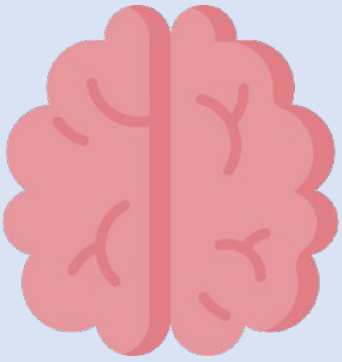

Revised & Approved

Abdullah Alsubaihi
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Pharmacology 439

MED439

Neuropsychiatry Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Pharmacology of Neurotransmitters

Objectives:

The main objective of this lecture is to understand the role of neurotransmitter in the etiology and treatment of CNS diseases.

We highly recommend studying physiology of Neurotransmitters before this lecture

Editing file

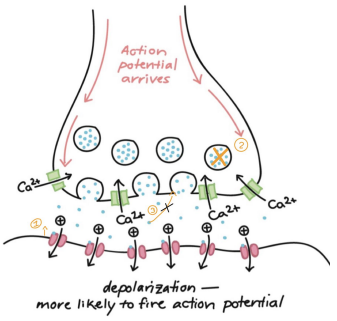
Neurotransmitters

Endogenous chemicals/chemical messengers that transmit signals from a neuron to a target cell across a synapse.

Overview:

1. They are packed into **synaptic vesicles** under the membrane in the axon terminal, on the **presynaptic side.**

2. They are released into & diffuse across the synaptic cleft to bind to a specific receptor on the **postsynaptic side.**



NTs can be modulated in many ways, such as:
- (1) Drugs that upregulate postsynaptic receptors
- (2) Drugs that result in depletion of NTs within the presynaptic vesicles e.g. Reserpine
- (3) Drugs that inhibit the reuptake of NTs back into the presynaptic terminal e.g. Prozac (antidepressant)

Neuropsychopharmacological science seeks to

- Understand how drugs can affect the CNS selectively to relieve pain, improve attention, induce sleep, reduce appetite, suppress disorder movement, etc.
- Provide the means to develop appropriate drugs to correct pathophysiological event in the abnormal CNS.

Importance of understanding neurotransmitters

01 Understand the etiology of diseases

02 Suggest the best drugs to be used

03 Understand the other clinical uses of any particular drug

Examples of neurotransmitters

Monoamines & other biogenic amines:	Amino acids:	Peptides:	Others:
Dopamine (DA) Norepinephrine (NE) Serotonin (5-HT)	Glutamate (Glu) Gamma aminobutyric Acid (GABA) Aspartate, Glycine (those were added later to the slides by male's dr)	Somatostatin, Orexin	Acetylcholine

★ **IMPORTANT Dr's note: what is important for me is to understand the pathways of these neurotransmitters, as well as their location of synthesis** (what's written in gold isn't extra, you have to memorize it. Similarities with physio might help)

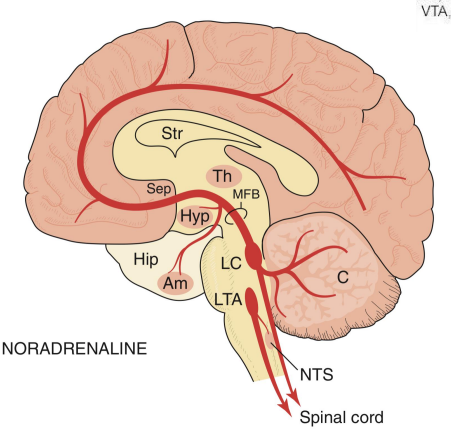
Norepinephrine

Pictures abbreviations key →

Ac, nucleus accumbens;
Am, amygdaloid nucleus;
C, cerebellum;
Hip, hippocampus;
Hyp, hypothalamus;
LC, locus coeruleus;
P, pituitary gland;
SN, substantia nigra;
Sep, septum;
Str, corpus striatum;
VTA, ventral tegmental area;

