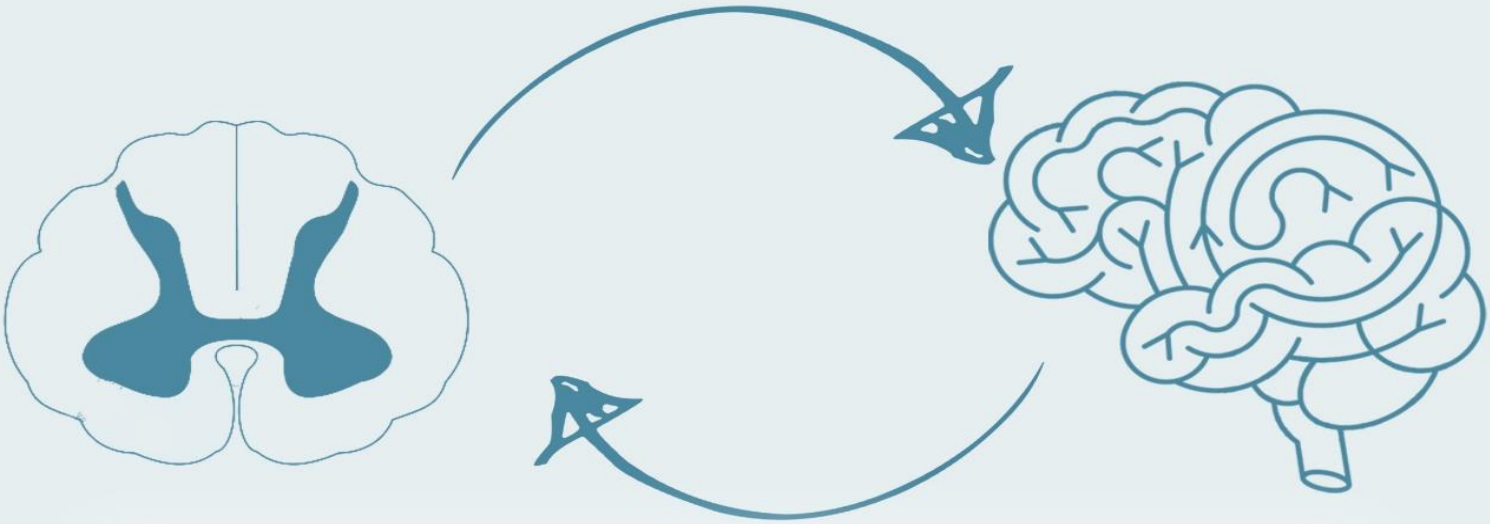

# CNS

## physiology

slides sheets

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| number | 19 |
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# Synapses and Neurotransmitters

Today we will talk about **neurotransmitters**, their location, receptors and function.

N**eurotransmitters** are chemical synapses that will transport the information from one cell to another.

The function of **neurotransmitters** depend on the receptors more than the **neurotransmitters** itself, the receptor will make the effect and the function on the postsynaptic cell. Mainly we can divide the receptors into two subtypes:

- The first type is ionotropic receptors; receptors directly open an ion channel and depending on the ion channel activation either excitation or inhibition occurs, and
- The second one is the metabotropic receptors; these receptors are second messenger receptors that will activate a second messenger which will exert multiple effects including:
  - The opening of an ion channel and working as the first type either inducing simple excitatory or simple inhibitory effects.
  - Also, the activation of several enzymes or internal signals inside the cell, which have prolonged effects in the cell thereby causing more than simple excitation or inhibition, instead it will change in the norm of the cell like changing the threshold, width of the action potential.

In general even if we're talking about a second messenger; any second messenger that makes the cell more excitable or easier to excite, we call it excitatory, and any second messenger that works on the cell or activates an enzyme for example leading to a less excitable cell or make the cell more resistant to excite we call it inhibitory. Therefore a second messenger receptor whether it was excitatory or inhibitory and works by many cascades like cGMP, PLC system, DAG, cAMP, it will have certain characteristics like; **prolonged effect , potent and induce changes in the cell it self and how it works.**

Because of that we usually call the **neurotransmitters** that work mainly by activation of a second messenger modulators (neuromodulators), they modulate the function of the cell and change the excitable characteristics of it. Example: imagine that you have integrated circuit (IC) inside a board and you take it and put another one the result not only make it excitable or not but you change how it already works.

