

Physiology - 10 -

Neuromodulators

Revision:

Neurotransmitters:

1- Fast

2- Slow; work mainly through *second messengers*, those are **Neuromodulators** because they came out from the cortex and they modulate the function and the behavior and ability of certain areas of cortex how to work. Most important neuromodulators are the **Biogenic amines** family, first of them is **Dopamine**- we talked about it in the previous lecture-.

While studying about neuromodulators we are concerned with its source and if there is a rate limiting step for its synthesis because it will be a target of drugs, its receptors and if there is a known distribution of them, and what disorders it involve with.

*NOTE: refer to the slides; I didn't have them to include extra information here.

Neuromodulators:

1. **Dopamine**

2. **Norepinephrine (NE) :**

**Epinephrine* is not found a lot in the CNS, mainly in the PNS, so we neglect it and talk only about NE.

NE has two types of receptors; *alpha* and *beta*. Each has subtypes; alpha (1 and 2), beta(1,2 ,3) . This classification depends on function, α_2 is mainly inhibitory for cAMP while α_1 is excitatory, mainly works through PLC system which mean mainly through calcium and they are activating cAMP.

Usually the inhibitory is the presynaptic subtype, so α_2 here is the presynaptic subtype/autoregulator. (as in case of dopamine, inhibitory presynaptic >> control for release or break out to get the feedback.)

(The Dr said that the function of each one in details is not important).

Synapses of NE is the same as dopamine (release > receptor > picking up by a transporter > degradation, mainly by monoamine oxidase **MAO** and a little bit by COMT).

The transporter of NE is also affected by **amphetamine** that makes a reversal for release or inhibition for the transporter. Another inhibitor is **desipramine**. And cocaine has no effect on it.

No NE comes from the cortex.

The source of all NE is a small size nucleus found in the brain stem, its distribution is to all CNS parts, goes rostrally to the cortex and caudally to the spinal cord ...>> **locus coeruleus**, which is almost the only source of NE in the body. It modulates the function of spinal cord, mainly controlling the pain. Also it activates and modulates the function of the cortex; it is distributed whole through the cortex. It is very active to external stimuli so that it pumps NE, this can be selected to some areas more than other or can be general.

Its functions: since it activates the cortex, it is mainly involved in sleep – wake cycle. It is also involved in attention, learning, memory and mood.

Note: RF (means net-like) there were stained certain bundles/axons appear on sections, after that some neurons are seen grouped as a nucleus → called as nucleus (and sometimes they were obvious without staining), other neurons were connected to each other but not grouped as nucleus those are RF, and with techniques like immunohistochemistry, we are more able to define small nucleus among unstained axons and which produces NE (Locus coeruleus) and another bird-shaped structure appears on the full length of the brain stem produce serotonin (dorsal raphe). All these nuclei receive branches from the major sensory cortex – inputs/collaterals – (especially pain) and feedback from cortex – and they interact with each other.

→ Overstimulation of locus coeruleus leads to Anxiety.

It is good to be alert for external stimuli, to wake up the cortex to think about that stimulus. But if it was too much waking up or if you pay attention to every stimuli, this is called anxiety – which is not good. [It is up regulated in anxiety and some cases of stress].

ADHD pts have low levels of NE, that's why NE reuptake inhibitors are used in treatment.

NE goes to all parts of cortex, in three main tracts:

- 1) It goes to the caudal part of frontal cortex where it works mainly through α_2 receptors to induce attention and waking up.
- 2) In more rostral part from the frontal it works through β_1 receptors to regulate the mood [so decrease in this pathway will not only affect the attention, it may lead to depression].
- 3) It goes to the limbic system, where it works through α receptors and affects the motivation, how much I am active esp. the emotional states. Also remember that locus coeruleus is related to reward [if you are energetic and want to do a lot

of things or you are down and not very active].

Note: these are direct tracts, don't pass through the thalamus.

3. Serotonin (5-HT):

It is not from tyrosine like the first two, it comes from **tryptophan**, there is no rate limiting enzyme, the rate limiting step for it is the presence or absence of tryptophan.

Tryptophan is an essential amino acid; its important sources are chocolate and banana, so when we feel down they can help by increasing serotonin level. (It works better in females more than in males due to the genetic difference).

