**Cont. of neuro modulators**

* **Norepinephrine** :

-Synapses of norepinephrine is similar to that of dopamine : release , degraded by COMT enzyme and MAO enzyme, or being picked up . (SO we get rid of it in these two pathways just like dopamine).

-cocaine doesn't affect norepinephrine , but it gives amphetamine that inhibit norepinephrine transporters (which is also a dopamine transporters inhibitor) . "amphetamine is an addictive drug"

-we have norepinephrine in all over the brain , but it mainly modulates the cortex( the biggest part) .

- the source of norepinephrine in the cortex is not from cortical neurons , the main source of norepinephrine is a nucleus located in brain stem ( **Locus coeruleus** ) .

- **Locus coeruleus** **( the only source of norepinephrine in the CNS) , LC** : is like an on/off button , when we hear a sudden noise , it gives us norepinephrine , so it mainly response to external stimuli that tells us to "attention" / alert us to external stimuli . [it modulates the cortex function telling it to pay attention] .

-And because it helps in attention , that means it is related to memory and just like any modulators of cortex , it's also related to waking up .

-extra norepinephrine "a lot of norepinephrine due to over activation of the LC nucleus" >> anxiety and stress (paying attention to any external stimuli).

- norepinephrine reach the cortex in 3 diff. pathways that will finally reach :

1-caudal part of prefrontal cortex , **modulating** attention , memory and information processing [REMEMBER THAT attention starts at prefrontal cortex , which tells parietal what exactly to pay attention for] .

[**increase =** anxiety and stress ].

[ **decrease =**ADD (attention deficiency disorder) or ADHD ( attention deficiency hyperactivity disorder), decrease in attention , usually in children , but may occur with adults]

2-rostral part of prefrontal cortex which is responsible for socializing and mood regulation , **modulating** our mood making us more social and if decreased there , it will cause depression (down regulate our mode).

3-limbic system which is more related to our activity (autonomic nervous system) and emotions .

* **Serotonin** هرمون السعادة:

-synthesized from the amino acid tryptophan , which is an essential amino acid .

- The availability of serotonin is dependent on the availability of tryptophan [Tryptophan is mainly found in banana and chocolate - chocolate makes you happy -] , and also level of serotonin depends on the rate limiting step which is tryptophan hydroxylase . "In females this enzyme is regulated by more than one thing , and it's more active than in males , that's why girls will feel happier after eating chocolate"

Conclusion : level of serotonin depends on how much tryptophan we get and the activity of tryptophan hydroxylase .

-serotonin is one of the best regulators for the cortex ( one of the best regulators for the mood)

-serotonin is the most abundant modulator of all previously mentioned modulators .

-source of it : Raphe nucleus of brainstem ( raphe always means something related to serotonin).

**-it has 21 different subtype of receptors !** (unlike other modulators that have one or two families of receptors like in G-protein coupled receptors) .some of these subtypes work through : ion channels receptors , increase or decrease cAMP , PLC "that works mainly through Ca+2".

**"the sildes that contain these subtypes are not included , don't even read it"**

-Because serotonin is found in all over the brain , and because it has 21 different ways to act , then we can say that serotonin plays role in all brain functions !! in mood , sleep, sexuality , impulsivity , aggression ,stress and also drugs of abuse are mainly targeted to serotonin ( the main hallucinogenic drugs act through serotonin ) .

**Remember : over activity of dopamine will result in schizophrenia (hallucinations)** , and some hallucinogenic drugs , that act through serotonin modulating it's sensory processing , making the hallucinations , **so also excessive serotonin will result in hallucinations .**

-as we said , serotonin plays role in almost all brain functions –mainly mood and sleep- that's why we will hear about a lot of disorders related to it , e.g. depression , schizophrenia , OCD(obsessive compulsive disorder الوسواس القهري ), eating disorders and autism .

-serotonin is an antipsychotics , antianxiety , antiemetics and antimigraine , each act on different subtype . [we will talk about them inshaAllah in pharmacology next year , so now forget about this slide].

-serotonin is a mood regulators ( used for depression) , e.g. Prozac is one of antidepressant drugs (selective serotonin re-uptake inhibitors) that increase serotonin in the synapse .

Some side effects of antidepressant drugs (excessive serotonin) will result in hallucinations and Akinetopsia .

* All these previously mentioned **monoamine** modulators will affect cortex , modulating it to a certain function . the best is being in balance with these three .



If any of these modulators increases , that will affect this balance , increase in norepinephrine for example will result in anxiety , hyperactivity … ,, increase in dopamine >> pleasure ,, increase in serotonin >> impulsive "do things without thinking" (impulsivity is a disorder).

So we need balance because there is interaction in between them >> dopamine act on cortex and affect serotonin , and serotonin act on the cortex and affect dopamine .. etc.

* Other type of neuro modulators (other than monoamine system) : **neuro peptides** .

 -neuro peptides : neurotransmitters with protein structure (REMEMBER THAT MONOAMINE WAS AMINO ACIDS THAT WAS MODIFIED TO FORM NEUROTRANSMITTERS) but here the amino acids are combined in a protein .