We have other terms that we already talk about which are: **agonist**, **antagonist** and the **allosteric inhibitors**.

**1)** If a molecule manufactured or generated and associated with the activating site of the receptors and caused its activation we call it **agonist** and usually we say that **neurotransmitters** are the ultimate agonist or the bioavailable agonist.

For example when we say dopamine receptor, dopamine here is the agonist that we deal with.another term is super agonist, Ex: we have a dopamine receptor, the bioavailable agonist for it is the dopamine but if we produced a molecule that can bind with dopamine receptor in the same place of dopamine (on the activating site) and this molecule made the activation stronger and better than dopamine we call it a **super agonist** (because in comparison to dopamine it is much better and causes more activation).

If we have receptor, its function is peeling potatoes and when we put one molecule of dopamine on it for one minute it will peel one hundred potatoes (100potatoes/min), we conclude that the **dopamine** is the bioavailable agonist and its activity is the production of 100 pieces of peeled potatoes in a minute. But if we made another molecule that will exert the same effect of dopamine but instead of producing (100potatoes/min) it produced (170potatoes/min), this molecule is thus called a super agonist.

**2) Antagonist** is any molecule that binds to the active site of the receptor and makes NO effect (it doesn't activate the receptor), rather it prevents the agonist from binding. Following the previous example, if we made a molecule that binds to the active site of receptor and there were no peeled potatoes produced -> this molecule is an antagonist.

This situation is a little different In our body because we always have bioavailable agonist thus when introducing the antagonist it will exert its effect by preventing the agonist from binding therefor the number of activated receptors will be less, hence if I put one agonist and one antagonist on the same receptor I will find that half of the time it will work with the agonist and the other half it will work with antagonist, so instead of giving (100potatoes/min) it will give (50potatoes/min).

This brings us to two related terms **affinity** and **efficiency**, if they are equal in affinity the result will be (50potatoes/min) but if the antagonist has double the affinity so 2/3 of the time will be occupied by the antagonist and 1/3 of the time by the agonist so the result is a third hundred= (25potatoes/min).

As for the efficiency we already said an agonist is any substance that will bind to the receptor and make it able to do the same effect as a **neurotransmitter,** but different agonists have different efficiency levels compared to the **neurotransmitter** therefore if we put a molecule and it produced only (5 potatoes/min) this molecule is an agonist but it has very low efficiency. Another example If I have a room that contains only dopamine it will produce (100potatoes/min), but if I put the low efficient agonist with dopamine for two minutes and this agonist has 1:1 affinity compared to dopamine the resulting amount of peeled potato will be (100potatoes/min) in the first minute by dopamine and on the second minute the agonist will bind and produces only (5potatoes/min) the result is 105.

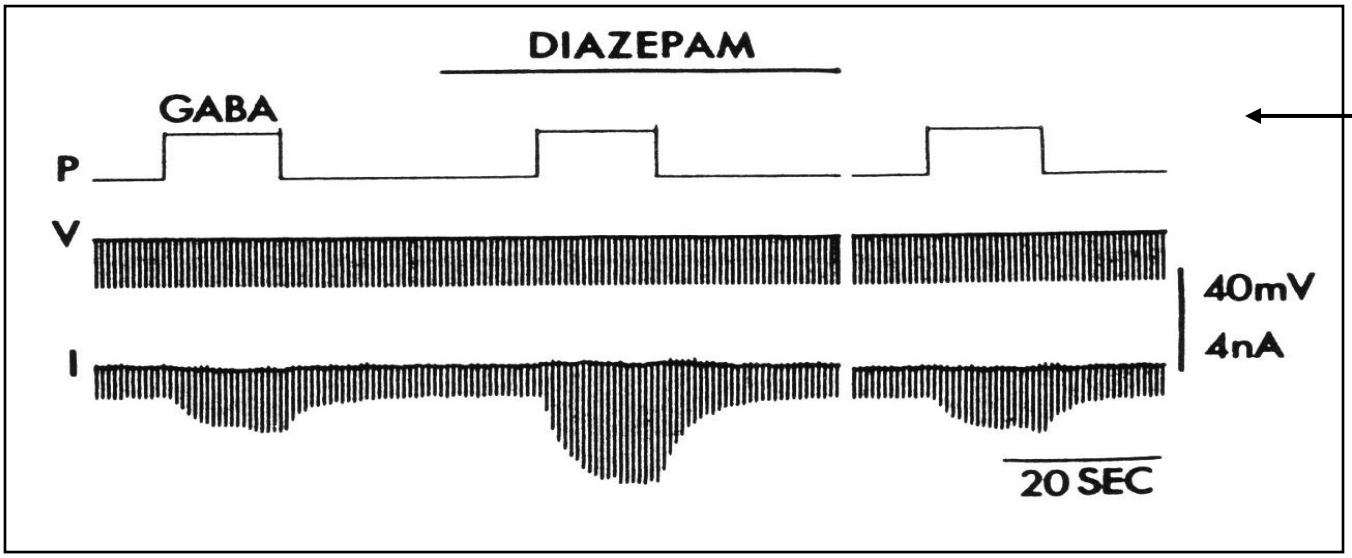
On the other hand if I didn't put the agonist and left the dopamine only the result will be 200. This low efficient agonist is thus called a **partial agonist** or **weak agonist** which works like an **antagonist**. If I put my weak agonist in a room which is empty from dopamine it will give 10, for sure if I have a number is better than have nothing but if I have certain amount of **neurotransmitter** this weak agonist will work as an antagonist and this is true; some drugs work as weak agonist (they are not real antagonist).

