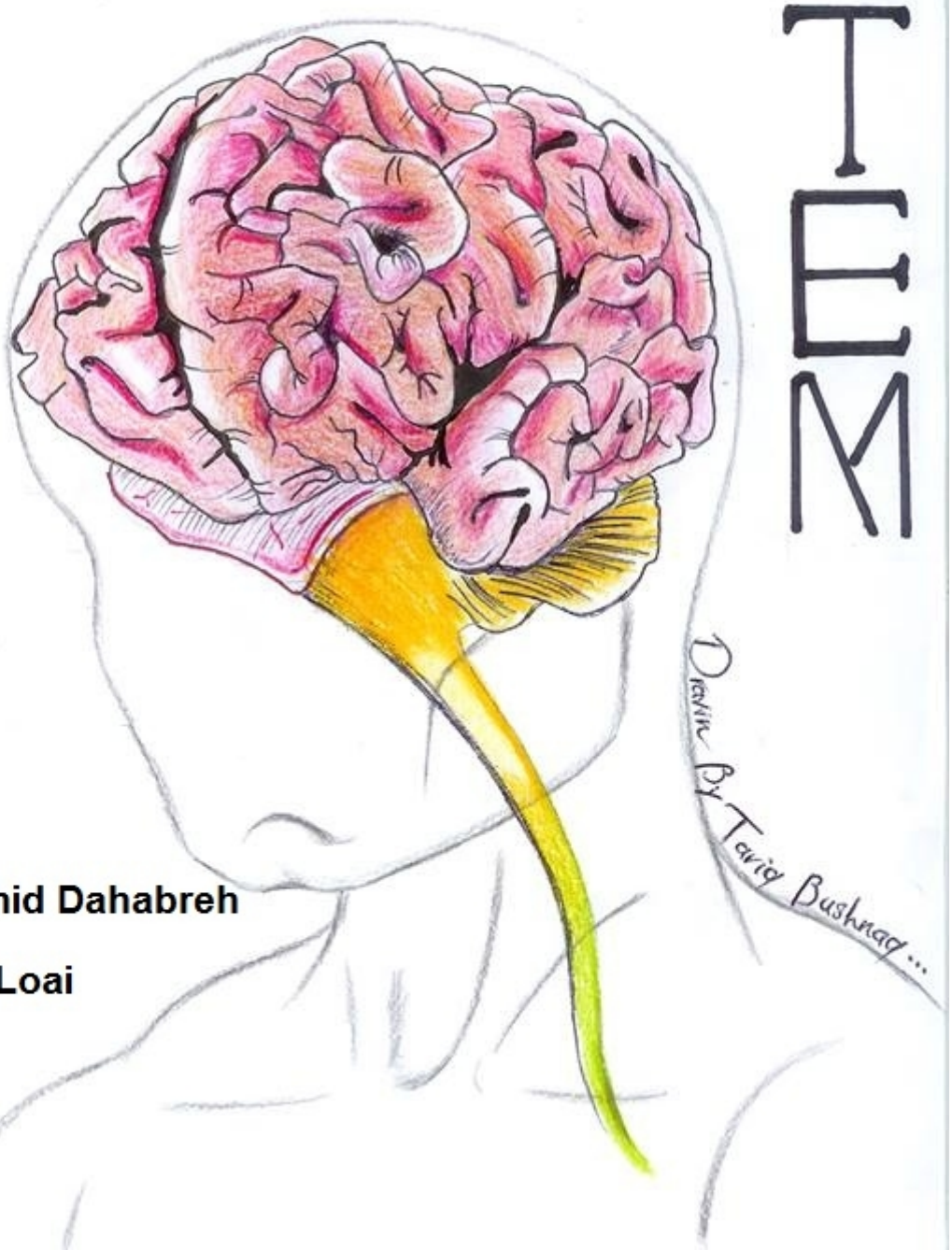
CENTRAL NERVOUS SYSTEM

- ○ Handout
- ● Sheet
- ○ Slide

- ○ Anatomy
- ● Physiology
- ○ Pathology
- ○ Biochemistry
- ○ Microbiology
- ○ Pharmacology
- ○ PBL



Drawn By Tariq Bushnaq ...

Done By: **Rashid Dahabreh**

Dr. Name: **Dr. Loai**

Lec #: **9**

Neurotransmitters (NTs)

Note: I tried to include everything that's important from the doctor's slides in this sheet so I don't think it would be necessary to refer back to them.

Let's dance now, shall we?

Regarding neurological Synapses, keep in mind that what's even more important than the Neurotransmitters themselves that will be released to the synapse are the receptors that these neurotransmitters are going to target because the type of these receptors will determine the effect of the neurotransmitters on the postsynaptic cell or neuron.

