Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 1

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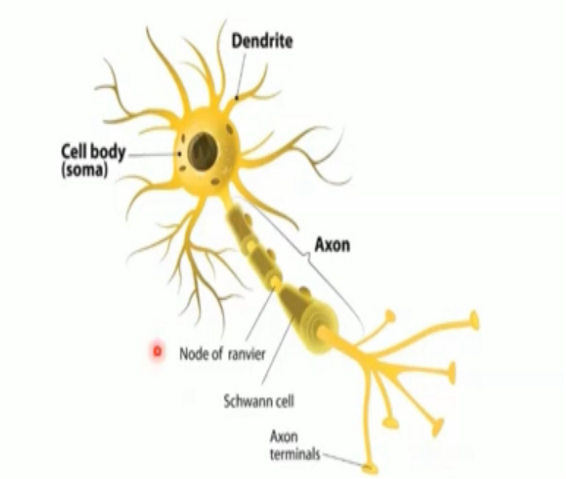
Introduction

بسم الله الرحمن الرحيم

The first thing we want to discuss in this lecture is the neuron, because the neuron is the functional unit in the CNS.

The neuron in general consist of cell body (soma), the cell body has multiple dendrites which the neuron uses to communicate with other adjacent neurons, and it projects an axon leading to the axonal terminals that play an important role in facilitating the communication between different neurons.



- The axon of neuron can be either **myelinated** or **unmyelinated** depending on the type of neuron and the region of the central nervous system (because the brain and the CNS have both gray matter and white matter which depend on abundance of myelinated or unmyelinated)

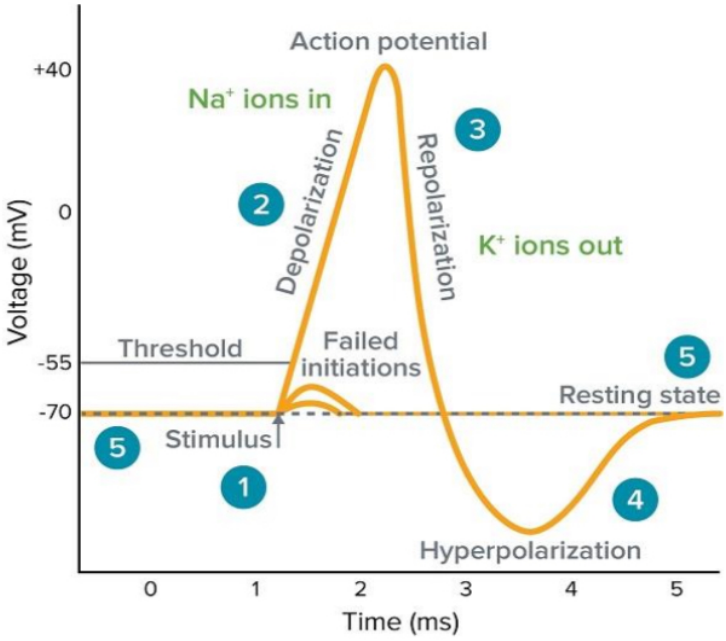
- The major function of neurons is to transmit signals, these signals can be translated into so many functions.

The main function of neurons is propagated by transmitting action potential that is a sudden pulse of an electrical signal that is transmitted through the neuron. This is how the neuron gets activated of neuron so it can transmit the signal to another neuron. So, the neuron is activated by electrical changes.

- الصورة هاي بتمثل الaction potential، تبعوا بالكلام مع الصورة

- The action potential has different phases:

1- In normal conditions (at the inactivating level), when the neuron is resting, the neuron will be in a resting membrane potential = -70. The resting membrane potential is created due to the difference between charges, in other words there is "voltage difference", when we said "voltage difference" this means that there is separation of charges, and when there is a potential this means that you have energy to do activity.



* The separation of charges happens through the lipid bilayer of the neuron (plasma membrane), and there is multiple cations (ex: Na+,K+) and anions travel across the plasma membrane, and there is negatively charged proteins which are trapped inside the cell (so they account for large extent of the negative charged inside the cell.