**3) Allosteric modulators**: any molecule that if we put it on the receptor it will bind with the receptor on a different site and change the way of activation of the receptor making it more active , facilitate binding of the agonist to the receptor and thereby increasing the efficiency and affinity of the agonist, or it makes the efficiency more only when the receptor bind to the agonist, for

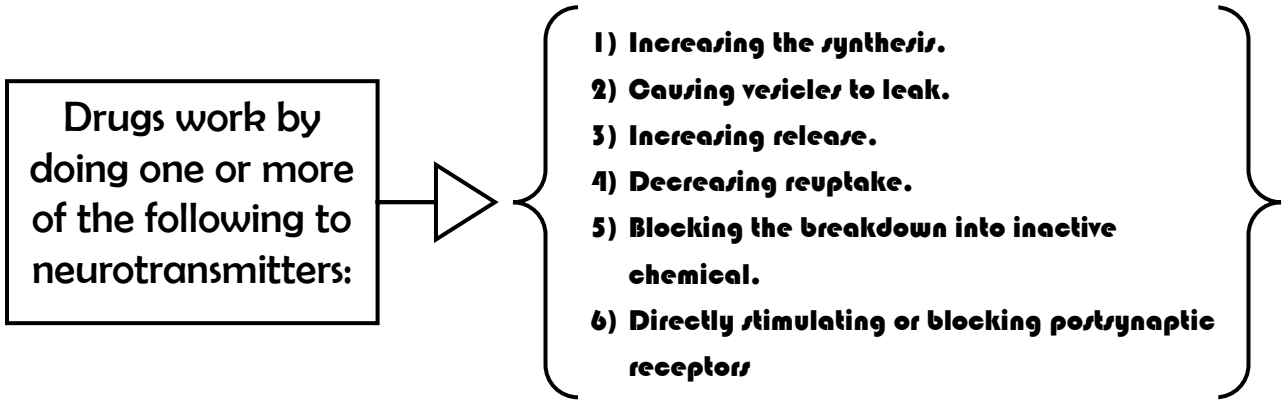
example if we make a molecule and we put it in the same receptor of dopamine for the potato peeling and in the presence of dopamine it give us (123potato/min) we call it an allosteric modulator, and if I manifest another molecule which doesn't bind on the same place of dopamine and it makes the response of dopamine receptor weaker (80potato/min), we call it allosteric modulator.

Anything that binds to another place than the receptor agonist and changes the efficiency of the receptor we call it allosteric modulator. There are a lot of types of allosteric modulator and there are misnaming for them: positive allosteric modulator, negative allosteric modulator, positive competitive, positive non-competitive, to make it easier, whatever the type of allosteric modulator; if the efficiency increase in the presence of the agonist-receptor we call it **allosteric modulator,** and anything decrease the efficiency or block it completely in order to prevent agonist from binding or if it binds to it and this binding prevent the production or the efficiency decrease we call it **blocker**.