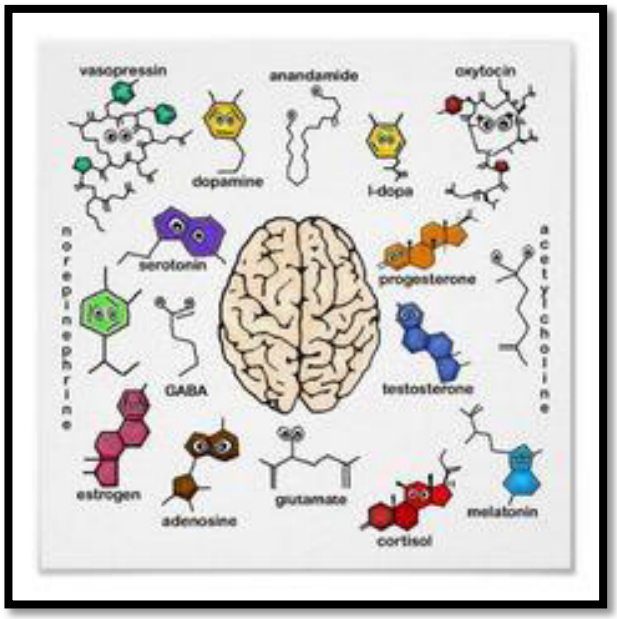
In general, what's the most important thing you need to know about neurological synapses?

1)You should know the neurotransmitters that act in the synapses as a starter and how are they synthesized (By especially knowing the rate limiting enzyme &/or substrate of the synthesis pathway) so we could regulate their synthesis and control their amounts in the brain .

2) The elimination mechanism of the NTs and where it's done .

3) The type of the receptors which they act on and the distribution for each receptor for each neurotransmitter

4) The role of NTs in CNS pathology.

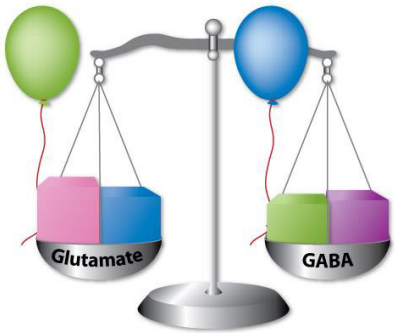


Types of Neurotransmitters:

More than 50 chemical substances do function as synaptic transmitters and the best way to classify the neurotransmitters is **according to the type of the receptors they act on**. That been said, we have two kinds of Neurotransmitters:

1) **Neurotransmitters that act on ion channel receptors**: They're FAST acting NTs, probably the most important ones are Glutamate and GABA (NOTE: 99% of neurological synapses in the cortex of the brain are either Glutamate-synapses or GABA-synapses,

keep in mind that any activity in the brain including making decisions or thinking is basically resembled as a modulation and a balance between excitation of synapses (Glutamate synapses) or inhibition of synapses (GABA synapses) whereas the other neurotransmitters in the brain work as modulators for long term effects where they reach the synapses and change some of neurons original characteristics making them more excited or less excited or even totally change the way they function .

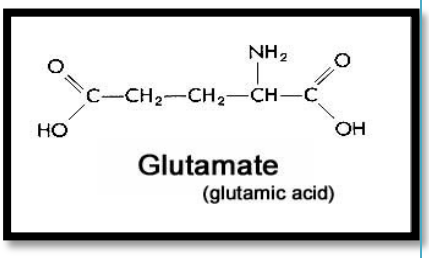


2) **Neurotransmitters that act on second messenger-coupled receptors:** They're SLOW acting NTs because they act on second messengers coupled receptors which are considered as MODULATORS because of their long term effect

We're required to know about certain Neurotransmitters such as:

Glutamte :

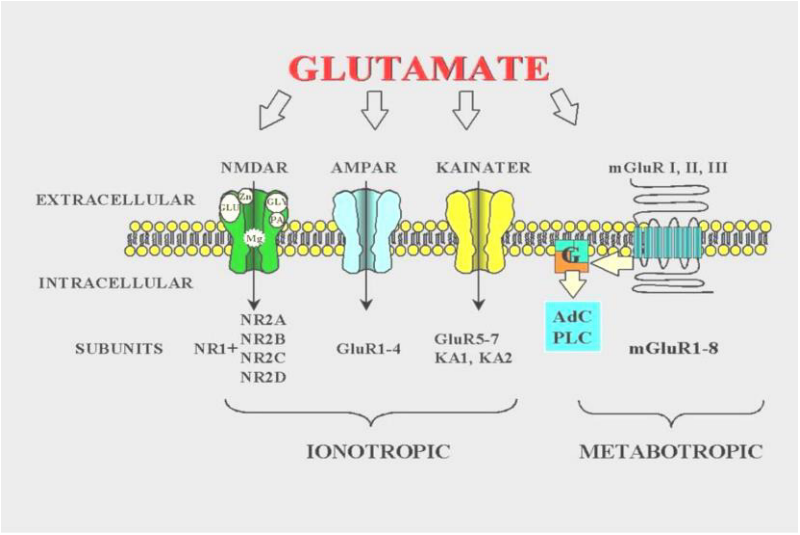
- It's the main excitatory neurotransmitter in the mammalian CNS
- 95% of excitatory synapses in the brain are **glutamatergic**
- It's the Precursor of GABA (the major inhibitory neurotransmitter)



