Neurotransmitters

* As we said before the main neurotransmitters in the **cortex** are **GABA and Glutamate**. (ion-gated channels & thus function quickly)

GABA and glutamate work together to modulate the cortex but they function in different ways.

* The other neurotransmitters such as, serotonin, nor epinephrine & dopamine are found in different areas such as the brain stem & subcortical areas. However, they are transported to the cortex to function there, BUT NOT on ion-gated channels like GABA; they function on G-protein coupled receptors (& thus they are slow regulators).
* Those modulators can regulate any area of the cortex.
* **Acetylcholine A :**

Synthesis from acetyl coA and choline:

 ChAT

Choline + Acetyl CoA Acetyl choline + CoA

Degraded by **acetylcholine esterase**.

Synapses simply happen by the release of Ach >> acetylcholine binds with its receptor.

When our body wants to get rid of Ach receptors it would degrade acetylcholine by acetylcholine esterase, & through that, the effect of the receptors no longer exists (no acetylcholine to bind to the receptors).

Therefore, a drug in which we want acetylcholine receptors to function would be an acetylcholine esterase inhibitor.

We have 2 types of acetylcholine receptors:

|  |  |
| --- | --- |
| 1 ) Muscarinic | 2) Nicotinic |
| 2nd messenger (its modulator) | Open direct ion channel  |
| Mainly in brain; & that’s why Ach works in the brain mainly by 2nd messenger system. | Not in brain |

* There are no ach-synthesizing neurons in the cortex, but like we mentioned before, Ach comes from the brain stem, subcortical & deep brain structures.
* Sources of Ach in the brain are mainly from **the nucleus basalis** and other brain stem nuclei (we don’t need to know them.)
* Even though the cell bodies are there (in the nucleus basalis) but they radiate to every place in the cortex, they go to all cortical regions and they take two pathways:

|  |  |
| --- | --- |
| 1st pathway | 2nd pathway |
| Directly to the cortex  | Go to the thalamus first then to cortex |
| Modulate the function of the cortex through activating it & through that, this pathway will affect:1- waking up(arousal)/sleep2- sustaining attention **\***  | Sensory function :Help us in processing sensory information and in enhancing perception |

**\*Note** :

Ach, as mentioned before, goes to all areas of the cortex, & through the first pathway will cause it to become more active.

* For example, when watching a movie, I need the cortex of vision to be more active than any other area of the cortex, and I need the enhancement of the processing of vision (sensory). Thus, the neurons which send signals to the area of cortex responsible for vision are more active in this situation than neurons which send signals to other cortical areas such as the prefrontal area.
* By increasing activity to a specific area, its attention should be targeted to something specific, so ach will increase the activity to an area according to what you are paying attention to.

Recall that the cortex is responsible for memory and cognitive function.

* If Ach decrease >> the efficiency of the processing in the cortex decreases >> cognitive function of the cortex also decreases damaging the memory >> Alzheimer’s disease –( one of the main pathological diseases which is caused by the loss of cholinergic cells in the nucleus basalis which are the cells responsible for producing ach to be transported to the cortex)
1. **Other neuro modulators, Biogenic Amines:**

Dopamine, Nor-epinephrine, Epinephrine and Serotonin

Synthesis : ( we took it in biochemistry for more details)

* They are all synthesized originally from Tyrosine
* **Tyrosine hydroxylase is the main enzyme**
* Enzymes present depend on the cell type; for example, a cell that is responsible for producing dopamine will contain enzymes specific for the production of dopamine

Synapses:

* Work like any other synapses

Degradation:

* We get rid of biogenic amines by 2 ways:
1. **Enzymes** undergo degradation mainly in the brain **>> MAO**: Monoamine Oxidase & COMT is also present but in lesser amounts.
2. **Picking up** for monoamines by Dopamine, Nor-epinephrine, & Serotonin by **biogenic amine** **transporter**s. One type of those transporters can transport all 3 of them. Some other types are more specific; one is specific for dopamine, one for serotonin & another for nor-epinephrine.