Noradrenergic neurons' cell body are mainly located in brainstem and the area of the pons.
The noradrenergic neurons ***originate*** in the locus coeruleus in pons, and the brainstem reticular formation

Noradrenergic terminals:
- Amygdaloid nucleus
- Hypothalamus
- Thalamus
- Cerebral and cerebellar cortices



Mood disorders and NE

↑ **NE level:** Mania

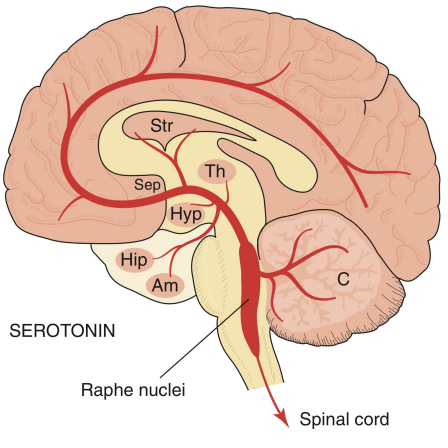
Treated by: drugs that ↓ NE.

↓ **NE level:** Depression

Treated by: drugs that ↑ NE.

Serotonin (5-HT)

- Primarily found in the CNS, GIT, platelets, etc.
- It's a popular thought that serotonin is responsible for feeling of well-being, happiness.
- **Function:** regulation of mood, sleep, appetite & pain perception.
- Most serotonin pathway ***originates*** from cell body (Serotonergic nucleus) in the Raphe nuclei or a midline regions of pons and the upper part of the brainstem.
- Serotonergic ***terminals***: Hippocampus, amygdaloid nucleus, Hypothalamus, Thalamus, Striatum (Putamen and Caudate nucleus), cerebral and cerebellar cortices



Diseases that are influenced by changes in 5-HT brain content:

- Depression
- Social phobia
- Obsessive compulsive disorders (OCD)
- Generalized anxiety
- Schizophrenia
- Vomiting

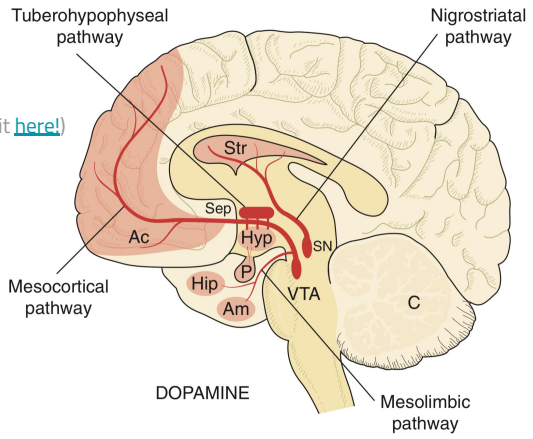
Dopamine

"★ For each pathway you should know where dopamine is synthesized & what's the pathway's main function."

Dopaminergic neurons originate in ***Substantia Nigra***

Dopamine have **4 main pathways** in the brain, each has specific function.

- **Nigrostriatal**:
  - Dopamine transmitted to the striatum.
  - Associated with controlling movement.
- **Mesolimbic** & **mesocortical**: related to cognitive and emotional reward. (read about it here!)
  Over activity lead to delusions & schizophrenia.
  - **Mesolimbic** pathway:
    - Dopamine transmitted into the limbic system via nucleus accumbens.
    - Associated with cognitive and emotional functions.
  - **Mesocortical** pathway:
    - Dopamine transmitted to frontal cortex.
    - Associated with memory, motivation, and emotion.
- **Tuberoinfundibular/**Tubero-hypophyseal: related to endocrine system
  - Dopamine synthesized in the hypothalamus and stored in the pituitary.
  - Regulate the secretion of prolactin from the ant. pituitary gland.



Effects on Dopaminergic Synapses (#Team437)

One of the causes of nausea and vomiting is activation of CTZ by dopamine.