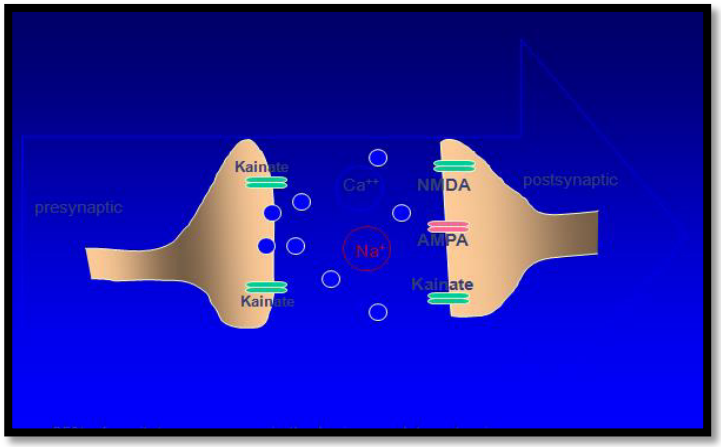
- **Glutamate works on 2 families of receptors:**

1) **Ionotropic receptors:**

-More common & more spread/ considered Ion channels receptors so they're fast acting/ All of these receptors are excitatory receptors (meaning they allow the entrance of Na & Ca upon activation) .



Note: Ionotropic receptors are of 3 types: **1- NMDA receptor 2- AMPA receptor 3- kainate receptor**. What's the difference between these receptors? They differ slightly in some aspects such as in how they react or in their functional position. Examples?

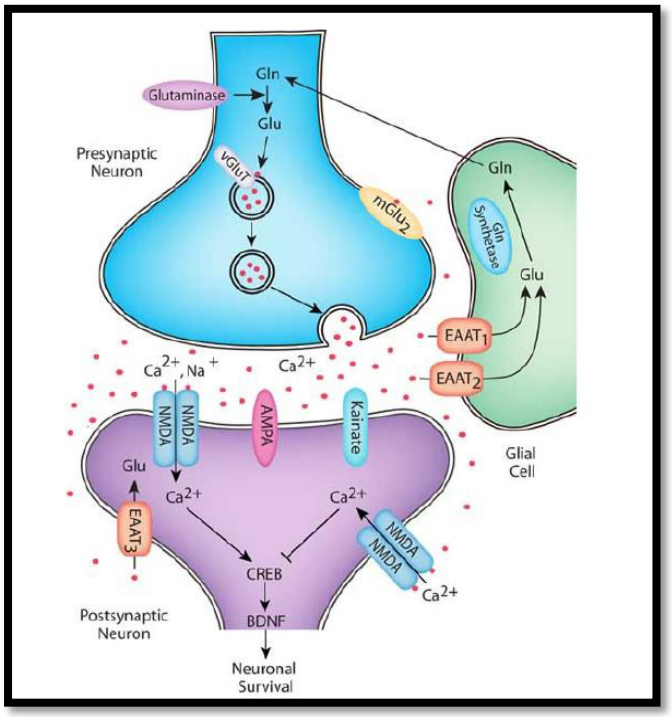


- The kainate receptor is the only one that's usually (but not always) a presynaptic receptor, what's the effect of this? Well, the kainate receptor is going to be a presynaptic receptor expressed on the same neuron that's releasing Glutamate to the synapse, the released Glutamate then would binds to them and that would lead to even more excitation (since the kainate receptors are excitatory ones and the Glutamate is the major excitatory NT in the brain) allowing the entry of more Na and Ca leading to more voltage changes and eventually inducing more Glutamate release. **In another meaning, the presynaptic kainate receptor is going to be involved in a POSITIVE FEEDBACK LOOP**.

- The NMDA and the AMPA are postsynaptic receptors but they differ in the time & the duration of opening in addition to the type of the ions they permit their entry to the cell. The NMDA receptor permits more Ca to enter than Na and it's usually slow opening with delayed closure unlike the AMPA receptor that allows more Na to enter than Ca and opens & closes faster. Thus, when there's excitation and release of Glutamate, the AMPA receptor would be the first one to open followed by the NMDA receptor allowing more and more Calcium to enter (Remember that Calcium functions in signaling transduction mechanisms in the cell. Therefore, it could modulate the function of neuron pushing it to become excited)

2) Metabotropic receptors:

Less common/ considered Second messengers couples receptors so they're slow acting / these receptors can either be excitatory or inhibitory



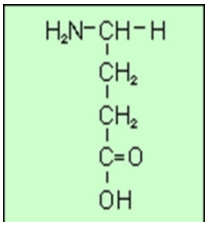
How Is the action of Glutamate eliminated (Clearance of Glutamate)? By either degradation of Glutamate by Enzymes OR it gets taken up from synapses by transporters (Excitatory Glutamate transporters that use ATP to function) and take them back to the neurons or surrounding cells such as Astrocytes and Glial cells.