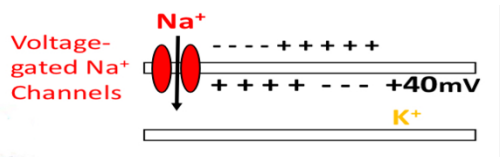
* the negativity of resting membrane potential is accounted for mainly by the leakage of K+ from inside the cell (K+ leakage channels) —> the membrane is more leaky for K+ than Na+ (6 times).

وبالتالي كونه بتسرب بوتاسيوم كثير لبرا هاد الاشي بخلي الpositive charge برا الخلية.

أما الNa+/K+ channel بتساهم بالchemical gradient بحيث تخلي الNa+ أعلى برا، والK+ أعلى جوا

2- Once the neuron receives the signal and becomes activated, the neuron switches to the "**depolarization phase**", this means that the activation happened and this activation triggers the opening of special channels called "voltage gated Na+ channels", they are very sensitive to changes in voltage, if the voltage across the membrane changes up to -55 (the threshold level of neuron) they suddenly open and allow the rapid influx of Na+ inside the cell then there will be inversion of the charge so the potential will reach (+30 - +40)

وهاد بسميه الdepolarization لاني عكست الpolarity تبعت الmembrane potential كانت negative وصارت positive.

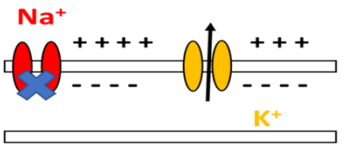


* The threshold level follow the rule of "**all or non**" —> If the stimulus doesn't reach the neuron to the threshold level, then no **action potential** will fire.

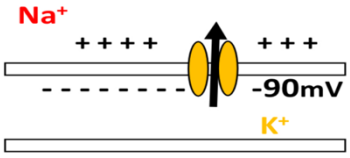
يعني ما في نص stimulus بعمل نص action potential، يا بوصله ليعمل action potential يا لا

3- The "**Repolarization**": the membrane turns back towards the negativity, this phase is mediated by:

1) inactivation of voltage gated Na+ channel, this prevent the entry of further sodium ion (happens at +30 - +40)
2) At the same time (at +30 - +40 membrane voltage), other K+ voltage gated channels open, this allow K+ to travel to the outside of the cell.



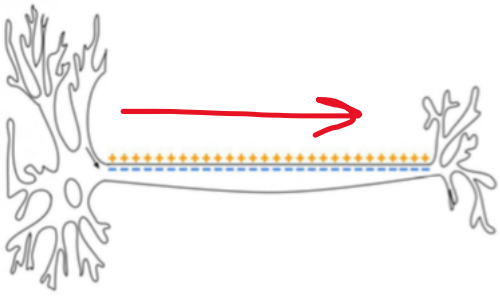
4- The target is to return to the resting membrane state after the ending of stimulus, but sometimes the opening of voltage gated K+ channels become prolonged, so more K+ will travel to the outside of the cell and the membrane potential will be -90 (more negative) —> **hyperpolarization**.



5- The K+ channels get closed, Na+/K+ pump will pump again and K+ will leak out of the cell. So, we will turn back to the resting state again.

الصور عند كل نقطة كانت عبارة عن cross section، وهون الneuron كامل.

You activate one segment of the neuron, the Na+ channels open then the action potential depolarization happens and this allows the signals to be transmitted from one section of the neuron to the adjacent section.