**Experiment:** P shows how the allosteric modulator work; on the top we see the amount of GABA they use on this receptor and the duration, the last line shows the current. GABA is inhibitory **neurotransmitter**, because of that it will make hyperpolarization, when we give one of the allosteric modulators alone there will be no effect but when we give GABA in the presence of allosteric modulator we will notice more hyperpolarization; it give potentiation for the receptor.



The effect on the synapse will begin after the production of **neurotransmitter**; action potential will open voltage gated ion channels on the axon terminals, calcium will enter and initiate the **neurotransmitter** release, **neurotransmitter** will bind to the postsynaptic receptor and do an effect for a certain time but after a while **neurotransmitter** must be cleared out, this clearing is done either by **degrading by enzymes**, **pick up by transporters** or **diffusing out**, all these steps: production, release, receptor binding, clearing out are potential targets for drugs, the change happen here and give an effect to the cells.




For **neurotransmitters** we mainly look on them as a two subtypes:

1) Mainly work through ionotropic receptors, they are fast acting neurotransmitters.

2) Mainly work through metabotropic receptors (second messenger receptor), neuromodulators.

## ☒ Fast Neurotransmitters:

1. **Glutamate**: The first one and the most common one on the fast-acting neurotransmitters is the **glutamate**, it is the main excitatory neurotransmitter on our body (it is 95% from the excitatory (not total) synapses inside our cells), why?

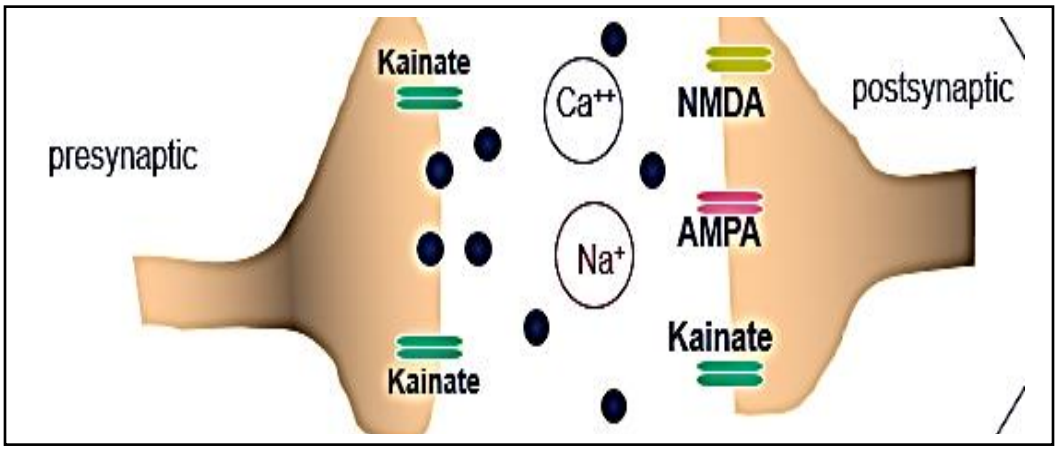
In all of the long pathways we talked about (ALS, PCML), vision, and auditory pathway the synapses between first order and second order neurons are **glutamate** synapses, most of the connections inside the brain are **glutamate** connections.

Actually **glutamate** is one of only two **neurotransmitters** that we find inside the cerebral cortex (the whole cortex contains only two **neurotransmitters** one of them is **glutamate**). The production of **glutamate** is not very important but it works through two types of super families of receptors (we have two families of **glutamate** receptors):

1. Ionotropic receptors: is the most common, more in number and more in distribution;
2. Metabotropic receptors: which are less common, less in number and distribution, we find them in smaller amount.

So glutamate works by metabotropic and ionotropic but because the ionotropic receptors are more in number (we found them more), we call glutamate a fast acting neurotransmitter. Some of the metabotropic receptors are excitatory and some are inhibitory, and we talked about an inhibitory metabotropic receptor in the case of retina.