As said before, Glutamate is the main excitatory neurotransmitter in the CNS. Therefore, many neurological pathologies or psychiatric disorders (such as Depression, Schizophrenia-like symptoms, cognitive dysfunction, Depression, and memory impairment) are related to dysfunction of Glutamatergic transmission. That's why targeting it by drugs is unlikable and uncommon unless in one pathological case related to Glutamate which is Stroke. What happens in case of a stroke?

Pathophysiology of a stroke: A stroke (whether hemorrhagic, embolic, or thrombotic) would lead to ischemia in the area of the brain affected by it = No oxygen Delivery which means no ATP production = Without any ATP, Transporters that take up Glutamate from synapses won't function (Remember They're ATP dependent) = Glutamate builds up in the synapses and that leads to over activation of NMDA & AMPA receptors leading to increase in intracellular Ca and eventually ends in Apoptosis and Cell death. Keep in mind that neural cells don't get regenerated upon death. Thus, death of neural cells in a sensory pathway would lead to loss of sensation OR death of cells in the motor cortex would lead to paralysis.

Clinical Note: Death of neural cells can be prevented in case of a stroke by giving a patient a medical injection within 20 to 30 minutes after the incident of stroke where the injection contains a drug that's a blocker or antagonist to the NMDA & AMPA receptors; This way, Glutamate won't work on them and you'd save the neural cells from death. Now you may think that the drug used would be GABA since it's the major inhibitory neurotransmitter but then you'd be wrong because the goal here isn't to decrease the level of excitation, which is what GABA would do, but to prevent the excitation totally by blocking the NMDA & AMPA receptors by antagonists. The only disadvantage of these injections is that they're only effective within the first 20-30 minutes from the incident of stroke, recent studies show that minimal effect would take place if the injection was given after an hour or two of having a stroke, but after that no effect would take place.

GABA:

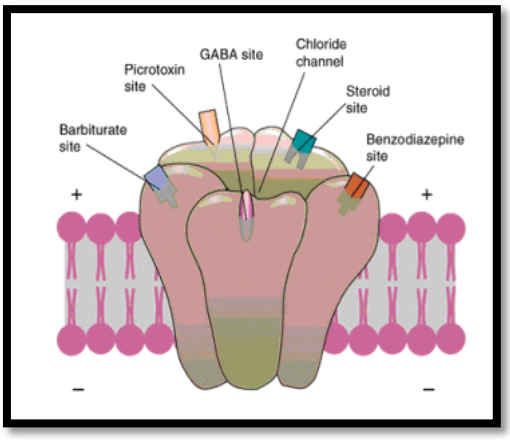


- The major inhibitory neurotransmitter in the mammalian CNS
- Synthesized from Glutamate

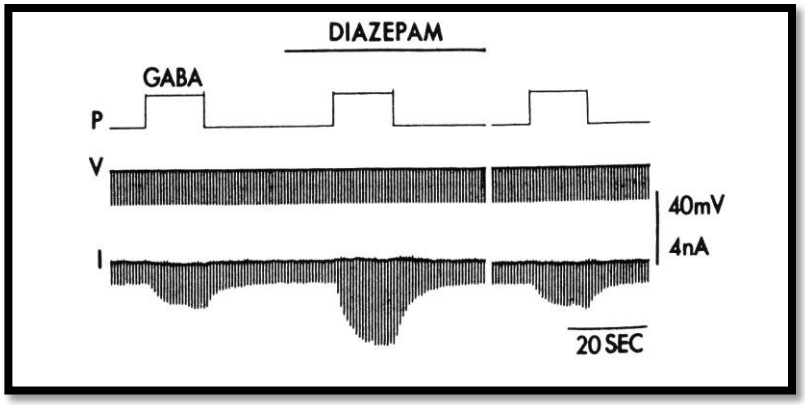
- **GABA acts on two families of receptors** (<u>These families are inhibitory receptors by binding to Cl channels and activating them allowing Cl to enter leading to inhibition</u>) :
  1) **Ionotropic GABA-A receptors**: more common and spread/ coupled to an integral Cl Channel / considered inhibitory receptors
  2) **Metabotropic GABA-B receptors**: less common and spread/ G protein-coupled receptors / also considered inhibitory receptors

- GABA functions to modulate and control the excitation of neurons (inhibition of excitation or decreasing the level of excitation helps for better processing)

About Ionotropic GABA-A receptors:



- An integral chloride channel is activated by competitive agonists: GABA and Muscimol .
- Blocked by convulsant Bicuculline (competitive antagonist) and Picrotoxin (noncompetitive antagonist- A blocker where it blocks the GABA-A receptor (Blocking the inhibition) which leads to convulsions or continuous seizures which may lead to death.