The source of serotonin is from **Raphe nucleus/complex** (we will hear many names: median raphe, dorsal raphe, raphe system, raphe nucleus). based on which level of the raphe it is found. the difference between them is at which part of the CNS it is distributed, mainly median and rostral raphe go to upper CNS (including cortex and cerebellum), while the caudal/lower part descends to the spinal cord to promote its function (one of them is pain).

The highest density of modulator fibers are for serotonin system. Serotonin is distributed to whole parts of CNS, mainly in sensory cortical areas, where it modulates how we feel and interrupt sensation. [also acetylcholine is related to sensory perception, the difference between their functions in the sensory areas is that one of them enhances perception, help you to be attentive to that sensory, while the other modulates how you perceive the sensory input].

It has **21 subtypes of receptors** [it was 17], which are arranged into major four subfamilies: [the list in the slides is required 😊].

- The 5-HT₁ → is inhibitory to cAMP synthesis.
- The 5-HT₂ → mainly through PLC system and need calcium.
- The 5-HT₃ → works through direct ion channels, mainly excitatory
- The rest are grouped in one family and they work through activating cAMP.

The most important are 1(a, b) and 2b >> these are the presynaptic subtypes.

Note: Presynaptic can give either +ve feedback loop or -ve feedback loop depending on whether it is going to increase or decrease the release of NT, If it was inhibitory (like 5-HT₁) -> -ve feedback, if it gives Calcium (like 5-HT₂) +ve feedback.

Serotonin problem is that it is found in all areas of the cortex and work through many receptors in different ways so it has a role in almost every function within the brain and related to: mood, sexuality, sleep, impulsivity, aggression, stress and even drug abuse.

So it could be involved in the pathogenesis of many disorders like: depression, schizophrenia, OCD, eating disorders and even autism.

The list of drugs in the slides (antipsychotics, anxiolytics, antimigrane, antiemetics) is not required, but you should know that we have a lot of drugs act through serotonin, but targeting different types of receptors to induce different functions.

SSRIs: selective serotonin reuptake inhibitors, which are important antidepressant drugs works by increasing the levels of serotonin.

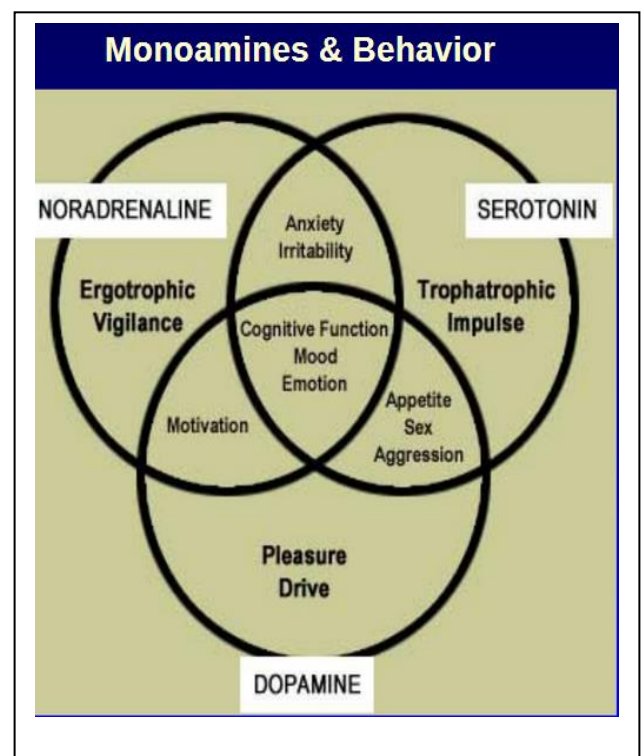
*remember that we have three monoamines/neuromodulators that heavily innervate the CNS, all of them go to the same area to modulate its function despite the variation in their distribution. The function eventually occurs by the balance between glutamate and GABA, so we need to retain a good balance>> through the neuromodulators .

*Principle of divergence and convergence in Neurotransmitters System:

- Divergence: one NT can work and do more than one function in different areas and through different receptors.
- Convergence: certain function in a certain area can be influenced by more than one NT.

This principle is important in monoamines due to the interfunction between them; one NT can modulate the other NT, such as the relation between dopamine and serotonin, and between serotonin and NE due to high connection between the dorsal raphe nucleus and locus coeruleus.