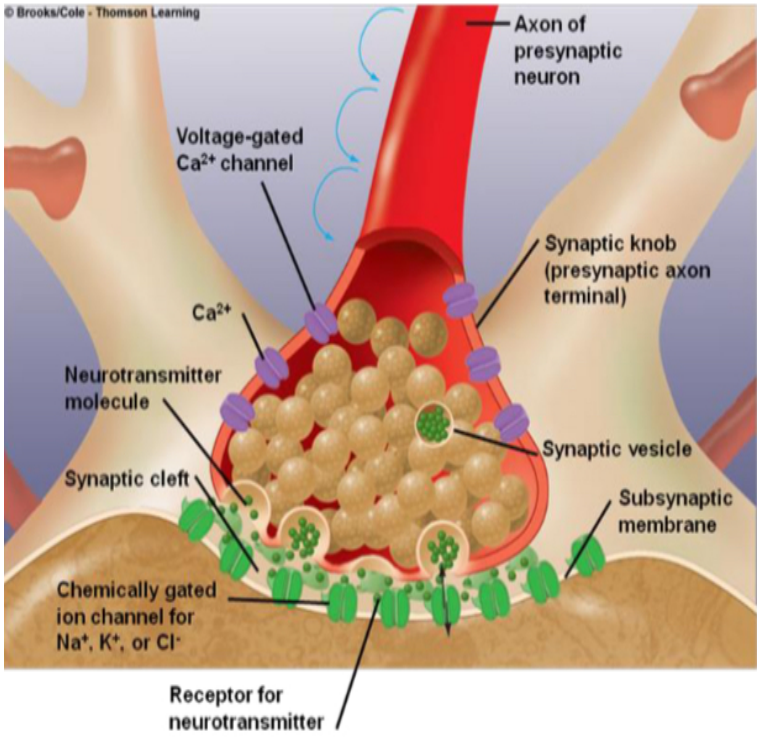
سؤال: ليش الsignal بتمشي باتجاه واحد (زي السهم الأحمر) ليش ما بتمشي لجزء وبعدها بترجعله؟ يعني ليش ما منقدر نرجع نعمل activation للNa+ channels؟

- منلاحظ انه بمرحلة الrepolarization أول اشي بصير بس يوصل الجهد ل40+ انه ال voltage gated Na+ channels اللي صارلهم activation بدخلوا بinactive state فبسكروا، فبهاي المرحلة ما منقدر نعمللهم كمان stimulation فاللي صارله activation من قبل ما رح يصيرله activation أكثر، فما منقدر نعمل activation الا للchannels الموجودين downstream.

أسئلة بالسلايدات للمراجعة:

- The resting membrane potential is established by the electrochemical gradient of K+
- Depolarization occurs mainly due to the influx of Na+
- Hyperpolarization occurs mainly due to the efflux of K+
- The type of ion channel that accounts for rapid depolarization is Voltage-gated Na+ Channels
- Action potentials move in one direction. T or F?

➢ The synapse:



- How 2 neurons communicate with each other?

One neuron transmits the signal to the other neuron through forming the synapse (the region of meeting of 2 neurons with each other, formed by the axonal terminals of one neuron "presynaptic neuron", the 2 neurons are separated by synaptic cleft, followed by the postsynaptic membrane or "postsynaptic neuron")

- The synapse is a very complex structure containing multiple channels, mediators, enzymes, etc..

- but we didn't answer the question yet, the signal can be transmitted from one neuron to the other by using chemicals called **neurotransmitters**. So, if one neuron is activated presynaptically, it can transmit the action potential to the next neuron bu using neurotransmitters.

*So, one of the important components of synapses is that: The synapse contains multiple vesicles packed with neurotransmitters and stored within presynaptic neuron.

➢ Neurotransmitters:

- Endogenous chemicals that enable neurotransmission (from one neuron to the other or from the neuron to the effector organ such as a muscle).
- Released by the arrival (or activation) of action potential (depolarization) at the nerve ending.

هسا هل هدول التعريفين كافيات حتى نحكي عن المادة انها neurotransmitter؟

في خصائص معينة زي هدول:

➢ What Makes a Chemical Substance a Neurotransmitter?

1) The chemical must be synthesized in the neuron (we can bring a chemical that can be neuroactive, can cause changes in neuron and initiate action potential, but we don't call it a neurotransmitter because it isn't biologically synthesized by the neuron it self. Examples: drugs & toxins)
2) When the neuron is active, the chemical must be released and produce a response in some target (must be released upon the activation of the neuron and should have effect on the target cells).

3) The same response must be obtained when the chemical is experimentally placed on the target.

4) A mechanism must exist for removing the chemical from its site of activation after its work is done.

يعني لازم يكون اله established mechanism بحيث يصيرله inactivation أو removing

➢ Types of CNS neurotransmitters:

- Acetylcholine (the main excitatory neurotransmitter in the PNS)

- Nicotinic and muscarinic receptors.