- Allosterically modulated by benzodiazepines and barbiturates which potentiate the effect of GABA, as shown in the following figure:

1)Upper line represents what drug is administrated and in what time (we give GABA and continue until a certain time

where the line flattens).

2)Second line is not important.

3)Third line represents a current which is a down current and clearly there is hyperpolarization (inhibition) upon inducing GABA (GABA= opening of CL channels= Cl enters= hyperpolarization and inhibition)

-The stage when we give Diazepam, which is a positive Allosteric modulator for GABA: Giving Diazepam but no GABA (the substrate) was present, the receptors are closed and no effect takes place BUT giving GABA at the same time and amount as Diazepam and for the same duration the receptors will open more and the effect of GABA would be more pronounced(more hyperpolarization and inhibition) due to the positive allosteric modulator, Diazepam.

Notice how once the GABA is depleted, Diazepam loses its function. So Diazepam is only an allosteric modulator (not an agonist). We have many allosteric modulators for GABA-A receptors such as : Diazepam, Barbiturate ,Benzodiazepines ,Ethanol (Alcohol) where it prolongs the time that the CL- channel remains open) and steroids which could be used in case of deep anesthesia before surgical operations because we want to turn off the cerebral cortex before the operation .

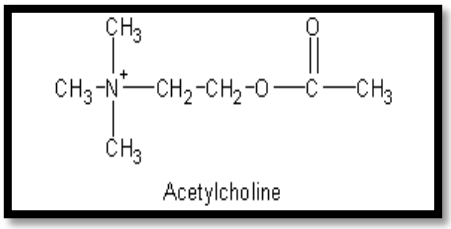
The Glutamate- GABA shunt:

We said that Glutamate and GABA are the major fast acting neurotransmitters in the brain where 99% of neurological synapses in the brain contain them. GABA is synthesized from Glutamate and then it's degraded into a form of Glutamate to restart the synthesis process. GABA and Glutamate are balanced & any imbalance would lead to many disorders but the most important one would have to be causing Epilepsy or Seizures (General excessive excitation state in the brain)- We'll get back to it later on.

Other neurotransmitters as mentioned are mostly considered modulators because they act on second messenger coupled receptors which are slow acting, examples on these Neurotransmitters:

Acetylcholine (Ach):

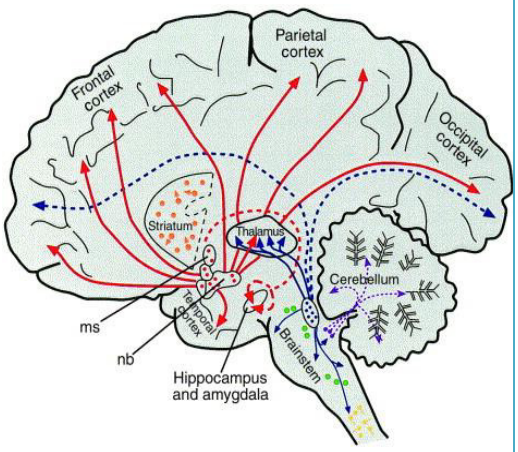
- Composed of Acetyl CoA +Choline
- Degraded in the synapse by Acetylcholine Esterase enzyme



Acetylcholine

- **Acetylcholine words on two kinds of receptors:**
  1) **Nicotonic receptors (Ion channels receptors**): Such as those found in neuromuscular junctions, they're also excitatory receptors.
  2) **Muscarinic receptors (Second messenger coupled receptor):** Could be excitatory or Inhibitory (Inhibitory such as those found in the heart).

- Acetylcholine source: It's not synthesized in the cortex but rather in The Nucleus Basalis which is found in the base of the brain- we also have two other small nuclei that synthesize Acetylcholine found in the brainstem.
- There are two distribution pathways for Acetylcholine in the brain:
  1) **Ventral pathway**: It will mainly go to the cortex directly (mostly to the frontal cortex) and activates it
  2) **Dorsal pathway**: It goes through the thalamus (which is responsible for processing sensory information) and then it continues to parts of the cortex related to sensation and activates it.

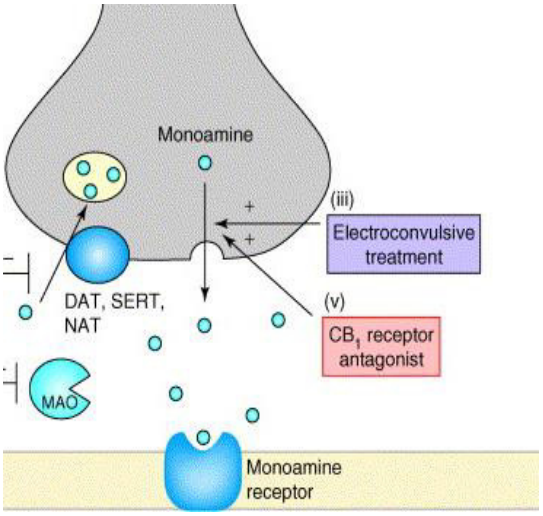


- **Function of Acetylcholine**:
  1) Arousal and Reward: It's an activation neurotransmitter so it would determine the level of activation of the cortex, that's why it has something to do with the waking up- sleep cycle
  2) More activation leads to more selective processing focusing on processing of certain sensory information- Enhancement of sensory perceptions(Like for example when you want to hear something, you want the brain to ignore processing of other sensory information you're receiving while listening and just focus on processing the hearing sensation)
  3) All areas of the cortex are always active but in a case like the one mentioned about (you want to hear something important), a certain area of the cortex becomes more active than the others due to Acetylcholine and that's why Acetylcholine is responsible for sustaining attention for example.