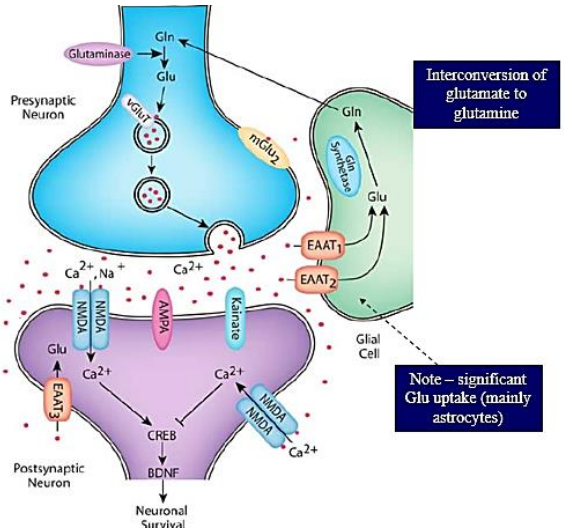
We will concentrate more on the ionotropic receptors, it is a one family but it has 3 subtypes; the first one is **NMDA receptors** the second is **Kainate receptors** and the third is **AMPA receptors**, they are excitatory receptors thus they allow the passage of sodium and calcium . NOW what are the difference between those three receptors?



**Kainite** is the only one that can be presynaptic, we have presynaptic ion channels so they will make positive feedback. Now we have the **AMPA** and **NMDA,** one of the differences between them is that **AMPA** is fast acting and allow the **sodium** only to pass, but **NMDA** is slow acting (open and closes slowly), and mainly allow the passage of **calcium**.

What is the difference between the entry of sodium or calcium to the cell ?(Note that we will not concentrate about which one of them is fast and which one is slow), the answer is that **calcium** make activation of several enzymes and **calcium** alone considered a second messenger receptor, basically PLC system (phospholipase C cascade) end with (one of the big steps it makes) an effect on the cell which is the increase of an internal level of **calcium**, so **calcium** per se is a second messenger and because of that **NMDA** work as ionotropic and metabotropic and this increase the complexity of **glutamate** effect because it is slow in action, this will make a difference on many cells, because if you give one shot of **glutamate** only **NMDA** will work and according to the postsynaptic it may give an action potential and it may not, on the other hand if you give a bigger shot of **glutamate, AMPA** and **NMDA** will work and this for sure will give excitatory potential because it is the slowest and it allows the passage of two charges: **NMDA** will let the graded potential to reach the level of the threshold for sure and if it is present for a long time the level of **calcium** will increase more and more and it will pass from dendrites to the cell body so the effect will be as a second messenger and changes on the cell will occur, we will see the role of these changes in the cell for creating the memories.

The **glutamate** cleared out by **glutamate** transporter (**glutamate** excitatory amino acid transporter) in the synapses it will take glutamate and return it inside the cells.



We find **glutamate** everywhere in the CNS 95% of excitatory **neurotransmitters**. Because it is one of only two neurotransmitters found in the cortex and its effect is complex, any deficit on **glutamate** can make any deficit in the body and actually in many disorders we find a deficit in **glutamate**, but the problem is that there are no much differences in the receptors in different places of the body so usually they don't try to play with it and target it for drugs therapy, but recently there are some targeted therapy trials.

We have one disorder that has a strong connection with **glutamate** which is the STROKE, stroke means there are ischemia and decrease in oxygen; decrease in oxygen so the level of ATP will decrease and we noticed that the **glutamate** cleared out by A-transporter which needs ATP, if there is no ATP, transporter will not work so there will be nothing that clears out **glutamate** from the synapse.

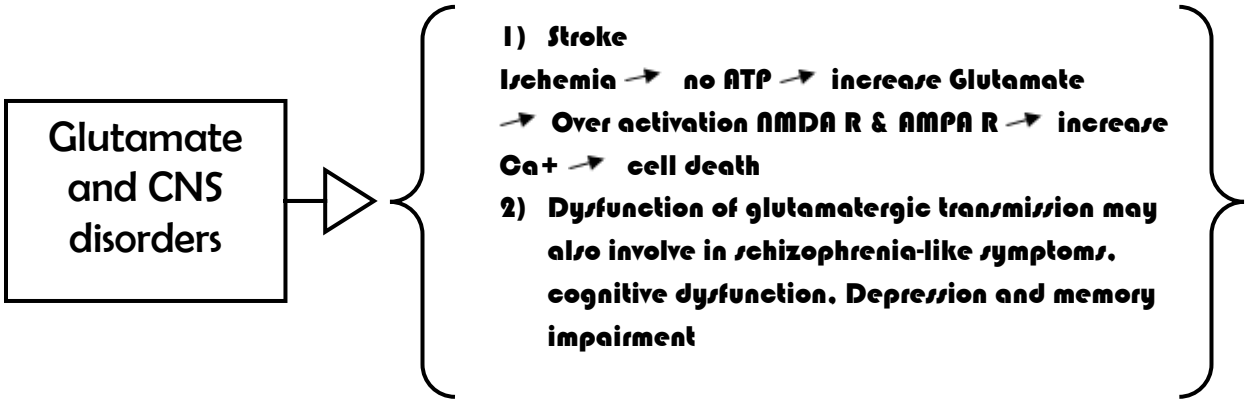
So what is the problem?