In chemoreceptor trigger zone (CTZ)

↓

Antiemetic effect (low dose)

In mesolimbic system
(Reward pathway)

↓

Ameliorate (improve) schizophrenia
(Psychiatric effect)

Blockade of postsynaptic dopamine receptors

★ Effects of dopamine antagonists

Dopamine inhibits prolactin secretion

In tuberoinfundibular pathway
(Hypothalamus - Ant. pituitary)

↓

↑ Release of prolactin
(endocrinal effect)

(cause False negative pregnancy test, distributed menstrual cycle and gynecomastia in males)

In nigrostriatal system
(basal ganglia)

↓

Predispose to Parkinsonism symptoms (neurologic)

The same pharmacodynamic action may have distinct psychiatric "neurologic" and endocrine effects

Diseases that are influenced by dopamine level:

- Parkinson's disease
- Attention deficit hyperactivity disorder (ADHD)
- Schizophrenia
- Depression and drug addiction

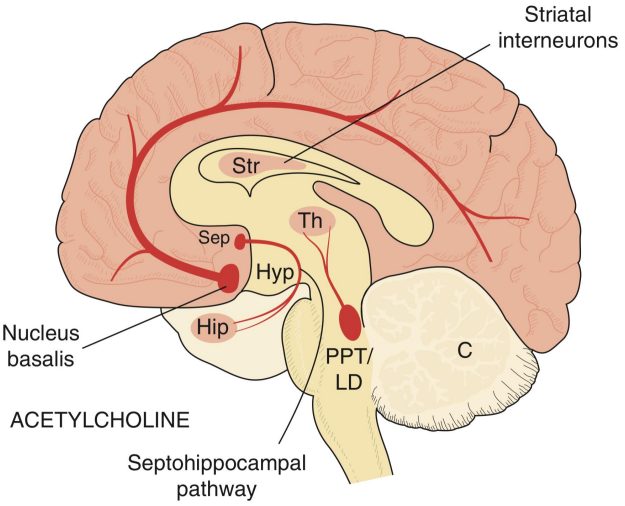
Acetylcholine

Acetylcholine is the very first neurotransmitter to be identified when Henry Dale -who won the Nobel prize for his discovery- brought two beakers and two hearts, one heart embedded in a solution in one beaker which was also connected to the vagus nerve and the other was not, this solution got leaked into the other beaker and after every heart pump (which was done by the vagus nerve) the other heart would pump too and that's because of the solution which later on was identified as acetylcholine, a neurotransmitter.

- Acetylcholine, the first neurotransmitter discovered
- Inside the brain Ach functions as a neuromodulator (A chemical that alters the way other brain structures process information rather than a chemical used to transmit information from point to point).
- Role: **Cognitive Functions**, such as: Memory, Arousal, Attention.
- Is Ach an inhibitory or excitatory neurotransmitter? Both depending on the receptor subtype that is activated.

Ach ***originate*** from: Nucleus Basalis in the Basal forebrain and mesopontine tegmental area

Terminate in: thalamus, striatum, hippocampus, cerebral and cerebellar cortices



Diseases that are influenced by changes in Ach

Parkinson's disease — Vs — **Alzheimer's disease**

↑ brain level of ACh

- Treated by: **Anticholinergic**

Damage to cholinergic Receptors (muscarinic) is associated with memory deficits.

- Treated by: **Cholinomimetics**

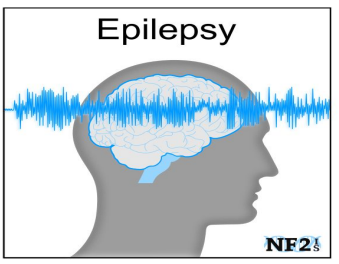
Other diseases:

- Muscarinic antagonists as hyoscine cause **amnesia**
- **Depression** may be a manifestation of a central cholinergic predominance.
- **Schizophrenia** may be due to imbalance between ACh & dopamine brain levels.