Clinical note: If Acetylcholine gets depleted, there won't be any activation of the cortex and no processing of information would occur leading to loss of memory (Remember that there's no memory stored without any processing and there's no processing without any memory) leading to Alzeihmer's disease (Loss of cholinergic cells in nucleus Basalis)

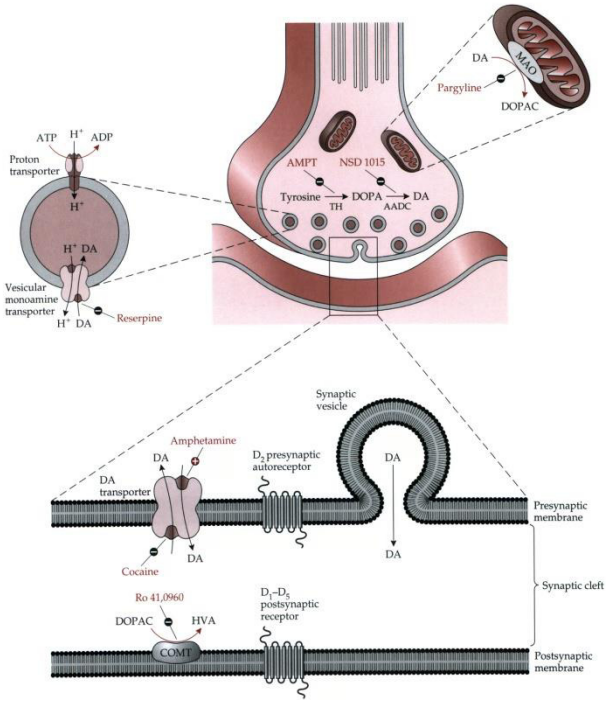
Biogenic amines:

- Neurotransmitters produced from certain amino acids, they include Dopamine Norepinphrine, Epinephrine, and Serotonin.
- Regarding the biosynthetic pathway for the Catecholamine Neurotransmitters, There's a rate limiting enzyme in the beginning of the pathway called **Tyrosine Hydroxylase** where its activity level would determine the amount of Dopamine, Norepinephrine, and Epinephrine in the brain.
- All biogenic amines function in the same manner in Synapses, released to the synapse and then eliminated by degradation enzymes (Like COMT enzyme which is found in the liver + mainly Monoamine oxidase- MAO enzyme) OR transporters that take them up from the synapse (We have different kinds of transporters, ones that are non selective and take up any biogenic amine, we have ones that are partially selective which may for example take up 60% of Dopamine whereas it would take up 40% of Serotonin (Mix transporters), and transporters that are only selective to one biogenic amine (like selective dopamine transporters for example)



Dopamine:

- Always work on G protein coupled receptors. There are 5 subtypes of these receptors (D1, D2, D3, D4, and D5) where D1 &D5 are the only excitatory ones and the rest (D2, D3, and D4) are inhibitory receptors. Also, The D2 receptor is the only one that's mainly presynaptic (Auto receptor) = So it functions as Negative feedback since it's inhibitory and presynaptic where it regulates the function of Dopamine transporter.



- Addictive drugs such as Cocaine and Amphetamines act on selective dopamine transporters and inhibit their function causing dopamine to build up in the synapses increasing dopamine signaling (Dopamine is the primary

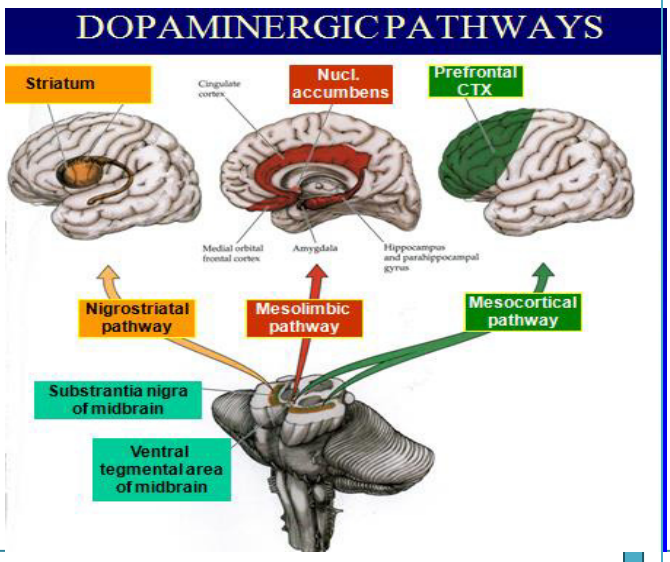
neurotransmitter involved in the reward pathway in the brain. Thus, drugs that increase dopamine signaling may produce euphoric effects, that's why you feel cool bro when you do cocaine)

- Source of Dopamine: 3 small nuclei, we'll focus on the two nuclei that are in the brainstem which are called Substantia Nigra and Ventral tegmental area.