Excitation will stay for a long time, the neuron will do action potential continuously without stop, this is not dangerous but over excitation for glutamate receptors will open the AMPA then NMDA, NMDA stay open for a long time because the glutamate is not cleared so the Ca++ is still entering, and we already know from pathology about calcium and apoptosis , when calcium increases too much it will run the process of apoptosis so because of that if the neuron works too much by **glutamate** for a long time **calcium** will enter, if small amount of **calcium** it will make some enzymes work, but if it increases to a certain level apoptosis will start and neuronal death will occur (this is what we call excitotoxicity of glutamate).

The problem of stroke is summarized by the excitotoxicity for neurons and death, so to deal with stroke we give **glutamate** antagonist.

Actually when we give **NMDA** antagonist the cells will not die even if the ischemia and stroke occur, but the problem occur if the **calcium** is already inside the cell thus the drugs will be of no benefit so we must give it within a short period. There is a magic needle, sometimes the doctor leave it with patients in case they feel that there is a stroke they must take it, this needle has an **AMPA** and **NMDA** antagonist and **NMDA** antagonist is much more, if you take it within 20 minutes to half an hour the stroke and ischemia will occur without dying of any cell, but some people say that up to an hour or two. If the drug was taken the

number of damaged cells might decrease also the spread of the stroke lesion will decrease. We cannot know if there was a real stroke, on the MRI we will not see any defect if there was no damage to the cells.




2. **GABA**: The next **neurotransmitter** is **GABA**, it comes from glutamate, it is the second **neurotransmitter** in the cortex (the whole cortex contains only glutamate and GABA), GABA found in a higher level in the cortex which means the cells that carry GABA in the cortex are much more than the cells that carry glutamate in the cortex. The effect of it is important and sometimes the process of thinking need GABA more than glutamate. If you see a rounded thing and it was an orange, you need to make processing to reach the cortex and to know that this is an orange.
At first this round thing will do an excitation of all circular objects stored in memory, after a period of time the inhibition for all circular things other than the orange will happen, and this is done by **GABA**.

**GABA** is very important for processing more than for excitation, because it will decrease the noise or make the processing directed for one thing not others like in the example of the circular object above, another example we already know is how the inhibition at the level of sensation pathway (as the effect of the lateral inhibition) will increase the resolution; make it more clear, and this shows us the importance of **GABA** and the inhibition for processing.

In **GABA** we have two type of receptors:

1. Ionotropic receptor (GABA A receptor) and because it is inhibitory, it mainly allows the passage of chloride to induce inhibition of the cell, also there is another type of receptors
2. Metabotropic receptor (GABA B receptor), also it is an inhibitory receptor (G-protein coupled receptor).

| Ionotropic (GABA A) | Metabotropic (GABA B) |
|---|---|
| Heterooligomeric protein complex that consists of several binding sites coupled to an integral Cl- channel | G-protein coupled receptor, seven transmembrane domain protein |

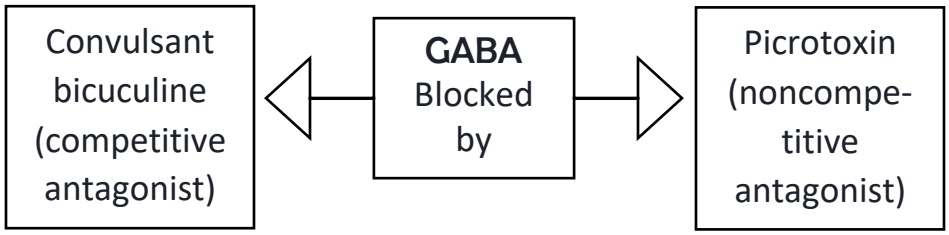
**GABA** ionotropic receptors are very common, very widely distributed in the cortex and because it is well distributed in the cortex, it has many effects and usually the effect is the inhibition of the receptors and what makes it more special is localization of the **GABA** attaching site in addition to the several allosteric modulator sites found in the receptor this helped in targeting several drugs that work on **GABA** (maybe directly bind to **GABA** site or on one of the allosteric site).