- Amino acids, examples:
  - GABA (gamma-aminobutyric acid)

    - GABA and GABA receptors
  - Glycine

    - Glycine receptors
  - Glutamate

    - AMPA and NMDA receptors

- Biogenic Amines, examples:
  - Catecholamines:
    * Norepinephrine
    - Adrenergic receptors

    * Dopamine:

    - Dopamine receptors
  - Serotonin

    - Serotonin receptors

- Peptides رح نوخد عنهم محاضرتين كاملين لقدام
  - Endogenous opioids

    - Opioids receptors
  - Substance P

➢ We can classify the neurotransmitters based on function:

- If the neurotransmitter was released from the neuron and resulted in the activation of the second neuron (mediating an action potential) —> we call it **excitatory neurotransmitters (**1- acetylcholine 2-glutamate (amino acid)**)**

- If the neurotransmitter was released from the neuron and resulted in the inactivatin of the second neuron —> we call is **inhibitory neurotransmitters (**1- GABA (gamma-aminobutyric acid) 2- glycine 3- endogenous opioids**)**

يعني اذا في عنا neuronal pathway، وهاد الneuronal pathway شغال وfiring بعدين رحنا طلعنا عليه inhibiting neurotransmitters، هاد الpathway رح يطفي.

- There is a group of neurotransmitters that **can be excitatory or inhibitory (Biogenic amines:** 1- catecholamines (norepinephrine&dopamine) 2- serotonin**)**.

طيب شو اللي بده يخلي هاد الneurotransmitter يكون مرة excitatory ومرة inhibitory ؟

1- Neuronal pathway (if the neuron is excitatory or inhibitory)
2- The receptor/ target organ.
3- Doses.

These neurotransmitters have different types of receptors (for example: serotonin has 7-8 receptor subclasses) —> so maybe the receptor it self has an excitatory or inhibitory function

جدول من الكتاب بلخص اللي حكيناه قبل عن الneurotransmitters وبأي مكان بشتغلوا من الدماغ:

NEUROTRANSMITTER		POSTSYNAPTIC EFFECTS
	Acetylcholine	Excitatory: Involved in arousal, short-term memory, learning and movement.
BIOGENIC AMINES	Norepinephrine	Excitatory: Involved in arousal, wakefulness, mood, and cardiovascular regulation.
	Dopamine	Excitatory: Involved in emotion, reward systems and motor control.
	Serotonin	Excitatory/Inhibitory: Feeding behavior, control of body temperature, modulation of sensory pathways including nociception (stimulation of pain nerve sensors), regulation of mood and emotion, and sleep/wakefulness.
AMINO ACIDS	GABA	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization. Mediates the majority of inhibitory postsynaptic potentials.
	Glycine	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization.
	Glutamate	Excitatory: Mediates excitatory Na^+ influx into the postsynaptic neuron.
NEURO-PEPTIDES	Substance P	Excitatory: Mediates nociception (pain) within the spinal cord.
	Met-enkephalin	Generally inhibitory: Mediates analgesia as well as other central nervous system effects.

كونه حكينا انه اللي بحكم شو الoutcome للneuronal signal انها excitatory or inhibitory

١) الneurotransmitter ٢) الreceptor

وبناءً ع هاد الحكي أي signal لأي neuron منقدر نعرفها انها excitatory أو inhibitory، ولذلك احنا منسمي الaction potential اللي بنتج من activation of excitatory neuron —>

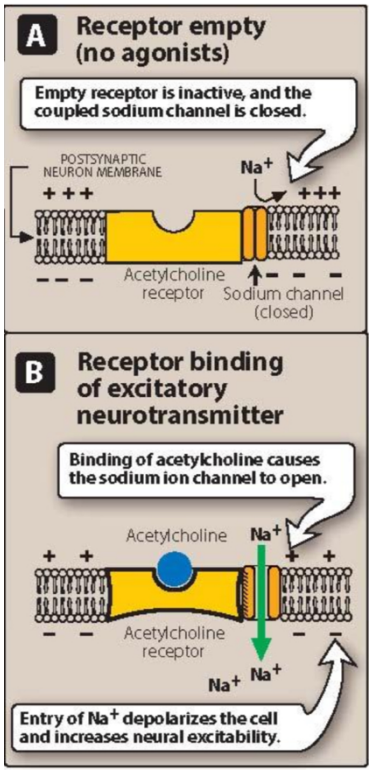
Excitatory Postsynaptic Potentials (EPSP)

