Pharmacology Team 431

(CNS BLOCK)

Lecture 1 : Neurotransmitters in the Central Nervous System CNS

[introduction to neuropharmacology]

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❖ **What is the importance of understanding the type of neurotransmitter in the CNS ?**

- To understand the etiology of diseases.
- To suggest the best drug to be used.
- To understand the clinical uses of any particular drug.

❖ **CNS Neurotransmitters in table :**

Neurotransmitter pharmacology in the central nervous system.*

Transmitter	Anatomic Distribution	Receptor Subtypes	Receptor Mechanisms
Acetylcholine	Cell bodies at all levels, short and long axons	Muscarinic, M_1; blocked by pirenzepine and atropine	Excitatory; ↓ in K^+ conductance; ↑ IP_3 and DAG
		Muscarinic, M_2; blocked by atropine	Inhibitory; ↑ K^+ conductance; ↓ cAMP
	Motoneuron–Renshaw cell synapse	Nicotinic, N	Excitatory; ↑ cation conductance
Dopamine	Cell bodies at all levels, short, medium, and long axons	D_1; blocked by phenothiazines	Inhibitory; ↑ cAMP
		D_2; blocked by phenothiazines and haloperidol	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
Norepinephrine	Cell bodies in pons and brain stem project to all levels	$Alpha_1$; blocked by prazosin	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		$Alpha_2$; activated by clonidine	Inhibitory (presynaptic); ↓ Ca^{2+} conductance Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
		$Beta_1$; blocked by propranolol	Excitatory; ↓ K^+ conductance; ↑ cAMP
		$Beta_2$; blocked by propranolol	Inhibitory; ? increase in electrogenic sodium pump; ↑ cAMP
Serotonin (5-hydroxy-tryptamine)	Cell bodies in midbrain and pons project to all levels	$5\text{-}HT_{1A}$; buspirone is a partial agonist	Inhibitory; ↑ K^+ conductance, ↓ cAMP
		$5\text{-}HT_{2A}$; blocked by clozapine, risperidone, and olanzapine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		$5\text{-}HT_3$; blocked by ondansetron	Excitatory; ↑ cation conductance
		$5\text{-}HT_4$	Excitatory; ↓ K^+ conductance
GABA	Supraspinal interneurons; spinal interneurons involved in presynaptic inhibition	$GABA_A$; facilitated by benzodiazepines and zolpidem	Inhibitory; ↑ Cl^- conductance
		$GABA_B$; activated by baclofen	Inhibitory (presynaptic); ↓ Ca^{2+} conductance Inhibitory (postsynaptic); ↑ K^+ conductance
Glutamate	Relay neurons at all levels	Four subtypes; NMDA subtype blocked by phencyclidine	Excitatory; ↑ Ca^{2+} or cation conductance
		Metabotropic subtypes	Inhibitory (presynaptic); ↓ Ca^{2+} conductance, ↓ cAMP Excitatory (postsynaptic); ↓ K^+ conductance, ↑ IP_3 and DAG
Glycine	Interneurons in spinal cord and brain stem	Single subtype; blocked by strychnine	Inhibitory; ↑ Cl^- conductance
Opioid peptides	Cell bodies at all levels	Three major subtypes: mu, delta, kappa	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; ↓ cAMP

1- Norepinephrine NE

- Works in adrenergic receptors as we know. Excitatory in alpha $\alpha 1$ and $\beta 1$, and inhibitory in $\alpha 2$ and $\beta 2$
- Increase in Norepinephrine (NE) Causes Mania, and is treated with drugs that decrease Norepinephrine such as Lithium
- Decrease in Norepinephrine (NE) Causes Depression, and is treated with drugs that Increase Norepinephrine, such as tricyclic antidepressants (TCAs)

Note that :

1- Amphetamines are CNS stimulants , They increase NE by many mechanisms including : inhibition of NE reuptake and other monoamines .. (much like how many antidepressants do)

2- Alpha 2 agonists (e.g. methyldopa) decrease the release of NE . They bind to a2 presynaptically .. inhibiting the release of NE

2- Serotonin

Although the CNS contains less than 2% of the total serotonin in the body, serotonin plays a very important role in a range of brain functions including :

- Mood control
- Regulation of sleep
- Pain perception

Diseases that are influenced by derangement of 5-HT:

- Affective Disorders (Mania and Depression) .. much like NE
- Schizophrenia (High level of serotonin)
- Obsessive Compulsive Disorders (low level of serotonin)
- Generalized Anxiety (low level of serotonin)
- Nausea and Vomiting (use 5-HT3 antagonists as therapy) .. (high level of serotonin)

Serotonin receptors :

- 5HT1 = has inhibitory effect
- 5HT2 = has excitatory effect
- 5HT3 = excitatory, responsible for the nausea and vomiting

For your info ..