-present in everywhere in the brain . more than 50 neuro peptide mainly found in hypothalamus.

-all neuro peptides work through G-protien coupled receptors, that's why they are : 1-neuro modulators ,2- they can function in small amounts , doing massive effect (due to signal amplification) .

-neuro peptides can do a lot of functions , as they are widely distributed all over the brain .

-neuro peptides are synthesized in the cell body and release from the axon terminals "far to some extent". After being synthesized in the cell body , it will be transported via transporting protein that will SLOWLY move 'till it reach the end of the axon .

SO , it’s a time taking process .

-serotonincan preserve itself by directly pick it up . BUT , in the case of neuro peptide , **IF** all the vesicles that have reach the end of the axon were secreted , we will run out of vesicles (neuro peptide) , and we will have to re- synthesize it in a time taking process ! BUT THIS IS NOT THE STORY , neuro peptide knows that they are difficult to be re- synthesized , so their effect is amplified , and is bigger and longer than other neuro modulators.

-SO GABA and glutamate are affected by neuro modulators , and if I want long time neuro modulators , neuro peptides will be used .

-some neurons only synthesize neuro peptides and other synthesize neuro peptide and serotonin , so upon action potential it will release the normal neurotransmitters and neuro peptides vesicles .

-neuro peptides are very complicated , and researches haven't clarified their disorders , so we will only talk about the neuro peptide that is related to **pain** .

* **Pain :**

-protective mechanism to alert us for dangerous situations. Pain is related to emotions ,Not only sensations .

**The doctor here mentioned that there is a slide with definitions that are very important!**

- Pain is usually transmitted through ALS pathway (slow pathway) ,its fibers is mainly unmyelinated ,but a few is myelinated ,so we have :

 1**. A-δ fibers** of pain is partially myelinated ,but still they are slow (they are **fast** in comparison with pain “20 m/s” ,but in relation to total speed of impulses is slow “120 m/s” ).

 2. **C fibers** (slow fibers) “1 or 0.5 m/s”

- the fast fibers are more responsible to detect localization of the pain and sharp pain ,but slower fibers have lower responsibility in localization.

-pain travel through ALS pathway (final destiny of ALS fibers is somatosensory cortex) ,,but pain give branches before that “in its pathway” ,like the branch that it give to spinal cord for reflexes, it also give many other branches at brain stem and sub cortical regions

-in **ascending pathway** of pain we have :

1**- spinothalamic tract “ALS pathway”** ,,in general this tract will go to thalamus ,then from thalamus to cortex

But we have to types of this tract :

-Neospinothalamic tract >>go to thalamus and then to somatosensory cortex

-Paleospinothalamic tract>> will stop at thalamus ,midbrain or other levels in brain stem

2**- spinoreticular tract** :doesn’t reach the thalamus, and stop at the reticular formation RF

-RF located in the brainstem ,

-in the brainstem we also have other nuclei like acetylcholine nucleus “nucleus basalis and other nucleus” ,norepinephrine nucleus “locus ceoruleus nucleus” and, serotonin nucleus “medial raphe all though the brain stem”

-RF as the name implies is like a network of nuclei ,and there nucleus is not specified

-in the past when they do dissection and see a nucleus like the red nucleus ,stain it and do experiment to know its function

- in fact dorsal raphe and other nuclei was in the past part of the RF ,and not specified >> now with the presence of neurohistochemistry ,we can stain cells according to its neurotransmitter type ,,we found that locus ceoruleus “for ex.” Was part of the RF but it form group of cells that produce norepinephrene ,and the same in serotonin and other nuclei,,that’s why they sometimes refer to as nuclei of RF

-RF activating system is mainly form of those nuclei “serotonin ,dopamine ,norepinephrine and acetylcholine”

-back to reticulospinal tract ,through this pathway pain will reach RF where we find nuclei of modulators “dopamine ,seretonine …etc” ,and other nuclei that’s not specified yet >>this is important because if we have pain ,we should modulate the cortex according to this pain “when I have pain ,my feeling and the way I process info will change according to this pain and this is done by modulators”

-so pain should reach modulators that modulate the cortex

3-final ascending tract of pain is **spinomesencephalic tract**: which will go to area in midbrain called periaqueductal gray, found around cerebral aqueduct

-3 areas we care about when we talk about pain : periaqueductal gray , locus ceoruleus “because it produce norepinephrene” and dorsal raphe “precursor for serotonin”

\*norepiniphrene and serotonin as they go to cortex,they also descend to spinal cord and modulate the function of the spinal cord “this is one of the most important functions in modulating pain”

>>as we have ascending tracts, we also have descending tract ,those desending tract is:

* One that descend from the periaqueductal gray
* One from locus ceoruleos
* One from dorsal raphe
* One from the cortex ,because as we know that cortex is responsible in controlling everything below it ,so it should conrol pain by descending fibers (some fibers are sent directly from the brain to SC and contol pain directly ,,but mainly it control pain through periaquiductal gray,locus ceoruleos and seretonin nuclei “dorsal raphe”) >>so by the control of cortex we can do something although we know that it’s painful, the cortex here tries to inhibit the pain and let me do that

\*any fiber that descend for controlling pain,,will modulate how this pain will be sensed ,by inhibit or increase, but mainly with pain we will talk about inhibition.