يمعنى انه هاد الneuron عمل signal أدت لل activation/excitation of the postsynaptic neuron

• Release of an excitatory NT

• NT binds to its receptor on the postsynaptic neuron

• Influx of Na+ or Ca++⟶ depolarization



*Example in the picture —>

The receptor is activated by the binding of acetylcholine, so it

Is ligand gate.

This receptor is an ion channel, so once it is activated by acetylcholine (excitatory neurotransmitter), the Na+ channels will open and this allows the rapid Na+ movement inside the cell —> depolarization and active action potential in the post synaptic neuron.

*تذكير سريع:

الفرق بين الligand channels & voltage-gated ion channels :

الligand channels بتحتاج ترتبط بمادة معينة عشان يصيرلها activation، أما الvoltage gated بتحتاج يصير في تغيير بالmembrane potential، ولكن الoutcome تبعهم واحد.. هم بس بختلفوا بطريقة الactivation.

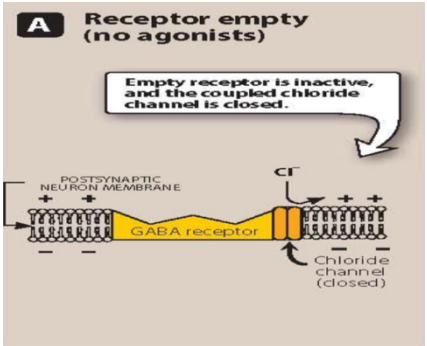
The Inhibitory Postsynaptic Potentials (IPSP):

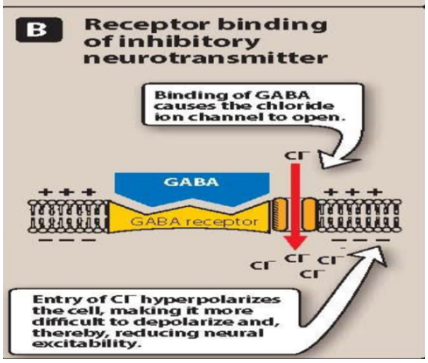
هون صار في active presynaptic neuron وصار في action potential وصل للaxonal terminals بس هاد أدى لإفراز inhibitory neurotransmitter زي الGABA او الglycine، فهاد الneurotransmitter رح يطلع من الpresynaptic neuron ورح يربط بالreceptor بالpostsynaptic neuron والنتيجة رح تكون inhibition.

• Release of an inhibitory NT

• NT binds to its receptor on the postsynaptic neuron

• Influx of Cl- or efflux of K+⟶ hyperpolarization

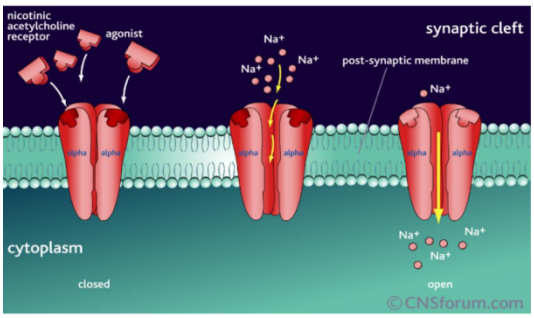




*Example in the picture —> GABA receptor (ligand gated ion channel for Cl-). So, when GABA is released from presynaptic neuron and binds to its receptor, the receptor will be activated and opened. This allow the entry of Cl- to the inside of the cell —> the membrane potential will be hyperpolarized.

وبالتالي بصير أصعب انه نعمل activation للneuron

❖ The predominant excitatory neurotransmitter in the brain is **Glutamate**.
❖ The predominant inhibitory neurotransmitter in the brain is **Glycine**.