- Dopamine pathways: it won't be distributed to all areas of brain, only to 3 specific targets which are:
  1) By the Mesocortical pathway to the cortex (not all of it but to the prefrontal cortex)
  2) By the Nigrostriatal pathway to the Striatum: part of the basal ganglia
  3) By the Mesolimbic pathway to the Nucleus accumbens (a part of the limbic system)

Response to stimuli either by exciting them or inhibiting them depending on the type of the receptors (D1, D2.. etc), for example:

1) The prefrontal cortex is involved in motivation to explore the environment: Curiosity, Interest, Cognitive flexibility, drive for social Engagement. When Dopamine reaches the prefrontal cortex, it will excite that area and makes it more active but if Dopamine didn't reach it or if it got depleted there, that would lead to Depression and relative hypofunction in Schizophrenia which would increase the negative symptoms like Cognitive blunting, Social isolation (a patient would much rather stay home in bed rather going to social activities), Apathy (loss of feelings or emotions, indifference towards something بتبطل تفرق معاه), and Anhedonia (inability to enjoy what is usually pleasurable like eating food for instance)



2) The Nucleus Accumbens is a part of the Reward system in the brain that consists of neural structures that's involved in reinforcement and repeating of behavior upon increasing dopamine signaling(The Reward system, especially the Nucleus Accumbens is responsible for pleasure, reward, and behavior reinforcing).

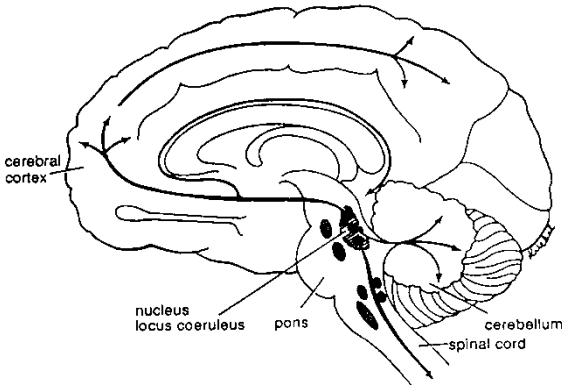
Rewards can either be addictive drugs such as cocaine, where it inhibits the Dopamine selective transporter and increases Dopamine signaling which increases the pleasure and from here, addiction to a drug develops since addiction is considered a behavior that is both rewarding and reinforcing OR it could be natural rewards such as getting Straight As in medical school or being the funny guy in class or even being like Ahlam #مقهورين_من_الملكا|||||||

Clinical Note: Hyperactivity of mesolimbic pathway leads to positive symptoms of Schizophrenia (like Hallucinations, etc).

3) The striatum, a part of the basal ganglia that plays a role in coordination of motor movements. Loss of Dopamine to it would lead to Parkinson's Disease.

Norepinephrine (NE):

- Considered as a neuromodulator
- Two types of receptors: α family + B family
- NE transporter found in the presynaptic membrane is affected by Amphetamine and Dispramine (both inhibit the uptake of NE and increase its level in the synapse) but not affected by Cocaine.
- Synapse is the same as dopamine: (release > receptor > picking up by a transporter > degradation, mainly by monoamine oxidase MAO and a little bit by COMT).
- Source of NE: Nucleus Locus Coeruleus in the brain stem
- Pathways of distribution: Pathways to the cortex and pathways to the spinal cortex



Functions of NE:

The Locus Coeruleus Nuncleus is highly responsive to a new external stimuli and that would push you to pay attention to that stimuli where NE is excitatory on the cortex and almost always Inhibitory on the spinal cord (to stop your movement in the moment of seeing or hearing a new stimuli to only pay attention to it and giving the cortex going to pay attention to now (

selective attention function as same as acetylcholine). Since it activates the cortex, it's involved in learning/ memory and sleep/wake cycle.

Clinical note: Over activation by the Locus Coeruleus Nucleus and having high levels of NE constantly means paying attention to something all the time (such as staying focused on the fact that you have lots of studying to do or the fact that you're going to be forever alone would eventually lead to Anxiety and stress response).

Note: The doctor started eyshlf8ing here big time so he didn't mention all the details in the slides but I included all of them just to be sure:

- **Distribution of receptors of NE receptors in the cortex:** NE goes to all parts of the cortex in 3 main tracts (that doesn't pass through the thalamus):
  1) It goes to the caudal part of frontal cortex where it works mainly through α2 receptors to induce attention, working memory, information processing , and waking up.