We have three main neuromodulators, each one is related to a certain modality of behavior, if a disturbance occurs in one or more of them we will end up with a problem. They should work together properly to have that good mood behavior with high productivity, because of that; new generations of antidepressant or antipsychotic drugs work through more than one function (ex: drugs act as Serotonin and NE selective reuptake inhibitor, SSRI and dopamine blockers).



[The drugs are not required, but the Dr mentioned an important one which is **Risperdal**, he recommended not prescribing it for children below 12 years (especially below 8) except in severe hopeless cases of **autistic children** - even if it is one of the two drugs FDA has approved for autism treatment-, because it works through many receptors which might lead to late functioning of the nervous system [it is impossible to go without changing the brain forever].

By that we finished talking about biogenic amines.

Neuropeptides:

proteins that are active as neurotransmitters. The most important are those which found in the hypothalamus to regulate the function of endocrine system. Its synthesis is in the short axon cell. All of them work through G protein coupled receptors, we will talk about **Opioids**.

*There are three families of opioids:

- Enkephalins >> work through delta receptors
- Endorphins >> work through μ receptors
- Dynorphins >> work through kappa receptors

***Enkephalins** : work through delta receptors to inhibit or excite (depending on the type of receptor it acts on). One of the main functions of opioids is modulation of pain through periaqueductal grey pathway to Raphe nucleus to descend and go down in the spinal cord with the intermediate serotonin receptors to modulate and inhibit pain function.

- remember: to modulate the function of pain, to block pain from getting up to the brain and to stop feeling pain from periphery; we can block the ALS system at the level of the spinal cord. In this case one of the main pathways is that we have opioid neurons (Enkephalins) that activate serotonin neurons that will descend through the spinal cord to activate another opioid neurons, to inhibit the transmitting of pain in the ALS and block it; in the synapses between pre and post synaptic in first and second order neurons.

And it can be trained; this is the way by which some people train themselves to walk on embers, by blocking pain sensation from getting to the brain.

***Dynorphins**: they are found in the spinal cord; modulate the function of sensation other than pain.

***Endorphins** : they are similar to morphine [which is not an endogenous NT, it is a natural product that works to suppress pain by acting on μ receptors, then they discovered that there must be an endogenous substances act on these receptors which are endorphins, these are produced internally by the brain and act on μ receptors] .

μ receptors spread in many areas of the brain, more than delta and kappa, mainly in the upper areas of CNS, such as; thalamus, brain stem, hypothalamus, midbrain even the cortex. It can modulate not only the function of blocking pain from reaching the brain, but also how we interrupt pain and blocking the suffering part of it.

It also can induce blocking to the centers in the brain stem and hypothalamus that are responsible for internal regulation; such as respiration and temperature regulation, so it has side effects and at high levels can induce death.

Kappa is less distributed, only in few amounts in spinal cord and limbic system. So we usually neglect it.

Non-traditional NT:

We took previously that a NT is whatever molecule that can be packed in vesicles, released upon arrival of the AP, go to the postsynaptic receptor, bind and affect it.

If we have NTs that don't obey these criteria...>>we call them non classical /non-traditional ones.

A . Nitric oxide (NO) :

*Normally it is a gas, which can't be packed in a vesicle because it will diffuse out. So it should be produced upon needed. It is synthesized by nitric oxide synthase; an enzyme its activation is induced by calcium in the cytosol, the neuronal type is NOS-1.

[Increased calcium >>activation of calcium cascade >> activation of NO synthase >>production of NO that will diffuse and go to its receptors to do certain function] .

*in the brain, there is some types of neurons that have certain types of NO synthase, produce NO (upon increase in calcium) that will diffuse and go to the neurons that have receptors for it, inducing calcium in these neurons .

*its main functions:

Because it induces calcium ...>> it is a vasodilator on non neurons (regulate the amount of blood reaching certain areas).

Work on neurons to induce calcium, esp. for memory. Although NO is good for blood and memory but if it exceeds a certain limit it becomes neurotoxic, like the glutamate.

* It is associated with glutamate induced neurotoxicity / Stroke:

If we have ischemia >>this will kill neurons by cytotoxicity [glutamate bound to its receptors >>induce calcium>> >>drive cell toward apoptosis],and all the neurons in that area will die even the ones that don't have glutamate receptors and the activity of NOS and the deficit might be increased, Why ?

