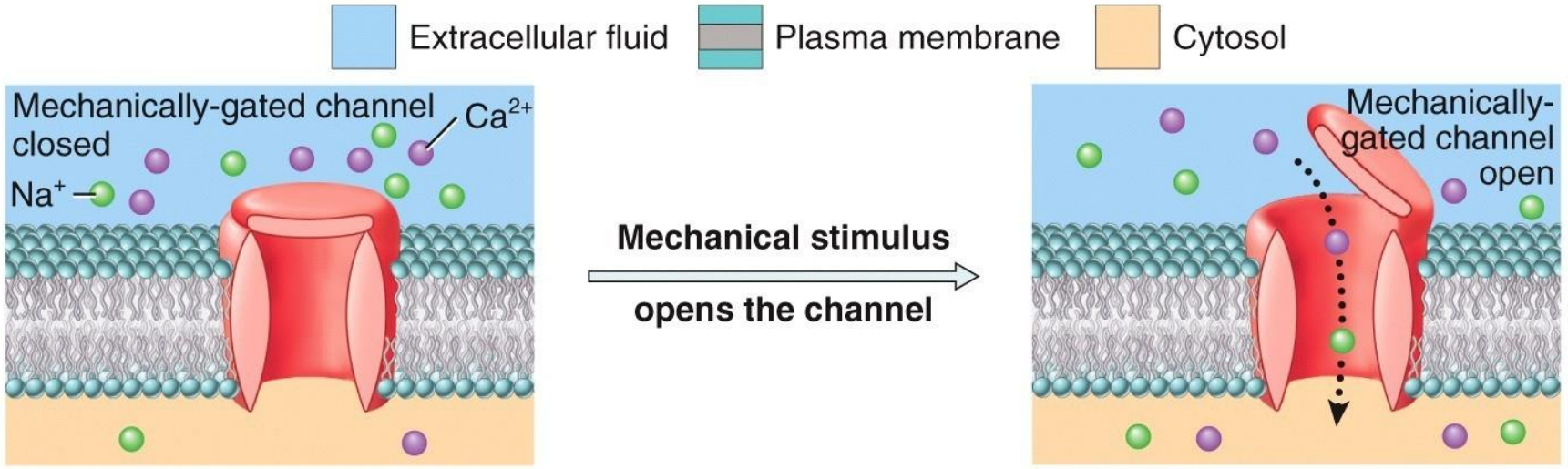
Ligand-gated channels respond to chemical stimuli (ligand binds to receptor)



(b) Ligand-gated channel

A graded potential occurs in response to the opening of ligand- gated ion channel

