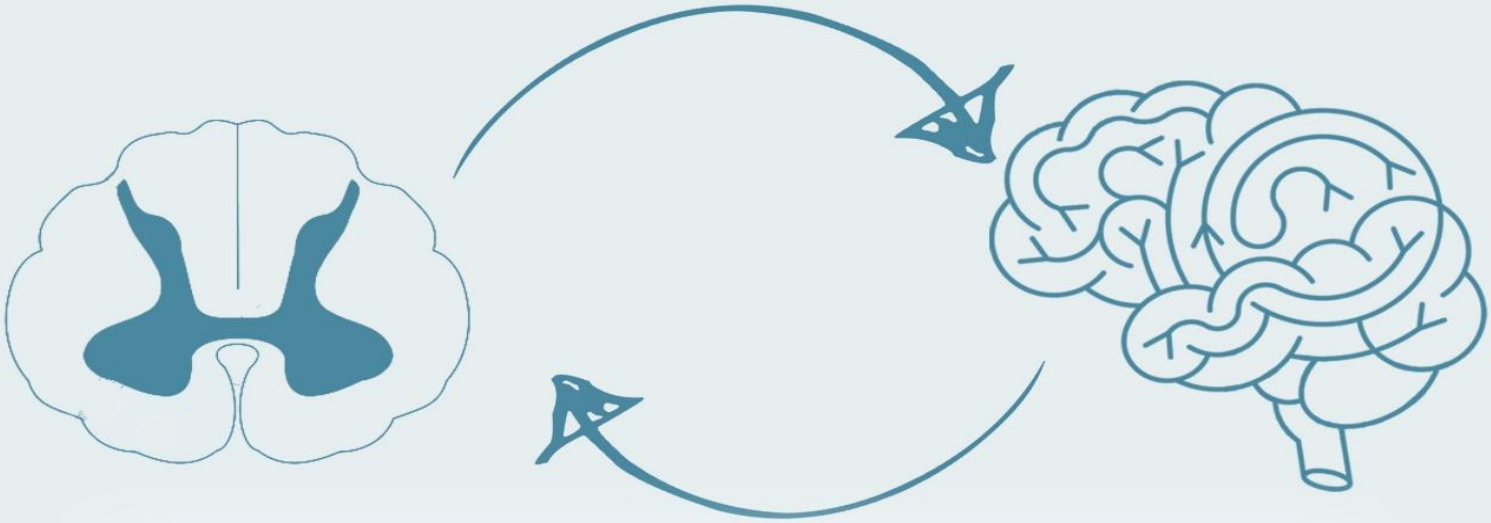

CNS

physiology

slides sheets

number	20
Done by	Nizar Alkhlaifat
Correction	Mohammed Al-Hyasat
Doctor	Loui Al-Zghoul

In the previous lecture we talked about acetylcholine as neuromodulater.

In this lecture we will talk about the second type of **neuromodulaters: Biogenic amines**.

General overview about biogenic amines:

- **Biogenic amines** : are collective of neurotransmitters derived from amino acids (mainly tyrosine and tryptophan).

  - Amines that are derived from Tyrosine are dopamine,norepinephrine...

  - Amine that is synthesized from tryptophan is serotonin.

✓ They all share one common thing -----> they all share the same synapse and synapse regulation, because in all of them will be released into the synapse and activate receptores. Also, they share transporters and clearing mechanisms.

➢ Clearing of biogenic amines is by:

1-Transporters: which may be selective (specific) transporter for only one of biogenic amines or non-selective transporter (more than one type of biogenic amines).

Note: non-selective transporter may not equally transport biogenic amines (ex: 60% dopamine-30%norepinephrine-10%serotonin).

2-Degradation by enzymes,happens by two enzymes,:

- ➢ COMT(catechol-O-mythel transferase) which exist more in the peripheral than central nervous system (especially the liver).
- ➢ MAO(monoamine oxidase) which is more in central nervous system and it's the target for drugs that help in regulating biogenic amines.

Note: In the past, they used to target COMT, but since they discover that MAO is more prevelant in CNS they start to target it in therapy.

Dopamine :

- There are 5 types of dopamine receptors (DA1-DA2-DA3-DA4-DA5), DA1 and DA5 are excitatory receptors, while the others are inhibitory receptors.

- All dopamine receptors are G-protein coupled receptors, so dopamine is considered super-modulator which work only by modulation.

- From all these types, what gives the complexity of dopamine is DA2 receptor which could be pre-synaptic or post-synaptic receptor. If it is pre-synaptic it will inhibit pre-synaptic neuron which gives it auto-regulation or reverse inhibition (negative feedback) (opposite to glutamate which gives positive feedback), and this is important when we give dopamine (or dopamine agonist) in blood because it may activate DA2 receptor on pre-synaptic neuron and inhibit the release of dopamine from pre-synaptic neuron.
- Note: As we said there are selective transporters for each biogenic amine, this selective transporter may have specific inhibitor or activator.
  In the case of Dopamine receptors are highly inhibited by cocaine and amphetamine (especially DA2 pre-synoptically), so by inhibiting it we increase dopamine release.