➢ Receptors of CNS:

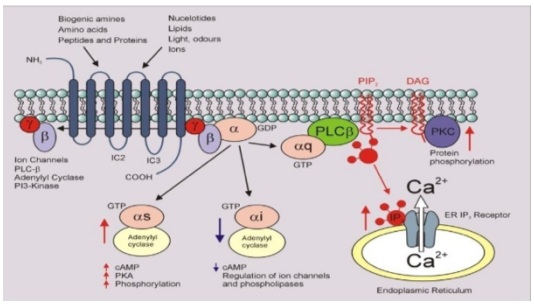
There is two main type of receptors:

• Ionotropic

▪ e.g., Ligand-gated ion channels

• Metabotropic

▪ e.g., G-protein coupled receptors (GPCRs)
▪ May or may NOT lead to ion channel opening.



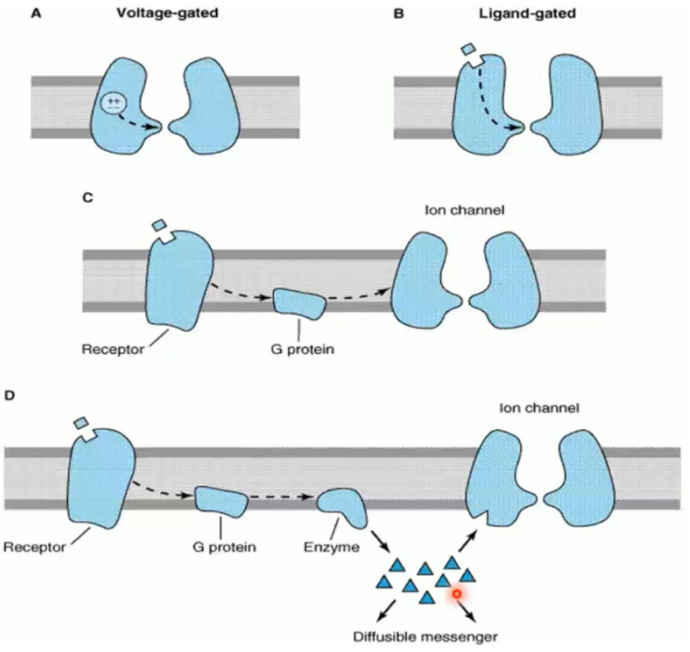
❖ **Note**: The acetylcholine has 2 types of receptors:

1- nicotinic receptors (ligand-gated)

2- muscarinic receptors (protein coupled)

وبالتالي زي ما حكينا انه الreceptor نفسه للneurotransmitter نفسه (زي الacetylcholine) ممكن يكون مختلف، يا بكون ligand-gated وقت يرتبط فيه الacetylcholine بصيرله activation وبتعمل excitatory postsynaptic potential أو بتكون protein coupled بأدي ل cascade of signal transmission within the postsynaptic neuron

*الملخص: اخدنا ٣ أنواع من الreceptors خلال المحاضرة:



1- voltage-gated ion channels (A in picture)

2- ligand-gated ion channels (B in picture)

3- G-protein coupled receptor: needs a ligand to activate it (neurotransmitter)

وهاد الreceptor اما بنتج عنه انه يعدللنا الfunction تبعت الion channels بغض النظر شو هي <— (C in picture)

أو تعمل second massenger signaling cascade وتغيرشغلات معينة بالpostsynaptic neuron <—

(D in picture)

➢ Types of CNS Receptors

زي ما قسمنا الneurotransmitters حسب الeffect تبعها ع الpostsynaptic neuron ممكن نقسم الreceptors بنفس الطريقة (بناءً على النتيجة اللي بتصير لما يحدث receptor activation on postsynaptic neurons)

❖ **Excitatory**:

• Ionotropic receptors:

- Nicotinic acetylcholine receptors

• Metabotropic receptors:

- Muscarinic acetylcholine receptors
- Dopamine (D1) receptors

❖ **Inhibitory**:

• Ionotropic receptors:

