Neurotransmitters (NTs)

we remember that signal transmission occurs between neurons within synapse area. when AP reaches the axon terminal of presynaptic neuron, NTs are released into the synaptic cleft followed by their binding to their postsynaptic receptors.

NTs are important in signal transmission, but Receptors are more important, and different receptors means different responses of the postsynaptic neuron.

In this lecture we are going to talk about the neurotransmitters and the receptors they bind to.

Receptor types:

1.Ionotropic: when NT binds, ion channel opens and ions enter though the membrane which causes graded potential (EPSP, IPSP) depending on the type of ions entering.

2.Metabotropic: when NT binds, it activates a 2^{nd} messenger (the most common one is G proteins). it works as neuromodulators because they have many effects on the neurons such as:

-enzymatic activity causes opening of ion channels (ionotropic like; not directly connected to the ion channel but there is an enzymatic activity and protein cascades via amplification, control, regulation and other features of the 2^{nd} messenger).

-Transcription activation or inhibition of genes.

-Internal signal pathway

G proteins types according to function:

-Activation or inhibition of Adenyl cyclase.

-Activation of phospholipase c to form DAG and IP3 which end in Ca+2 release that can be itself a 2^{nd} messenger.

-Coupled with tyrosine kinase, important for survival and growth.

Important concepts:

*Agonist: any molecule that activates the receptor when it binds it.

*Antagonist: any molecule blocks the binding of the agonist to the receptor or inhibits its function upon binding.

*Allosteric modulation: molecules that bind in an allosteric site which results in increase or decrease in the activity of the receptor. It's also called uncompetitive antagonist (negative modulators) or agonist (positive modulators) depending on the effect.

*it works only when the agonist is binding the receptor.

After Signal synthesis, packaging in vesicles, release upon stimulation to the synaptic cleft and binding to postsynaptic receptors, termination occurs by: - picking up via transporters in post/presynaptic membrane or in the adjacent Glial cells. - enzymatic degradation.

So, any effect on any step of this mechanism from the synthesis of the NTs to the termination will affect the concentration of the NT in the cleft and therefore its function. (these steps are drug targets)

****We have more than 50 type of NTs in the brain that differ in composition, location, function and the way they work.**

They are categorised into:

(1) Fast: NTs that work mainly on ionotropic receptors.

1.Glutamate: The main (95%) excitatory NT in the brain. It exists in long pathways that include multistep processing such as auditory, somatosensory and visual pathways, in addition to its presence in cortex. *(Cortex has two main NTs: excitatory glutamate and inhibitory GABA).

*processing, memory, thinking and analysis are a result of interactions between glutamate and GABA.

*Glutamate synthesis has been taken in biochemistry lectures so we are not going to talk about it here.

Glutamate receptors:

-metabotropic: works by 2nd messenger method, it can be excitatory or inhibitory and it's not common in CNS.

-Ionotropic: it's the most common and widely spread receptors (fast). It has 3 subclasses differing in their location and composition:

(1) NMDAR: (slow acting) causes Na^{+1} and Ca^{+2} influx but Ca^{+2} mainly; needs a long period (large amounts or multi release) of glutamate availability to be activated. it has a role in processing and analysis, it's conditionally activated (certain conditions must coexist with Glutamate binding to cause its activation) by Membrane Potential, its relationship with Mg^{+2} and other NTs like Glycine

(2) AMPAR: (fast acting) causes Na^{+1} and Ca^{+2} influx but Na^{+1} mainly; needs a short period (small amounts) of glutamate availability to be activated.

*AMPARs are firstly activated followed by NMDARs.

*The effect of Na and Ca: their influx forms graded EPSP that leads to AP.

**Ca has an extra function by working as a 2nd messenger (by the prolonged activation of NMDAR, it enters the cell and activates the 2nd messenger cascade and other enzymatic activities that lead to modulation in function since the activation is long so it works like metabotropic receptors). This has a role in short to long term memory processing.

(3) KAINATER: excitatory (either allow Na^{+1} or Ca^{+2} to enter) and the only presynaptic receptor (positive feedback on synapse and release of glutamate). It can also exist in postsynaptic membrane.