Mechanically-gated channels respond to mechanical vibration or pressure stimuli



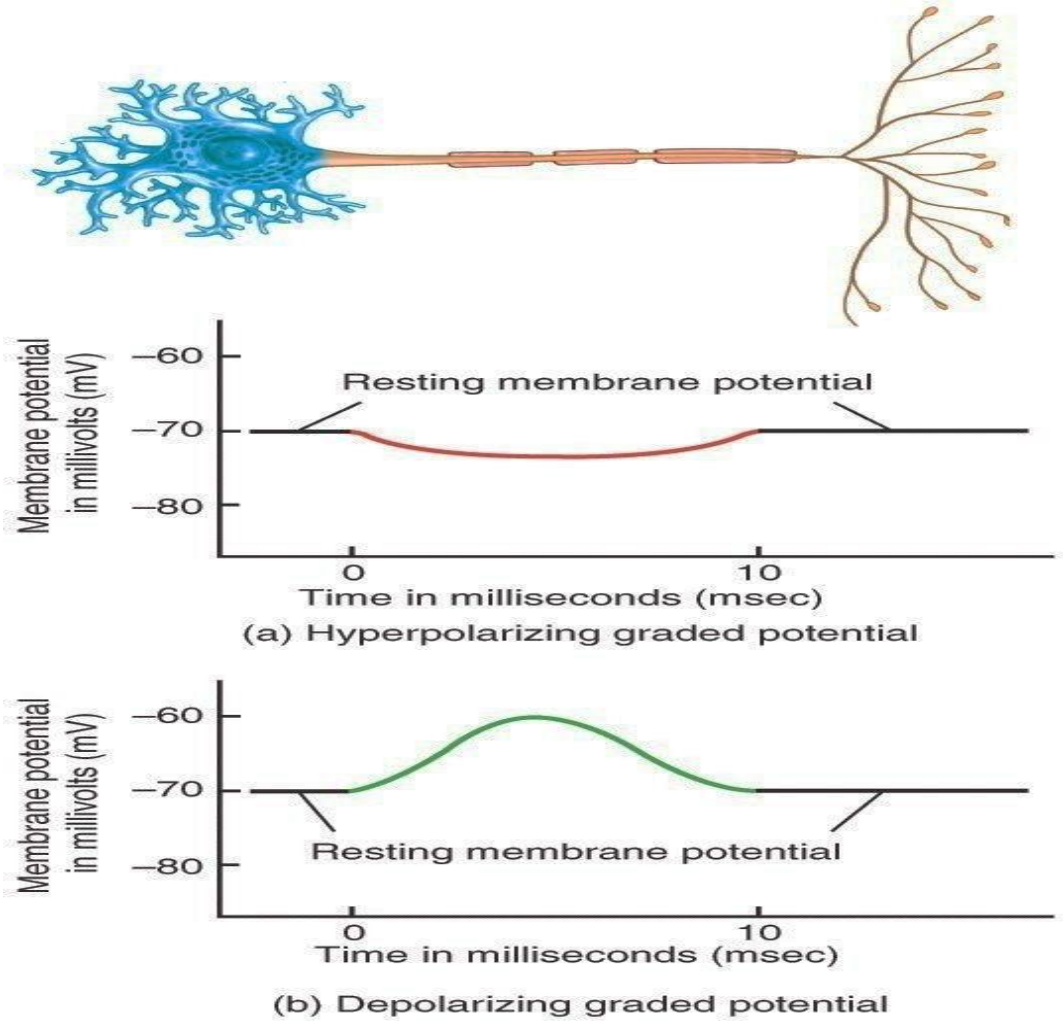
(c) Mechanically-gated channel

A graded potential occurs in response to the opening of a mechanically-gated

Graded Neuronal Potentials

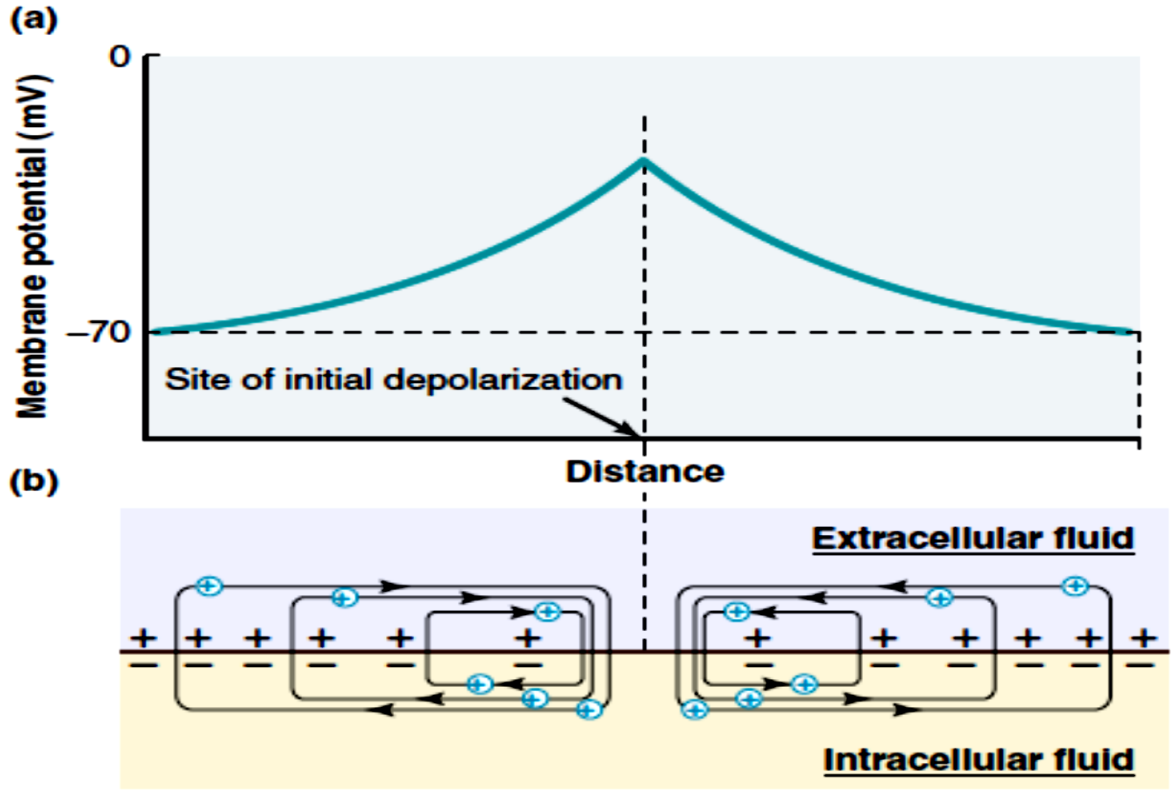
- Small localized Changes (deviations)) in resting membrane potential initiated by an appropriate stimulus
- Graded potentials are brought about by external stimuli in sensory neurons, (receptor potentials) or by neurotransmitters released in synapses, where they cause graded potentials in the post-synaptic cells
- Graded potentials are the only means of communication used by some neurons play very important roles in the initiation and integration of the long-distance signals by neurons

This is for example an EPSP signal potential, localized and its amplitude depend on the amount of (.....)
(action potential أتوقع حكى)



Graded potentials are localized and travel only a short distance form site of stimulation