Glutamic Acid

- An **excitatory** neurotransmitter, along with Aspartate which is also an excitatory neurotransmitter.
- Potential therapeutic effect of glutamate antagonists:
  - Reduction of brain damage following strokes & head injury.
  - Treatment of epilepsy
  - Drug dependence.
  - Schizophrenia.

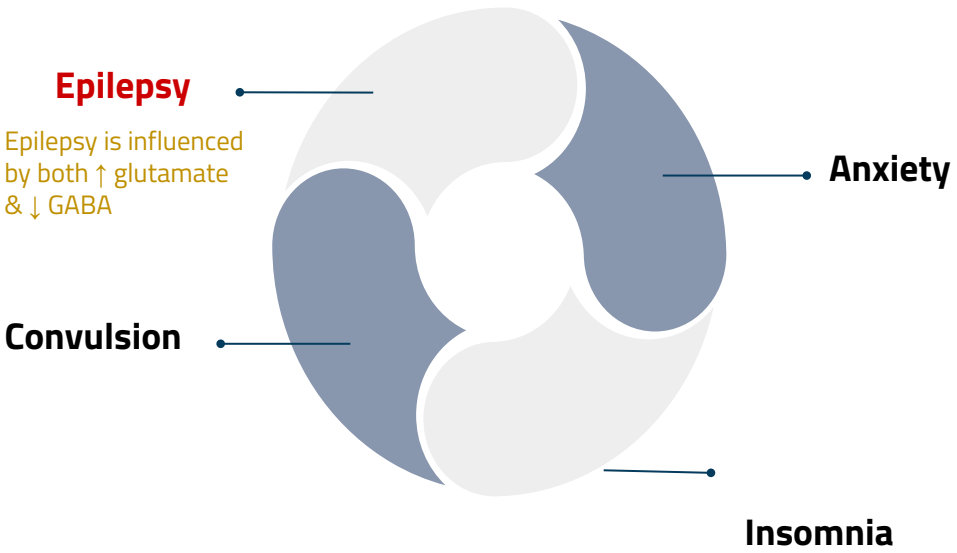
An ↑ in its levels predispose to: Epilepsy



Gamma-Aminobutyric Acid (GABA)

- **Main inhibitory neurotransmitter** in the brain.
- Present throughout the brain (CNS); there's very little in peripheral tissues (PNS).

Diseases that are influenced by ↓ in GABA level:



Conclusion

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

Neurotransmitter ★ Table is imp for MCQ	Anatomic distribution	Receptor subtypes	Receptor Mechanisms
Ach	Cell bodies at all level, short and long axons	Muscarinic, M_1 Muscarinic receptors are membrane receptors (metabotropic): blocked by **pirenzepine** & **atropine**	Excitatory; $\downarrow K^+$ conductance;$\uparrow IP_3$ & DAG IP3 DAG system increase cellular second messenger pathway that releases Ca^{2+} from the ER, thus exciting cells. One can see that cAMP sometimes activates and sometimes inhibit cells; depending on which enzymes it phosphorylate. For more understanding, it is recommended to skim "Cell signaling" foundation block's biochemistry lecture
		Muscarinic, M_2: blocked by **atropine**	Inhibitory; $\uparrow K^+$ conductance; $\downarrow$cAMP
	Motoneuron- Renshaw cell synapse (mainly in the spinal cord)	Nicotinic, N Nicotinic receptors are channel proteins (ionotropic)	Excitatory; $\uparrow$ cation conductance
Dopamine	Cell bodies at all level, Short, Medium and long axons Exert slow inhibitory effect	D_1: blocked by **phenothiazines**	Inhibitory; $\uparrow$cAMP
		D_2: blocked by **phenothiazines** & **haloperidol**	Inhibitory (presynaptic); $\downarrow Ca^{2+}$ conductance; Inhibitory (postsynaptic); $\uparrow K^+$ conductance; $\downarrow$cAMP (by G protein coupled activation of K on postsynaptic).
NE	Cell bodies in pons and brain stem project to all level - **α1 stimulation** → G protein activation of phospholipase C → generation of IP3 and DAG → release of Ca from ER → excitation. - **α2 stimulation** → inhibit adenylyl cyclase → $\downarrow$cAMP.	α_1: blocked by **prazosin**	Excitatory; $\downarrow K^+$ conductance;$\uparrow IP_3$ & DAG
		α_2: activated by **clonidine**	Inhibitory (presynaptic); $\downarrow Ca^{2+}$ conductance Inhibitory (postsynaptic); $\uparrow K^+$ conductance; $\downarrow$cAMP
		β_1: blocked by **propranolol**	Excitatory; $\downarrow K^+$ conductance; $\uparrow$ cAMP
		β_2: blocked by **propranolol**	Inhibitory; $\uparrow$ electrogenic Na^+ pump; $\uparrow$ cAMP
5-HT	Cell bodies in midbrain and pons project to all levels	5-HT_{1A}: **buspirone** is a partial agonist	Inhibitory; $\uparrow K^+$ conductance, $\downarrow$cAMP
		$5HT_{2A}$: blocked by **clozapine**, **risperidone** & **olanzapine**	Excitatory; $\downarrow K^+$ conductance; $\uparrow IP_3$ & DAG
		$5HT_3$: blocked by **ondansetron** (antiemetic in cancer chemotherapy)	Excitatory; $\uparrow$ cation conductance
		$5HT_4$	Excitatory; $\downarrow K^+$ conductance
GABA	Supraspinal interneuron: Spinal interneuron Involved in presynaptic inhibition	$GABA_A$: facilitated by **benzodiazepines** and **zolpidem**	Inhibitory; $\uparrow Cl^-$ conductance
		$GABA_B$: activated by **baclofen**	Inhibitory (presynaptic); $\downarrow Ca^{2+}$ Inhibitory (postsynaptic); $\uparrow K^+$
Glutamate	Relay neurons at all level	Four subtypes: NMDA blocked by **phencyclidine**	Excitatory; $\uparrow Ca^{2+}$ or cation conductance
		Metabotropic subtypes	Inhibitory (presynaptic); $\downarrow Ca^{2+}$ $\downarrow$cAMP Excitatory; $\downarrow K^+$ $\uparrow IP_3$ & DAG
Glycine	Interneurons in spinal cord and brainstem	Single subtype; blocked by **Strychnine**	Inhibitory; $\uparrow Cl^-$ conductance
Opioid peptide	Cell bodies at all levels	Three major subtypes: mu, delta, kappa	Inhibitory (presynaptic); $\downarrow Ca^{2+}$ $\downarrow$cAMP Inhibitory (postsynaptic); $\uparrow K^+$ $\downarrow$cAMP

Extra Summary

Drug	Function/Associations
Norepinephrine (NE)	• **Mania**: ↑ NE level: Treated by: drugs that ↓ NE. • **Depression**: ↓ NE level: Treated by: drugs that ↑ NE.
Serotonin (5-HT)	• **Function**: in regulation of mood, sleep, appetite and pain perception • Social phobia • Depression • Obsessive compulsive disorders (OCD) • Generalized anxiety • Schizophrenia • Vomiting
Dopamine	• Parkinson's disease • Attention deficit hyperactivity disorder (ADHD) • Schizophrenia • Depression & drug addiction
Acetylcholine (ACh)	• **Function**: Memory, Arousal, Attention. • Inhibitory & Excitatory. • **Parkinson's disease** ↑ brain level of ACh. Treated by: Anticholinergic • **Alzheimer's disease** Damage to cholinergic Receptors (muscarinic), associated with memory deficits. Treated by: Cholinomimetic • **Amnesia** caused by muscarinic antagonists as hyoscine • **Schizophrenia** may be due to imbalance between ACh & dopamine levels • **Depression** may be a manifestation of a central cholinergic predominance.