**Dopamine:**

A modulator which works mainly by **G protein receptors**, we have 5 types of dopamine receptors:

3 inhibition receptors & 2 excitation receptors

Most important one & the only one that we need to know:

**D2** >> inhibitory, mainly presynaptic (is an autoreceptor by inhibition) >> -ve feedback inhibition (will cause inhibition of itself)

Dopamine synapse:

Dopamine is released; we have MOA (small amount of COMT in brain as we said) and transporters >> so at the end dopamine will either be degraded or taken up.

To **control** the dopamine functioning; the body controls it either by controlling the **receptors** (by using antagonists or agonists) or by controlling **the amount of** **dopamine produced** by the brain (by increasing it being picked up or by preventing degradation).

All neurotransmitters are controlled by agonists/antagonists, but the other way is by controlling the function of the transporters and enzymes of degradation.

For example;

* an MOA **inhibitor** >> increase dopamine
* Cocaine transporter **inhibitor** >> increase dopamine

Most common transporters inhibitor/blocker: Amphetamine, stremate drugs, and cocaine.

 Cocaine: stimulant drug.

The source of dopamine in the brain (not the cortex as we mentioned before):

**The substantia nigra** and the **ventral tegmental area** of midbrain

From there dopamine will go to all areas of the brain through three pathways:

1. From substantia nigra to the basal ganglia and striatum. This pathway is called the **Nigrostriatal pathway**.
* Its function is to modulate the function of the basal ganglia.
* If it becomes damaged >> it will lead to Parkinson’s disease.
1. From ventral tegmental area to the limbic system. This pathway is called the **mesolimbic pathway.**
* Function of limbic system; emotion, memory and reward.
* Therefore dopamine’s function through this pathway is to modulate emotion, memory and reward.
* If the body suffers from a problem which leads to an increase in dopamine >> the person will have distortion in emotion or reward system (Cocaine targets to do that).
* Recall that part of the limbic system is the septal nuclei. One of these nuclei is the nucleus accumbens (which is responsible mainly for reward & pleasure)

Thus if dopamine increases >> the pleasure will increase (the person will be more “pleased” & will feel happier). This is why when a person tries cocaine once, he/she would like to repeat it again & again, to feel more pleased. Cocaine inhibits transporters; this will lead to an increase in dopamine, causing the person to feel more pleased.

Notice that this also works the opposite way. When someone does something wrong, or makes a mistake & doesn’t get punished for it, he/she would be pleased about it, & would repeat the mistake.

However, if dopamine level increases beyond a certain limit, it will turn on the pleasure system to a point where a person might suffer from schizophrenia (causing hallucinations, not being able to analyze).

**Schizophrenia**: it’s a complicated disorder, has 2 types of symptoms:

1. +ve symptoms (active):

Hallucination, imagining things that don’t exist, انفصام شخصيات

1. -ve symptoms (withdrawal):

Nothing satisfies the patient; becomes anti-social & non-interactive; nothing makes him/her happy.

**Extra notes**:

* Overdose affect other function/regulator and other transporters >> death
* Body doesn’t secrete cocaine; it is only taken as a drug.
* Prefrontal cortex “sees” what causes pleasure and orders the body to do it. The prefrontal cortex is the one that “motivates” the person to keep going, it is the one that reminds the person of “his goals, targets, or what he wants”.
1. From ventral tegmental area to prefrontal cortex. This pathway is called the **mesocortical pathway.**
* Its function is to modulate the function of the prefrontal cortex (social, planning and personality)

If a patient suffers from schizophrenia and hallucination, & you give him something to decrease dopamine (a dopamine antagonist or something that works to increase degradation enzymes or picking up of dopamine), the prefrontal cortex will not have dopamine to modulate its function, & thus the patient will not feel any “motivation” to do anything; will not feel interested to get any rewards. (the prefrontal cortex is the one that reminds the person of the reward). This is called **anhedonia.**

Notice that in this case, the patient used to suffer from +ve symptoms, but they were depressed to –ve ones due to the drugs.