Neurons has NMDA R ,it is overactive and opened in stroke → increase Ca^{+} → then at a certain level Ca^{+} activate NOS → produce and diffuse NO in high amount → it will go to neighboring neurons (even if it wasn't ischemic) → increase calcium there and eventually drive cells toward apoptosis.

B . Brain derived neurotrophic factor [BDNF] :

It is considered a non-traditional one, not only because it acts through tyrosine kinase receptor that will activate tyrosine kinases, which induce functions in the cell, but because it mainly works through postsynaptic to presynaptic, its receptor is found on the presynaptic, and it is not an autoreceptor,[because it is secreted from postsynaptic despite it is found on presynaptic] >> this errs the theory which says that synapses are one directional.

*remember that the end function of tyrosine kinases is cell survival and growth. The signal is at the end of the cell, while the survival and growth mainly initiated in the cell body. So the signal should be transmitted to the cell body... how this occurs??

When BDNF binds to its receptor, this complex will be packed into a vesicle that will be transported back through the axon to the cell body, and there they will do their function by inducing living and growth.

One of the experiments done on this topic is bringing neurons, putting cell bodies in an area/chamber and the axon terminals in another one, then we bring a neuronal growth factor – one of them is BDNF. If we put them in the cell bodies, they will not survive, but if in axons we will detect them in the cell bodies and they induce survival.

→Remember the general principle here in simple words; that what work will survive and what doesn't work will die and be eliminated. So, each neuron survival and function depends on the neuron previous to it (because it delivers the AP), so the neuron sends BDNF to it (the previous neuron) and both survive.

*It is important during the development in early life, to make a good shape and communication of the CNS. (In early life the SMA communicates with the whole brain and during activity and experience there will be elimination for unneeded/unwanted neurons, this is done by BDNF and other neuronal growth factors.)

But also it is important in adults' life, because as what we know that neurons number will not increase but the complexity of the axons and dendrites increase/decrease depending on the experience, esp. for memory.

We have different subtypes of memory:

- 1) Declarative >> which is available to consciousness.

It includes the answers for any question [what is ur name , in which

universityetc.]. Giving you fast answers and explanations. it has special site in the brain , stored in the cortex

2) Non declarative >>which is not available to consciousness

Here we remember things not related to questions.

Motor skills, puzzle solving skills

Not stored in the cortex.

*how does memory occur ???

We have an internal signal >> induce it to a circuit in the brain, it keeps rotating as long as we use it, this is a working or short term memory. In long term memory

This circuit will be converted from non permanent (just a signal) to a permanent circuit; this electrophysiological conversion must be associated with anatomical one, which is called long term potentiation [LTP] or long term depression [LTD].

***Long term potentiation** : if we have a presynaptic neuron with an induced AP ,this leads to release of NT that will go to the postsynaptic neuron, here the membrane potential may reach the threshold>>so generating AP , or won't reach the threshold >> no AP .

In this case if we have two neurons, the first doesn't induce an AP on the second one [only sub threshold excitatory postsynaptic potentials-EPSP-]this is normal. if the first one acts on multifrequency which results in summation of these EPSP>>generating AP on the second neuron . Now the second neuron is active and will do its function, it will send BDNF to the first one to induce its growth and strengthen the relation between them. [How it is strengthened physiologically?? If the same AP that previously made sub threshold on postsynaptic neuron, comes now after potentiation , it will induce AP on the postsynaptic one].

Potentiation>> a permanent relation is built between the two neurons.

***long term depression**: if the synapses between the two neurons were inhibitory, such as in the cerebellum.

*how this process is expressed anatomically ??

The neuron has received BDNF >>induce growth and survival. Growth is by sending more collaterals of axons, more axon terminals, the axon terminals get bigger. These can be stained and seen under anatomical microscope >> we call them spines [interaction sites or synapses].

Notice the difference between the dendrites in the pictures in the slides .

NOTE: here you should differentiate between division and development of neurons!

They don't divide, they only develop by sending more collaterals and terminals [axons and dendrites], getting thicker and having more NTs , but there is no effects on the cell body .

*So all these are involved in memory formation at the cellular level, also calcium at a certain level is good, induces growth and survival. So NTs acting through calcium are usually associated with memory formation in the brain.

DONE BY: LARA RAMADAN.

و اعلّموا

أن مممّمكم ليست في ورقة تنالونها !!

و لكن في أمة تحيّيونها ...!

علي الطنطاوي