- ✓ Dopamine is released from two areas in the brain:

1-ventral tegmental area.

2-substantia nigra.

- ✓ From there dopamine will go to three main targets:

1-basal ganglia (regulation to it) .

2-prefrontal cortex.

3-Limbic system (collective of subcortical structures that are highly connected to each other and regulate unconscious processes like emotions).

- Note: dopamine is neuromodulator so we will not find it in the cortex.

1-Basal ganglia: its function is regulation of movement. Dopamine go to it and modulate how it regulate movement, so if there is a problem in dopamine there will be a problem in regulation of movement which we call it movement disorder (Parkinson disease). So we treat Parkinson disease with dopamine or a precursor of dopamine.

2-Limbic system: one of the most important targets of dopamine in this area is nucleus accumbens, which is activated in happiness emotions, so if it get activated you will feel happy and rewarded, so anything you will do that activate this nucleus will give you happiness and you will try to do it again, and that's why we call it reinforcement or rewarding. So anything that will activate this nucleus (like increasing dopamine in this area by cocaine) will be highly addictive.

*Prefrontal cortex: it's the area that control your behavior and decisions, and it always want you to be happy, so it can relax and stop working, so when dopamine is released in nucleus accumbens you will feel happy and prefrontal cortex will stop working, so when you take drugs like cocaine which increases the release of dopamine in nucleus accumbens the prefrontal cortex which control your behavior and decisions (by selective activation and inhibition to other areas in CNS) stop working and other systems in your cortex will be free from the control of prefrontal area. One of these systems is visual system, when visual system makes over-processing without the inhibition and control of prefrontal cortex, it will start to see hallucinations. These symptoms are known as positive symptoms of schizophrenia.

*Note: the limbic system make you feel happy, but what think and make decisions to make you happy is the prefrontal cortex.

*Note: Schizophrenia is divided into two stages, positive and negative symptoms.

- Schizophrenic patients will have episodes of positive symptoms marked by hallucinations followed by episodes of negative symptoms marked by isolation and depression. There are time-lapses between positive and negative symptoms.

So, to help them we give them drugs that inhibit the release of dopamine to stop positive symptoms.

3-prefrontal cortex: it's important in attention, personality and defines the targets for cortex processing. If the dopamine in this area is in the right amount, it will work perfectly, but if the dopamine is dysregulated, there will be problems in prefrontal cortex processes (motivation, consequences, seeking happiness) and the patient will have anhedonia, People who experience **anhedonia** have lost interest in activities they used to enjoy and have a decreased ability to feel pleasure because the part of the brain that is responsible for processing these things in life (the prefrontal cortex) is inactive. Its symptoms are cognitive decline, social isolation and apathy. These symptoms may be experienced as side effect of dopamine decreasing in schizophrenia therapy because we give him dopamine antagonist to decrease dopamine level in limbic system but it will also decrease in prefrontal cortex.

- With more understanding of dopamine receptor, a drug may target dopamine receptor in limbic system but will not affect prefrontal cortex, and that's what we need in schizophrenia therapy.

Norepinephrine:

- ✓ Two types of receptors: alpha and beta, most of them are excitatory receptors but few of them are inhibitory like alpha-2 receptor.
- ✓ Like dopamine, the clearing process is by (MAO and COMT) or by transporters (which are inhibited by amphetamine only but cocaine doesn't have any effect on it).
- ✓ Amphetamine is given as selective norepinephrine transporter inhibitor.
- ✓ Norepinephrine exist in a small area in the brain known as locus coreulus in brainstem, from there it will distribute norepinephrine fibers to all CNS targets like cortex and spinal cord.

- Its effect is excitation to cortex and inhibition to spinal cord. When there is a stimulus, locus coreulus will send norepinephrine to cortex, especially the prefrontal cortex, so prefrontal will send orders to focus your attention on this new stimulus and inhibit other stimuli, and when prefrontal decides that this new stimulus is not important, it will send signals to locus coreulus to send epinephrine to spinal cord to inhibit this stimulus.

- If there is low amount of norepinephrine in locus coreulus, there won't be any activation to prefrontal cortex from it and there won't be selective attention to stimuli and there will be fast shifting in attention for any stimuli even if it's minimal stimuli and you won't be able to focus your attention on one thing. This kind of disorders is known as ADHD(attention deficit hyperactivity disorder) or ADD(attention deficit disorder which is type of ADHD when predominant symptom is attention deficit rather than hyperactivity), which affects elderly and young patients.