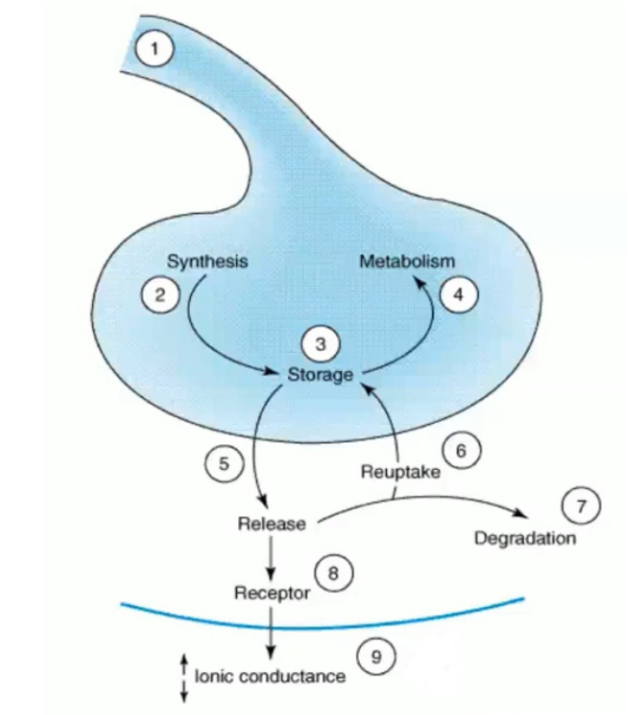
- $GABA_A$ receptors

• Metabotropic receptors:

- Opioid receptors
- $GABA_B$ receptors

➢ The role of pharmacology:

The drugs can target any component of the neurotransmitter cycle.



طيب شو اللي بصير بالneurotransmitter cycle ؟

* نتبع بالخطوات مع الرسمة:

١- الaction potential بيجي من الaxon ويؤدي لل release of neurotransmitter

٢- هسا احنا انه من خصائص الneurotransmitter انه يتصنع داخل الneuron، وبالتالي في اله synthesis pathway

٣- الneurotransmitter لازم يصيرله storage & packaging في الsynaptic terminals

٤+ ٧- حكينا انه أي neurotransmitter لازم يكون اله metabolism & degradation pathway

٥- وقت يصير لل neurotransmitter تخزين، ولما يصير في activation لل neuron بصيرله release من ال presynaptic neuron لل synaptic cleft

٦- بعدين ممكن جزء من ال neurotransmitter يصيرله reuptake and recycling على ال presynaptic neuron

٨- ممكن يروح على ال postsynaptic target ويربط بال receptor تبعه

٩- واذا ربط بال receptor تبعه هيك بصير في activation سواء كان excitatory او inhibitory

وبالتالي هاي هي ال neurotransmitter cycle وممكن نتدخل بأي خطوة فيها دوائيا..

- Sites and Mechanisms of CNS Drug Action:

- The first step: "release of neurotransmitter"

As we said that the neurotransmitter is only released upon the activation of the presynaptic neuron by the arrival of action potential to the synaptic terminal. Can we prevent the occurrence of action potential in presynaptic neuron?

The answer is yes! And this is the mechanism of action of: •Local Anesthetics •General Anesthetics

- The second step: "synthesis of neurotransmitter"

We can either inhibit the synthesis (such as certain type of drugs that inhibit the enzyme tyrosine hyrdoxylase that is responsible for the synthesis of catecholamines, so we can prevent the neuron from norepinephrine synthesis for example) or promote the neurosynthesis of neurotransmitter (by drugs such as L-dopa, and it's used for the treatment of parkinson disease)

- The third step: "storage"

We can interfere with storage (ex: dopamine and catecholamines are stored within noradrenergic vesicles in presynaptic neurons

وبضلهم جاهزين لحتى يصيرلهم release، عشان تدخل ال dopamine & norepinephrine داخل ال vesicles في channels/transporters بسميهم VMAT

طيب اذا ما سمحت للدوبامين يدخل ال vesicles هيك مش رح اقدر استفيد منه، وبالتالي هل في دوا ممكن يعمل inhibition لل VMAT channels هاي؟ اه في، واسمه reserpine

- شو النتيجة بتكون لو استخدمت الدوا؟

You're going to interfere with the release of neurotransmitter and prevent the signal from propagating from one neuron to the other.