One of the most common allosteric site is general anesthesia. when we increase the **GABA** and thus increase its effect this will cause inhibition to the cortex so the excitation of the cortex will turn down, in this case, the person will fall asleep because of that, most of the general anesthesia work as a very potent allosteric modulator for **GABA**, example of allosteric modulator on **GABA** is alcohols.And Because GABA is very widely distributed dealing with general anesthesia is limited.

**GABA** is related to one disease which is the increase in the number of electric charges in the brain also called seizure and the epilepsy is the disease in which seizure happen with. Increase in charges means there is rhythmic activity for some neurons that will make activation for other areas which will spread and cause localized rhythmic activity and excitation, therefore problem in seizure is that there is an increase in the excitation so we deal with it by inhibition and we make inhibition

by **GABA**. Usually we don't give **GABA** agonist but we give another allosteric modulator (benzodiazepine, and barbiturate which are old famous drug therapy for seizure, they will potentiate the effect of **GABA**).

Another important allosteric modulator sites of **GABA** are sites that make negative allosteric modulator we call them blockers and they will block **GABA**, they will make manifestation for excitation so seizure is one of the symptoms And example of these blockers are certain toxins, chemicals and plant toxins collectively called picrotoxins which may cause direct seizures.



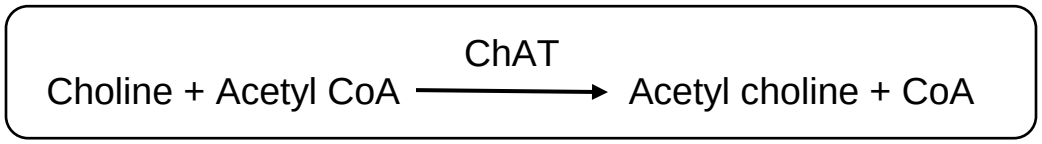

The old and most common drugs for the treatment of seizure and epilepsy are the potentiator for **GABA** but nowadays to decrease the side effect there are other new drugs, they try to decrease the excitation or increase the inhibition in other way, as when we go to the enzymes that increase the production of **GABA** or the ones that cause degradation for **GABA** and we controlled with them by decreasing the degradation or increasing the production, in this case we will have more **GABA**, and more inhibition hence it will help in the treatment of epilepsy.

**GABA** and glutamate have the same synthetic pool, both are produced from each other so the increase of **GABA** automatically will decrease the glutamate. Other ways and other drugs work on the decrease of excitation are the drugs that can deal with ion channels like voltage gated sodium ion channels, if I found something that will decrease the excitation, activity and increase the width, in this case absolute refractory period will increase thereby decrease the chance of synchronized strategy to happen, we call all of these things the new generation of epilepsy drug.

## ☒ Neuromodulators:

They are the **neurotransmitters** that will come from outside the cortex because as we said the cortex contain only 2 **neurotransmitters**, so usually the cells of these modulators will be outside the cortex they will send axons to the cortex and make modulation to how the cortex function and most of them work mainly by a second messenger, they will cause excitation and inhibition for the cortex and sometimes for a specific period they will change how that cortex process things.

**1. Acetylcholine**: is a **neurotransmitter**, when there is release of **acetylcholine** there is degradation by **acetylcholine** esterase and by this, we end the effect of it.




The **acetylcholine** has two types of receptors:

1. The first one which is the most common in the body is the nicotinic receptor because it is a fast ion channel type found on the skeletal muscles. It is an ionotropic receptor allow the passage of **sodium** mainly and a small part of **calcium** (excitatory in nature).
2. Muscarinic.

In the body we have muscarinic receptors in some sites but in the cortex we have both nicotinic receptors and muscarinic and both are present almost in equal division, some people say muscarinic is more, others say the opposite, so some say that we must put it with the fast acting and others say that we must put it with modulators, but in general because it comes from outside the cortex, so we consider it a modulator ,because it is a modulator for cortex more than directly interfering with processing (excitation and inhibition), nicotinic receptors are excitatory and most (not all) of the muscarinic receptors are inhibitory.