The membrane potential of a cell can be depolarized by using a stimulating current generator, and the potential can be recorded by a pair of electrodes, one inside the cell and the other in the extracellular fluid,.
(a) Membrane potential is closer to the resting potential with increasing distance from the depolarization site.
(b) Local current surrounding the depolarized region produces depolarization of adjacent regions. Ie grades potentials are **decremental**

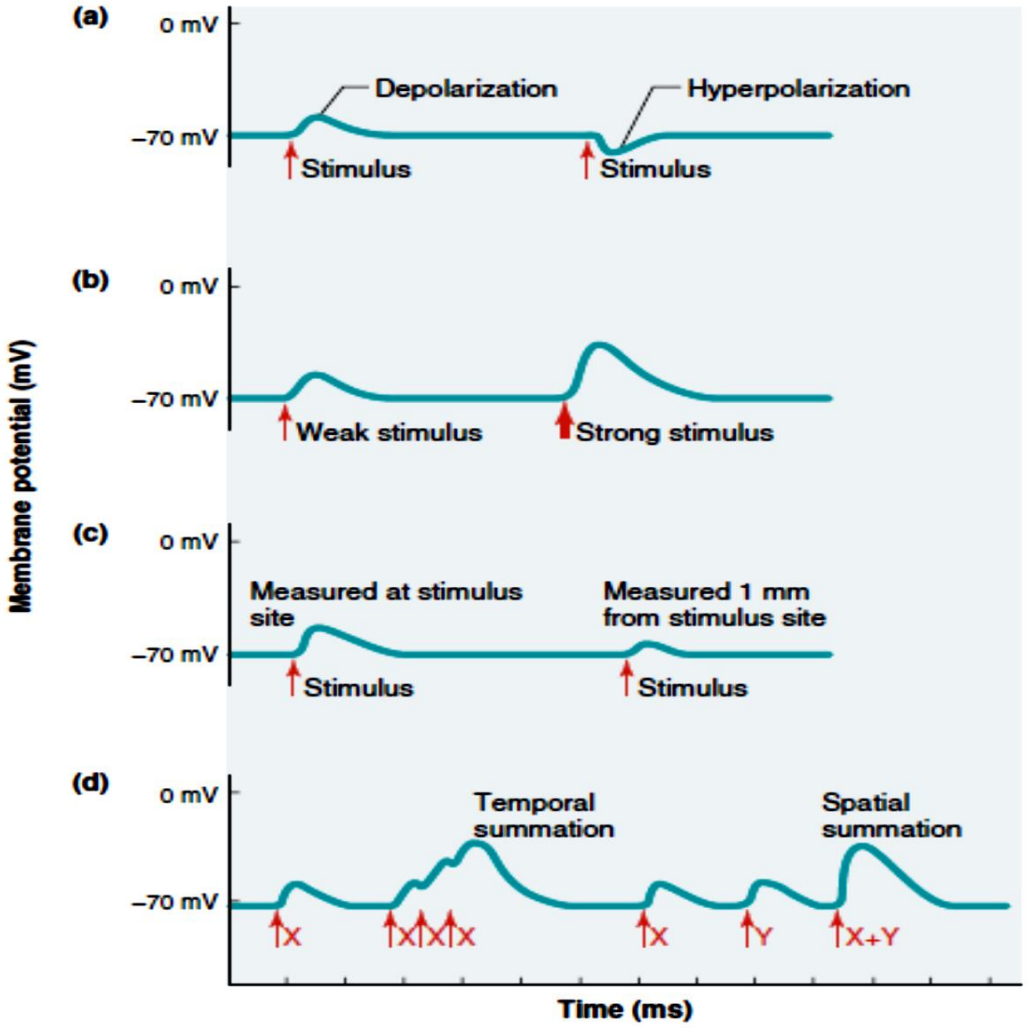


Decremental: assume that you'll record an electronic potential or a local potential at this site, if you move away of the cell body it's gonna decline, its amplitude will decline, also they don't propagate like the none-or-all, they propagate like the local time therapy, if the speed of the cell body it will propagate

الكلام بعد هيك مش مفهوم للأمانة بس في جدول تحت ملخص للحكي كامل

Graded potentials and their properties

- Graded potentials are neuronal potentials which can be recorded for examples at synaptic site or in various types of sensory receptor
- Example of graded potentials are synaptic potentials and receptor potentials
- Graded potentials properties :
  - can be depolarizing or hyperpolarizing
  - can vary in size and amplitude depending on stimulus strength
  - are conducted detrimentally, localized and do not propagate long distances
  - can be summed. Temporal and spatial summation



Comparison of graded potentials and action potential

Characteristic	Graded Potentials	Action Potentials
Origin	Arise mainly in dendrites and cell body (some arise in axons)	Arise at trigger zones and propagate along the axon.
Types of channels	Ligand-gated or mechanically gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Not propagated; localized and thus permit communication over a few micrometers.	Propagate and thus permit communication over long distance.
Amplitude	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All-or-none; typically about 100 mV.
Duration	Typical longer, ranging from several msec to several min.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of an action potential) or depolarizing (excitatory to generation of an action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present, thus spatial and temporal summation can occur.	Present, thus summation cannot occur.

Thank you for your attention