  2) In more rostral part from the frontal it works through β1 receptors to regulate the mood [Hypofunction of this pathway leads to Depression].

  2) It goes to the limbic system, where it works through α receptors and affects Emotions and the energy level (Are you energetic and willing to go out and do something or not?). Increasing NE to the Limbic cortex would results in Psychomotor agitation and decreasing NE to the limbic cortex results in Psychomotor retardation

EXTRA INFO/ Definition from wiki: Psychomotor agitations are series of unintentional and purposeless that arise from mental tension of an individual such as pacing around the room, wringing one's hands طقطقة الاصابع, or bitting off fingers.

Serotonin:

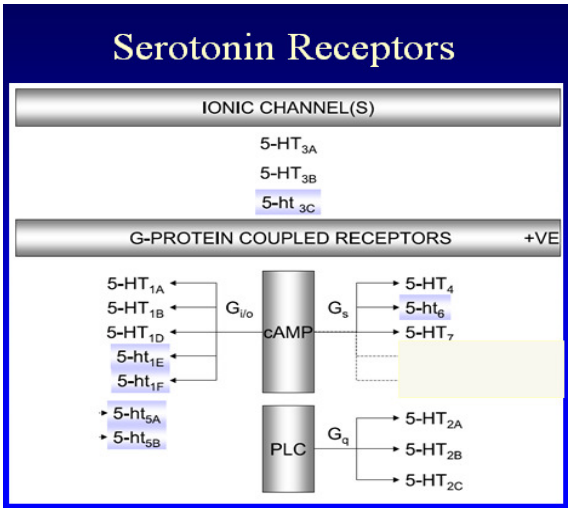
- Synthesized from Tryptophan (not from Tyrosine like the others). Tryptophan is an essential Amino acid mainly obtained from food like Chocolate or Bananas and that's why we don't have a rate limiting enzyme in the synthesis of Serotonin from Tryptophan, the rate limiting step would be the presence or absence of Tryptophan.
- The source of Serotonin is from Raphe Nucleus or complex in the brainstem (goes to many sites in the CNS and that's why the

complex is identified by many names according to the site they innervate : Median Raphe/ dorsal Raphe/ The Raphe system/ Raphe nucleus)

- Serotonin has the highest percentage in the amount of innervations of the areas in the brain, especially the cortex, among all neurotransmitters in the CNS.

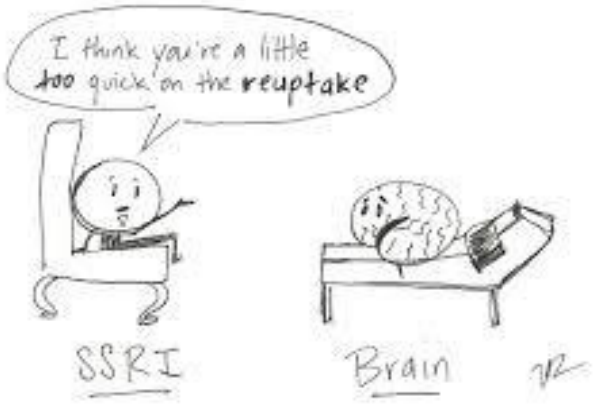
- It has 21 subtypes of receptors which are arranged into four major subfamilies: (The doctor focused on the following slide big time):

1) The 5-HT1 : Inhibitory serotonin receptors to cAMP
2) The 5-HT2: Excitatory serotonin receptors, works through the phospholipase system (PLC system) and it needs calcium
3) The 5-HT3: mainly excitatory serotonin receptors, they work directly through ion channels.
4) The remaining receptors are grouped in one family and they work through activating cAMP.



Serotonin is found in all areas of the brain, it modulates the function of many pathways in the brain (associated with mood, sleep, sexuality, impulsivity, aggression, stress, and even drug abuse & adduction). Therefore, it's associated with many pathological disorders in the CNS such as Depression, Schizophrenia, OCD, eating disorders, and Autism.

- Due to its large distribution and many functions, it's considered as a target for many pharmacological drugs such as (Antipsychotics, anxiolytics, antiMigrane, & antiemetic) but the main one you'd deal with mostly is SSRIs (Selective serotonin reuptake inhibitors), which are significant antidepressants drugs that work by building up the level of serotonin on receptors.



End of the sheet.

ما عليكم من الي يقولون عن هالشيت طويلة وصعبة, ترا كلها معلومات من المحاضرة... ولا,
#مقهوريين من الي كتب الشيت, صح ولا لا ابو يامن؟ صححححححححح نياهاهاها

Seriously though, if Britney Spears thought she was stressed in 2007 then maybe she should try going to med school. :p

Shout out to the best people on earth; Mo2ns Al-Badayneh , Mohammad Nawaisah, Jamil Sahouri, Abduallah Shurman, Mohammad Darwesh, and Ahmad Masri.