Glutamic Acid	• **Excitatory** neurotransmitter.
	• **Epilepsy:** ↑ Glutamate level predispose to it
	• **Glutamate Antagonist used in:**
	  ○ Reduction of brain damage following strokes & head injury
	  ○ Treatment of epilepsy
	  ○ Drug dependence
	  ○ Schizophrenia

Gama-Aminobutyric Acid (GABA)	• Main **inhibitory** neurotransmitter in the brain.
	• ↓ **GABA is associated with:**
	  ○ Epilepsy
	  ○ Anxiety
	  ○ Convulsions
	  ○ Insomnia

MCQs

#Team438, Check their explanation here.

Q1: A 72-year-old man is brought to his physician by his son. The son complains that this patient has been becoming forgetful, confused, moody, and aggressive over the past few months. One drug that may be used to treat this patient's symptoms is donepezil. Which of the following describes an effect of donepezil?			
A- Decreases synaptic acetylcholine	B- Decreases synaptic dopamine	C- Decreases synaptic norepinephrine	D- Increases synaptic acetylcholine
Q2: A 48-year-old man with schizophrenia on thioridazine for 20 years develops bilateral facial and jaw movements and rhythmic motions of his tongue. Physical examination of the heart, lungs, and abdomen are unremarkable. What is the most likely aberration on a neurotransmitter level?			
A- Acetylcholine	B- Dopamine	C- Serotonin	D- Norepinephrine
Q3: In patients with Parkinson's disease, histologic studies suggest an imbalance in brain neurotransmitters. In contrast to normal individuals, the patients with Parkinson's disease have an abundance of which of the following neurons and associated neurotransmitters?			
A- Acetylcholine	B- Dopamine	C- Epinephrine	D- Norepinephrine
Q4: A 43-year-old man with depression who has been in and out of the psychiatric unit because of noncompliance with medications decides to take intranasal cocaine on a regular basis. He notes that he feels better and thinks that this helps his depression. Through which of the following mediators does this effect likely occur?			
A- Dopamine	B- Epinephrine	C- Glutamine	D- Norepinephrine
Q5: Stimulation of inhibitory neurons causes which of the following effects at the postsynaptic membrane?			
A- Binding of GABA at the postsynaptic membrane	B- Depolarization	C- Stimulation of epinephrine	D- Transient decrease in permeability of chloride
Q6: Four patients present to their primary care physician with various complaints and problems. Which of the following patients would have the most limited response to their symptoms if given a prescription for diazepam?			
A- A 24-year-old woman with chronic pelvic pain	B-A 36-year-old man with chronic anxiety	C-A 42-year-old man with seizure disorder	D-A 45-year-old woman with seizure disorder

1	2	3	4	5	6
D	B	A	A	A	A

SAQ

Q1) Mention 3 diseases that are influenced by a change in 5-HT

Q2) Mention 2 examples of neurotransmitters formed of amino acid

Q3) List the potential therapeutic effect of glutamate antagonists.

Q4) Mention receptor subtypes of dopamine, and drugs that are block them

Q5) What is the anatomic distribution of GABA?

Q6) What is the mode of action of Ach?

Answers

A1) Social phobia, vomiting, depression

A2) Glutamate and GABA

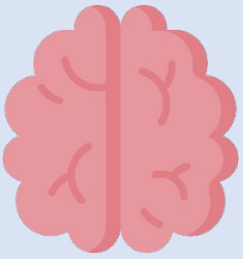
A3) Reduction of brain damage following strokes & head injury, Treatment of epilepsy, Drug dependence-Schizophrenia

A4) D_1: blocked by phenothiazines. D_2: blocked by phenothiazines & haloperidol

A5) Supraspinal interneuron: Spinal interneuron Involved in presynaptic inhibition

A6) Excitatory and inhibitory

Feedback Form



Pharmacology 439

MED439

Neuropsychiatry Block

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