- Serotonin found in GIT , neurons and platelets (When the platelets bind to a clot, they secrete serotonin, where it serves as a vasoconstrictor)
- 5HT3 antagonist (e.g Setrons) have become widely used in chemotherapy-induced nausea and vomiting
- All of serotonin receptors and their subtypes are G protein coupled .. except 5HT3 which is ion channel
- The amino acid Tryptophan is the precursor of the neurotransmitter Serotonin (5-hydroxytryptamine)

3- Dopamine

Diseases which are influenced by the level of Dopamine:

- Parkinson Disease. Low level of dopamine in nigrostriatal pathway
- Psychosis (Schizophrenia). High level of dopamine in mesolimbic pathway
- Nausea and vomiting. High level of dopamine in CTZ (chemoreceptor trigger zone)
- Infertility. Low level of dopamine in tuberoinfundibular pathway

For better understanding .. we should know every single pathway /area of dopamine and the effect of activation or blocking them :

- Nigrostriatal pathway
  1- In this system .. dopamine is critical for initiation of movement
  2- In case of low dopamine in this pathway whatever the cause might be, it will cause parkinsonism
  3- Treatment is by dopamine agonist such as levodopa
- Mesolimbic pathway
  1- In this system .. high dopamine levels may cause psychoses/schizophrenia
  2- Dopamine antagonists are used in schizophrenia/psychoses
- Tuberoinfundibular pathway
  1- In this pathway .. dopamine is critical to prevent hyperprolactinemia .. it means dopamine inhibits prolactin release
  2- In case of low level of dopamine , this leads to hyperprolactinemia .. and infertility in women / gynecomastia in men
  3- Dopamine agonist suppresses prolactin as treatment
- Chemoreceptor trigger zone
  1- High dopamine level trigger vomiting and vice versa ..

Now .. we know that Dopamine agonists good in pathways become bad through the others

Question ..

Schizophrenic patient is taking antipsychotic which antagonizes dopamine .. what are the adverse effect may happen ?
Answer: Dopamine is critical in two pathways above .. Nigrostriatal and Tuberoinfundibular pathways .. so we can say some of the S\E are (psudoparkinsonism) and (gynecomastia if he is male /infertility in female) .. remember those adverse effect happened because we are blocking dopamine to treat psychosis

In short terms :

DA agonist = treat parkinsonism , prevent hyperproactinemia .. but may cause psychosis and vomiting
DA antagonists = treat psychosis , supress vomiting .. may cause Parkinson-like effect and hyperprolactenima

4- Acetylcholine (Ach):

- Acetylcholine is both an Excitatory and Inhibitory neurotransmitter.
- Ach is involved in cognitive functions such as: (Memory, Arousal and Attention).

CNS Diseases which are linked to Ach derangement:

- Damage to cholinergic receptors (muscarinic) is associated with memory deficits as in Alzheimer's disease
- ↑ Ach in the brain predisposes patients to Parkinson's Disease.
- Muscarinic antagonists as hyoscine (Scopolamine) cause amnesia.

For better understanding ..

If u remember we said parkinsonism is linked to (low dopamine level) .. and now with (high Ach levels). In our brain in the nigrostriatal pathway we have balance between these two transmitters .. if Ach is high and/or DA is low in that pathway , this will cause parkinsonism , so we can say the pharmacology of Parkinson's disease is to restore dopamine and/or by antimuscarinics deceasing Ach levels

5- Glutamic Acid:

- Glutamic Acid is an Excitatory neurotransmitter.
- ↑ in Glutamic acid level predisposes patients to Epilepsy.

Potential therapeutic effect of glutamate antagonists

- Reduction of brain damage following strokes & head injury
- Treatment of epilepsy
- Drug dependence
- Schizophrenia

6- GABA (gamma-Aminobutyric acid):

- GABA is an Inhibitory neurotransmitter.
- Present throughout the brain; there is very little in peripheral tissues
- ↓ in GABA level is associated with Epilepsy , anxiety , convulsions & insomnia.

Without understanding the involvement of neurotransmitters in the etiology of CNS diseases, Doctors could not select the proper drug for any particular disease.

Summery

neurotransmitter	High level	Low level
Norepinephrine	Mania	Depression
Serotonin	• Affective Disorders • Nausea and Vomiting • schizophrenia	• Affective Disorders • Obsessive Compulsive Disorders • Generalized Anxiety
Dopamine	• In mesolimbic system => schizophrenia • In CTZ => nausea & vomiting	• In nigrostriatal system => parkinson's disease • In tuberoinfundibular pathway => infertility
Acetylcholine	• Predispose to parkinson's disease	• Alzheimer's disease • amnesia
Glutamic acid	• predispose to epilepsy	
GABA		• Epilepsy, anxiety, convulsions, insomnia

Questions :")

A 45-year-old man who has been injured in a car accident is brought into the emergency room. He suffered from a head injury which caused brain damage. Which one of neurotransmitter reduces the damage?

A, ACH B, Dopamine C, Glutamate antagonists

Increase the level of ACh could cause:

A, Alzheimers disease B, amnesia C, Parkinson's disease

Answers: C,C