- The fourth step: “metabolism”

We will discuss in next lectures about drugs that interfere with metabolism of neurotransmitters. We have different enzymes (such as COMT and MAO) , each enzyme is concerned with the metabolism of certain neurotransmitter, and there is drugs that interfere with them such as •Antiparkinsonian •Antidepressants

- The fifth step: “the release of neurotransmitter”

There are drugs that interfere with the release of neurotransmitter from the presynaptic neuron, we call these drugs —> **CNS stimulants**, many of them are drugs of abuse

رح نوخدهم بمحاضرة لحالهم

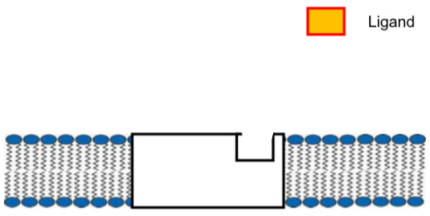
- The sixth step: “receptor binding”

We can interfere the neurotransmitter at the delivery of the receptor.

والأدوية اللي بتشتغل ع هاي الreceptors ممكن تكون:

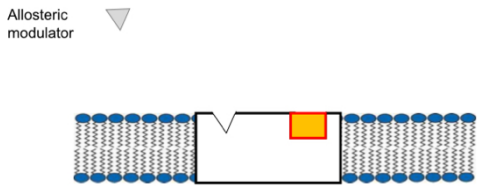
•Agonist —> results in the activation of the receptor

•Antagonist —> it competes with the activating ligand and prevent it from binding to the receptor



•Biased agonist

•Allosteric modulators —> if it was positive it will increase the affinity of the receptor to the original ligand and if it was negative it will decrease the affinity of the receptor to the ligand



- The seventh step: “signaling in postsynaptic neuron”:

We have drugs that can interfere with signaling, especially if the receptor was metabotropic receptor —> Intracellular effects: •cAMP degradation inhibitors

- The eighth step: “degradation”

There are drugs that inhibit the degradation of neurotransmitters, so the neurotransmitter will be more available in the synaptic cleft and its action will be more prolonged.

Example: drugs used in treatment of Alzheimer’s Disease, such as: •Acetylcholine esterase inhibitors

- The last step: “neurotransmitter reuptake”

بعد ما الneurotransmitter يصيرله release ويعمل الaction تبعه على الpostsynaptic neuron وبعدين يصيرله degradation، ممكن كمية منه نرجع نوخدها ونخزنها بvesicles وهيك بوفر energy

- There are drugs that interfere with the reuptake of neurotransmitters, such as:
•Antidepressants

*أسئلة بنهاية الملف:

1- GABAA receptors are example of:

a) Excitatory ionotropic receptors.

b) Inhibitory metabotropic receptors.

c) Voltage-gated channels

d) Inhibitory ionotropic receptors.

e) Excitatory metabotropic receptors

Answer: d

2- Which ion is allowed inside the cell upon GABAA receptor stimulation?

Answer: Cl-

3- You are the leading physician-scientist of the research and development team in a pharmaceutical company. Your team is working on the development of novel therapies to treat Parkinson’s disease. Parkinson’s disease is characterized by decreased dopaminergic stimulation in the brain. In your research proposal, you include several strategies to improve parkinsonism by targeting different biochemical processes of dopamine signaling. Which of the following mechanisms will NOT be included in your proposal?

a) Inhibition of the vesicular monoamine transporter 2 (VMAT-2).

b) Inhibition of catechol-O-methyltransferase (COMT)

c) Designing more efficacious D2 receptor agonists.

d) Designing novel therapies that promote the regeneration of substantia nigra dopaminergic neurons.

Answer: a

نهاية التلخيص، سامحونا إذا كان في أخطاء غير مقصودة..

Good luck Hope.

"وإن أصابكَ عُسْرٌ فانتظر فرَجًا
فالعُسرُباليُسرِ مَقرونٌ ومُتصِلُ!"