****R in the receptor name abbreviation goes for 'receptor'.**

Termination of Glutamate: it's picked up by neurons or glial cells (mainly) though: Glutamate transporter or EAAT.

Glutamate exists widely in the CNS, so any **abnormalities** in its system of synthesis, release, binding and termination will cause several CNS malformations. Glutamate associated disorders are related to Schizophrenia, it can also affect the sleep cycle, cognition, depression and memory.

Unfortunately, Glutamate is difficult to be targeted since its widely spread, but nowadays scientists are trying to target its metabotropic receptors. However, there are no true clinical trials because targeting wide-spread Glutamate causes big side effects.

Glutamate associated clinical applications:

1.Stroke (cell death by stroke): caused by ischemia that means no ATP and therefore no EAAT which causes excess glutamate in the synaptic cleft. NMDAR opens for a longer time which allows excessive Ca^{+2} (2^{nd} messenger) to enter. Excessive Ca triggers apoptosis (in this case it's called excitotoxicity), and because of that, ischemic changes in brain differ from other sites' ischemia; it's not coagulative necrosis but liquefactive (not dead by loss of Oxygen and enzymes stop functioning but by the cell killing itself).

There are many efforts to target these NMDAR receptors by antagonists to reduce the symptoms of stroke. but it's found to be ineffective so far since the patient arrives to hospital too late so the receptors are already activated, or maybe we need a high concentration of drug to target the widely spread glutamate receptors.

2.General anaesthesia: it causes cortical shutdown by stopping glutamate transmission via glutamate antagonists like ketamine and phencyclidine (targeting NMDAR to reduce the postsynaptic activation). Such anaesthetics are not commonly used nowadays because they cause dissociative anaesthesia and other big side effects.

2.GABA: the main inhibitory NT in CNS, and it persists more than Glutamate (since inhibition is somehow more important than activation)

Receptors:

-Type B metabotropic

-Type A Ionotropic (well-studied): Cl^- entrance causes IPSP (inhibition). It contains GABA site (for agonists and antagonists binding) and allosteric site (for allosteric modulators such as: barbiturates, benzodiazepine, general anaesthetics and alcohols. (positive and negative allosteric modulators))

*GABA and glutamate are synthesised from one pool (GABA Glutamate shunt) with well balance. However, any imbalance (increased glutamate (excitation) or decreased GABA (inhibition)) in their synthesis results in epilepsy and seizures. This imbalance maybe because of genetic enzymes, receptor abnormalities, ion problems or trauma.

*Epilepsy drugs are made to increase GABA activity. Also, we use this treatment method to shutdown cortex in GA and short deactivation of some pathways like anxiety.

(2) **Neuromodulators** slow acting and work through a 2nd messenger. They are located outside the cortex (subcortex or brainstem) sending their fibres to cortex.

1.Ach: it persists in PNS and CNS, and it's degraded by Ach esterase.

Receptors:

-Nicotinic: fast acting (ionotropic), Na mainly and Ca influx. (it's also located in the neuromuscular junction and its release causes muscle contraction). But Nicotinic receptors in CNS are presynaptic and have indirect effect on the postsynaptic neurons by prolonged release of GABA, Glutamate, dopamine and serotonin. It has a role in cortex activation (arousal) and sleep wake cycle.

-Muscarinic: (metabotropic) by 2nd messenger, its subtypes are:

Excitatory: M1, M3, M5 inhibitory: M4, M2

*Ach exists as interneuron in basal ganglia in striatal complex to regulate direct and indirect pathways, in addition to its existence in ventral ganglia (nucleus accumbence that is responsible for reward function of Ach). It has also two main sources: nucleus basalis (of Meynert) in subcortex and Pedunculopontinus nucleus in brain stem.

Ach function and destinations: the nerve fibres go to:

-Thalamus: it's responsible for perception enhancement (conscious awareness of sensation) since the coexistence of Ach with sensation causes more processing so you become more conscious of it.

-Cerebellum

-Hippocampus: it's involved in the limbic system and short to long memory regulation.

-Prefrontal cortex: it's responsible for Sustaining attention by its selectivity. So, Ach pumping to associated nuclei in thalamus and cortical areas makes this attention sustained. (Example: the gorilla video and Ach release in vision associated nuclei in thalamus and cortex).