- The treatment for this disorder is by giving drugs that stimulate the release of norepinephrine like amphetamine and desipramine (selective norepinephrine transporter inhibitor). If we increase the doses more than what we need, the prefrontal will be hyper-activated and the patient will think more of the consequences and will be more afraid of them which we call it anxiety. Also, because it affects prefrontal, if we decrease norepinephrine, prefrontal will be inactive so there will be no motivation and so it will cause depression.
- Like acetylcholine, it is responsible for attention and learning , but opposite to acetylcholine it is also responsible for memory. ALSO, it has a role in mood regulation.

Now let's divide the prefrontal cortex to areas depending on the type of receptors in that area:

1-posterior part of prefrontal: norepinephrine here is more associated with attention and memory, and the receptor here is alpha-2 receptor.

2-rostral part of prefrontal: here it is more associated with mood regulation, and the receptor here is beta-1 receptor.

3-psychomotor agitation in the very lower frontal part: involved with anxiety and associated with limbic system.

Serotonin:

- Derived from tryptophan, there is no rate limiting step for synthesis of serotonin from tryptophan, so we consider the rate limiting step here is the presence of tryptophan in the first place.

Note: in the previous two biogenic amines, the rate limiting step was tyrosine hydroxylase.

- Serotonin is secreted from several nuclei distributed along the brainstem known as raphe complex (contain the cell bodies) which send nerve fibers to all CNS, so serotonin is widely distributed in CNS, and as a neuromodulator it is the highest distributed neuromodulator in cortex, especially in secondary cortical sensation (sensory areas)(vision, somatosensory,…).

- Serotonin has 21 subtypes of receptors, which do not work in the same mechanism. Some of them work as direct opening ion channel, others work as second messenger by stimulating cyclic AMP, others work as second messenger by inhibiting cyclic AMP, and others work by PLC system (phospholipase c) by increasing calcium lipid. And to increase the complexity of serotonin more, there are 3 of these 21 subtypes are found pre-synaptic, and from these 3 subtypes some of them are inhibitory and some of them excitatory (PLC). And because of all this complexity serotonin is involved in almost everything in CNS.

- One of the theories associated with serotonin disorders is decreased serotonin level on cortex and especially prefrontal cortex which will cause problems in cortex and prefrontal cortex processing which will cause mood disorder and depression, so we treat it with selective serotonin reuptake inhibitors to increase serotonin level. And as you see, the prefrontal cortex

receive serotonin, norepinephrine and dopamine. So, new generation drugs for depression involve all of these neuromodulators to treat depression.

- One of the new generation drugs to treat depression is Risperidone or Risperdal, which is one of the most common drugs for treatment of psychiatric disorder or mood-instability disorders. But because it contains alpha1 and alpha2 agonist, it may be described for children under 12 years old that have ADHD or autism and that is wrong because this drug interacts with all receptors we mentioned before, and that's dangerous because we can't control its effects on the brain. After 12 years, the brain is more mature and the effect of risperidone is less severe on the brain.

The last type of neuromodulators is neuropeptides.

Neuropeptides:

- Neuropeptides in general are proteins that work as neurotransmitters. The difference between them and classical neurotransmitters is that the classical neurotransmitters are manufactured in axon terminals, but neuropeptides are manufactured in cell body and then transported to axon terminals, and because of that, there amount is small and very potent. Sometimes the neuron has classical neurotransmitter and neuropeptide.

- All of neuropeptides work by second messenger receptors.

- **Opioids:** general neuropeptides that decrease pain and suffering in body and they are divided based on their receptors into three subtypes because according to the localization of the receptors the general effect will be controled.

- The three subtypes are:

1.Enkephalin(delta receptor).

2.Endorphine(mu receptor).

3.Dynorphin(kappa receptor).

- ✓ Enkephalin (delta receptor): small neurons, distributed mainly in periaqueductal grey (responsible of pain) and spinal cord(direct inhibition to transmission of pain from spinal cord to higher systems in brain), but because they are neuropeptides, there axons are not long, so they activate raphe complex which contain serotonin, and serotonin in this pathway will go down and activate interneurons that inhibit transmission of pain from spinal cord. So, sometimes we give the patient SSRI (selective serotonin reuptake inhibitor) to decrease pain and elevate mood.

- ✓ 2-Endorphin (mu receptor): similar to morphine, actually we created morphine and discovered mu receptor before discovering endorphin. They are distributed in all CNS, in low amount in spinal cord, but present in all centers in brainstem (reticular formation, thalamus, brain stem and cortex) and because of that they are able to decrease conscious pain, perception of pain in thalamus, emotional stress of pain in midbrain and brainstem and hypothalamus. But the problem here is that its effect on brainstem is inhibitory, so a high dose of it will inhibit respiratory center in brainstem and there will be respiratory arrest.
  - In the past, we gave it to inhibit cough by inhibiting brainstem reflexes, and it also inhibits nausea and vomiting, and decreases temperature in hypothalamus.

  And because it regulates a lot of centers in sub-cortex and inhibits it, it slightly activates nucleus accumbens, so we can say it has euphoria effect which we don't see in other morphine-like drugs.

*Note: euphoria effect is seen in morphine and slightly in endorphin.

THE END