\*This saying is to clarify the idea of pain:

"اذا سقطت شجرة في الغابة ولم يسمعها أحد فهل أصدرت صوتا؟!!"

-if a tree falls ,it may produce a sound or not ,,but as long as nobody here it >> then **its not a sound**

-pain is the same, if a patient is anesthetic ,and we apply an action on him that should produce pain ,and he didn’t feel it as a pain >> then its not considered pain

-and if there is a source of pain ,and I feel it as ticking or touch >>then its not a pain ,its ticking or touch sensation

-pain is complex thing, it involve emotions ,,if we didn’t excite this bad sensation, and we didn’t perceive it as pain >> then its not pain anymore, it become other sensation

(((if you didn’t sense the pain >> then its not a pain)))

>> that’s why when the cortex control the pain and inhibit it ,I can do sth painful without sensing any pain

 “some people may sense pain as pleasure !, others can move on coal without sensing the pain,even though there feet will burn” because this is how there cortex control it and suppress the pain,,

\*this suppression is done mainly by three descending tracts:

1- from periaqueductal gray

2-from locus ceoruleos

3-from dorsal raphe

4- that control these 3 and less important than them is tracts from the cortex which may send fibers directly to SC ,or indirectly to other tracts or to the hypothalamus “responsible for emotion” >>so the response that the patient will show- and the pain he will feel- if I hit him depends on his emotional state “he’s angry or happy”

\*hypothalamus is like the cortex ,send info to the modulators and modulate them

\*how these fibers control the pain ,and what they contain??

Mainly they contain **opoids** which is :

* a neurotransmitter
* the main analgesic we have
* neuropeptide,with the smallest have 5 aminoacids
* devided mainly to 3 families ,,we will talk about 2 of them: enkephalon and endorphins.
* They have more than one receptor , mu “**μ”** and delta “**δ”**
* morphine is one of the opoids

\*fisrt family in opoids is enkephalon, work through delta receptors

- we said that one of the descending pathways controlling pain is coming from periaqueductal gray,which take sensation from hypothalamus,and it can delete sensation of pain in order to be able to do certain functions, by descend fibers that prevent pain from ascending to cortex“thus preventing pain sensation”

>> so I will have stimuli in the hand,that will reach the SC ,and there on the synapses there will be blocking to this synapse, this stimuli will not reach the brain ,so I will not sense the pain “theres no pain”

-how this inhibition of pain occur step by step?

\*\*Enkephalon neuropeptide will descend from periaquiductal gray to dorsal raphe,, so activate serotonin

-enkephalon is a neuropeptide so its production is hard, and send it to far place is also hard >> so they can’t descend to the SC to do inhibition there “at the synapse” and prevent the stimuli from ascending, instead they only descend to dorsal raphe ,and dorsal raphe send info that descend to the SC “by serotonin” ,and there serotonin will activate another enkephalon neuropeptide >> which will inhibit the synapse at the SC level by binding to its receptor

-so when I have pain it will be sent to the SC ,and there before releasing neurotransmitter “to send the pain to the cortex” ,,there will be blockage of this release by the descending neurons (signal doesn’t reach the brain and we didn’t feel a pain )

 (( enkephalon descend from periaqueductal gray >> dorsal raphe >> serotonin activated >> descend and activate another enkephalon >> do inhibition ))

\*remember that:

- hypothalamus can control the periaqueductal gray ,and cortex can control both of them

-first we sense the pain,,but then it will be inhibited either by the **cortex** “cognitive inhibition” ,or by the **hypothalamus** “if im happy” ,or by the **periaqeductal gray** “if I feel boring of this pain and I don’t want it anymore”

-enkephalon found in periaqueductal gray and SC

\*the second family of opoids in endorphin ,work by μ (mu) receptors ,morphine also work by those receptors

- How endorphin were discovered?

- in the past they discover that morphine is used to release pain, and then they found that they work by mu receptors “**mu** named so relating to **m**orphine”>> but in our body we don’t have morphine ,and its not logic to have a receptor in our body for sth come from outside only,,and they search for sth resembles morphine, produced by our body and bound to μ receptor >> then they discover the endorphin family (which is a neuropeptide that suppress pain also)

\*\* **δ receptors** found mainly in periaqueductal gray,, but mu receptors found almost in all places “cortex,hypothalamus,midbrain,brainstem” ,,all these places work on pain,but each will modulate it in a certain way

* **note that μ receptors found near centers of respiration and other vital signs ,,so μ receptors and morphine can modulate also those ,,that’s why they are dangerous at high levels.**

**Done by :**

**Haya JadAllah & Batool Hiari**

**Good luck :))**