*sustained attention and perception enhancement are related to each other.

Any Abnormality in Ach system causes impairment in sleep cycle, confusion, perception or the ability of the prefrontal cortex to sustain attention. The patient cannot remember (process) well because there are many stimuli interrupting the main stimulus in the absence of sustained attention resulting in complete loss or unrelated (شرق وغرب) memories. And this condition is called Alzheimer disease (AD).

AD pathophysiology: cholinergic neurons degeneration in nucleus basalis causes less Ach and less functioning and memorization. The firstly affected areas in the brain is the hippocampus resulting in inability to convert short term memory to long term memory.

*short term memory impairments are the early symptoms of AD.

AD Most Treatments target: Ach agonist or Ach esterase inhibitor.

2-Biogenic amines: neuromodulators synthesised from Amino acids. They have the same release features such as control, vesicle packing, release, transport back from synaptic cleft to neurons and degradation by: COMT (catechol o methyl transferase, it's used to be the only drug target) and MAO. They are many subtypes: nonselective, slight selective (picks up some more than others) or completely selective, and this makes them Complicated to be targeted.

These NTs are: Dopamine, epinephrine (not very important in CNS), norepinephrine and serotonin.

Synthesis of these NTs has been taken in biochemistry, but remember that Dopamine decarboxylase step is the rate limiting step.

Dopamine receptors: GPCRs. 2nd messenger neuromodulation.

Excitatory: D1, D5 D2,3,4 INHIBITS

*D2: in some areas exists in the presynaptic membrane so decreases the NTs release which makes Dopamine difficult to deal with.

*Transporter uptake is inhibited by cocaine and amphetamine which increases dopamine concentration in the synaptic cleft.

pathways and destinations:

-from Substantia Nigra to the dorsal striatum of BG. it's responsible for direct pathway activation and indirect pathway inhibition through: D1,3 activates the direct pathway, D2 inactivates the indirect pathway.

*loss of this function by dopaminergic neurons degeneration results in a hypokinetic disorder called Parkinson's disease.

-from the ventral tegmental area in midbrain to the limbic system mainly nucleus accumbence (its related to emotion, pleasure, reward and motivational activity in cortex.

*Nucleus accumbence is Part of the Ventral striatum associated with ventral basal nuclei and it contains the motivational lobe.

- From the Ventral tegmental area to the Prefrontal cortex: it's responsible for foresight, social engagement, curiosity and cognition.

*mirror neurons are responsible for social interaction through mimicking others in learning, behaviour and reinforcement.

Dopamine is released normally upon doing behaviours that make you happy, achieved or rewarded. However, it can be increased Externally by addictive drugs (cocaine, amphetamine) causing hyper activation of nucleus accumbence and the motivational lobe. This results in hyper frontal cortex and incoordination of cortical processing (either by unreal stimuli (activation of 2ry or association cortex) or bad interpretation of existed stimuli and both result in hallucination).

This condition occurs by: addictive behaviours and drugs, genetic abnormalities, desensitization of receptors.

*The prefrontal cortex always Seeks the highest motivation and the higher the dopamine released the higher it's sought. 'Addiction'

*This results in Seeking the motivation and happiness through the drug instead of other normal dopamine releasing behaviours.

Schizophrenia: a disorder caused by excessive dopamine levels.

Symptoms:

*positive symptoms (hallucination) increased dopamine levels.

*negative symptoms (relative hypofunction, decreased dopamine levels): no cognitive ability, social isolation, no motivation, no curiosity, apathy, anhedonia (nothing makes me happy). (depression like symptoms; if alone it's called depression).

Schizophrenia episodes:

+ve symptoms (or by addictive drug) → dopamine reduction or exhausted brain → normal dopamine levels in mesolimbic pathway but low in mesocortical pathway → -ve symptoms → increase dopamine (Schizophrenia or by addictive drug) → +ve symptoms and so on…

Sorry for Any mistakes although it tried my best to include every single info.

Study hard and wish you all the success in your exams.

"If you can dream it, you Can do it"

-Walt Disney-