We find it outside the cortex and the cell bodies of it are found in two areas; one on the base of the forebrain (in the lower part of the front part of the brain),this is called nucleus basalis (collection of nuclei which are the biggest and most common ), on the other hand we have other nuclei in the upper half of the rostral half of the brain stem they also produce **acetylcholine** and a big part of them go to the cortex (so the source of it is the nucleus basalis and brain stem). From here it will go and make modulation for the cortex so there will be two pathways; part will go to the thalamus and from thalamus it will go to cortical area which binds with that thalamic nuclei, on the other hand, there are some fibers (some pathways) go directly to the cortex, the position of those which go directly to the cortex is the nucleus basalis.

Because they go to the thalamus and cortex, acetylcholine will mainly be involved with cortical areas which are related to the thalamus and therefore the sensory pathways because they involve most of the thalamic nuclei, thus when these sensations pass through the thalamus, acetylcholine can make potentiation for thalamus nuclei and sensory cortical area.

These acetylcholine receptors are Excitatory in nature they will make activation for sensation and because of that, the physiological function is the enhancement of sensory perception. When I make activation for **acetylcholine,** is it important to make activation for all cells that go to all sensory nuclei in the whole sensory cortex? Or can I cause activation for olfactory pathway only (for example)? I can select the pathway thus helping in the selective enhancement of perception.

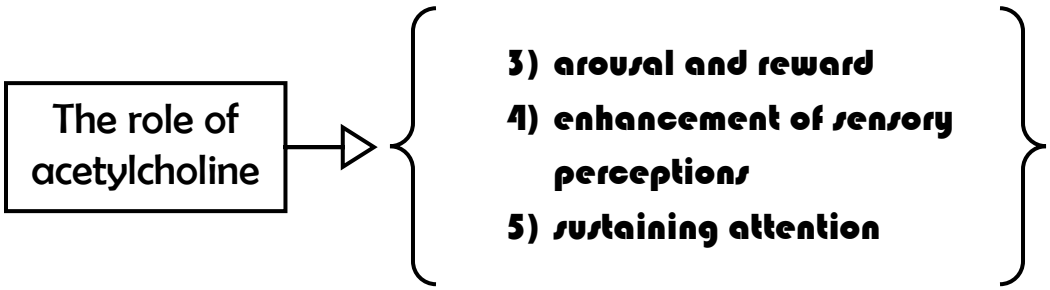
For Example: I receive 20 sensations from different things and different sites of the body and I decided to make excitation for one or two of them, the **association cortex** mainly will focus on these two which means I will be more aware of these two, that also means I will learn them and concentrate on them and thus saving these two pathways I am attentive to.

Therefore Acetylcholine is related to **learning and memory** because it is related to selective enhancement for sensation (another word for selective enhancement for sensation, when I say to you that you are making selective enhancement for two sensations out of all that means you are concentrating on these two, so it is related to attention).

We remember in yesterday lecture, when we saw the video we said that the prefrontal cortex make focus and attention on vision if it gives an order to make selective enhancement on white color and delete the black we will not see the gorilla, in reality, what happened is that the prefrontal will decide what color to concentrate on but to do so we need **acetylcholine** to cause sustained attention towards the color through making the vision more attentive and decreasing the attention towards other sensations; olfactory and touch.

I will make **acetylcholine** go to the places which are mainly related to the white color thus making sustained attention for white so it is related to enhancement of sensory perception and sustained attention.

Because it related to the attention it will help in **memory and processing**, and because it makes excitation for the cortex therefore it will have a role in the **waking up and arousal**, we will see this when we talk about sleep, if there is no **acetylcholine** there is no **sustained attention** so when the patient wants to remember what happened yesterday the prefrontal cortex tries to make attention to that area to make processing.




When I look to someone in front of me or when the doctor is talking in front of us, the prefrontal cortex, ( if I want to hear) will increase the **acetylcholine** which will try to explain what the doctor says and put it in sequence, but if there is no **acetylcholine** this selective and sustained attention will not occur.

In the previous example of vision if you wanted see white but the **acetylcholine** directed to the white instead of going to its related processing in the association cortex, it entered into other areas and began to pull other information, it cannot store or give sustained attention and it cannot take out information.

This will give me DEMENTIA (loss of **acetylcholine** will give dementia) and in ALZHEIMER disease, the main pathophysiological effect of it is the decrease of **acetylcholine** in neurons to the cortex, specifically the degeneration of acetylcholine neurons in the nucleus basalis.

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