MED 443
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TEAM 443
PHARMACOLOGY

Pharmacology of neurotransmitter

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- The main objective of this lecture is to understand the role of neurotransmitters in the etiology & treatment of CNS diseases.

- It is recommended to study the physiology of neurotransmitters before this lecture.

- For every NT, make sure to cover the following:
  1. Function
  2. Site (in general)
  3. Associated diseases
  4. Whether it is excitatory, inhibitory, or both
  5. Receptor types & subtypes

Abbreviations

- **Ac:** nucleus accumbens
- **Am:** amygdaloid nucleus
- **C:** cerebellum
- **Hip:** hippocampus
- **Hyp:** hypothalamus
- **LC:** locus coeruleus
- **LTA:** lateral tegmental area
- **MFB:** medial forebrain bundle
- **NTS:** nucleus of tractus solitarius
- **P:** pituitary gland
- **PPT/LD:** pedunculopontine & laterodorsal tegmental nuclei
- **SN:** substantia nigra
- **Sep:** septum
- **Str:** corpus striatum
- **Th:** thalamus
- **VTA:** ventral tegmental area

Neurotransmitters

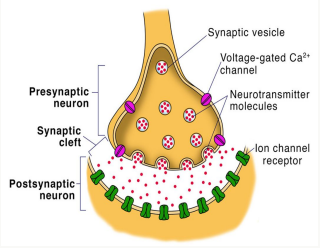
Definition

endogenous chemicals that transmit signals from a neuron to a target cell across a synapse.

Criteria

Criteria that identifies NT:

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.**

Effect: *excitatory* or *inhibitory* depending on the NT & receptor.

Examples

Monoamines & other biogenic amines	• Dopamine (DA) • Norepinephrine (NE) • Serotonin (5-HT)
Amino Acids	• Glutamate (Glu) • Gamma aminobutyric acid (GABA) • Aspartate • Glycine
Peptides	• Somatostatin inhibits the secretion of other hormones
Other	• Acetylcholine (Ach)

In CNS diseases all the NT have been affected but there is a specific NT have been affected the most so we consider it as a main cause of a specific type of CNS disease

Neuropsychopharmacological Science

Seeks To

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

Importance

Understanding neurotransmitters helps:

1. Understand the etiology of diseases.
2. Suggest the best drugs to be used.
3. Understand the other clinical uses of any particular drug.

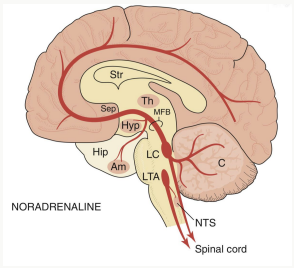
To conclude
Without understanding the involvement of neurotransmitters in the etiology of CNS diseases, doctors could not select the proper drug for any particular disease.

Norepinephrine (Noradrenaline)

The doctor focused on the functions of neurotransmitters as well as their location of synthesis

Overview

- NE binds to α & β adrenergic receptors.
  Some are *excitatory* (α_1, β_1) & others are *inhibitory* (α_2, β_2).
- Cell bodies lie in pons (locus coeruleus).
  They project diffusely throughout the brain (cortex, hippocampus, thalamus, hypothalamus, cerebellum) & spinal cord.



Disorders

↑ NE levels → **mania (OVER ACTIVATION)** → Rx: Drugs that ↓ NE

↓ NE levels → **depression** → Rx: Drugs that ↑ NE

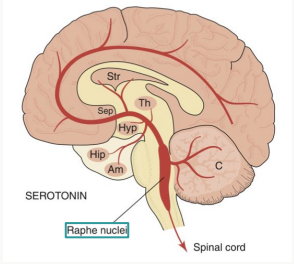
Serotonin

Overview

- **Primarily found in:** CNS, GIT, platelets, etc. (not just CNS).
- **Plays an important role in:** regulation of **mood**, **sleep**, **appetite** & **pain perception**.
  - It's a popular thought that Serotonin is responsible for feeling of well-being & happiness.
  - It decreases appetite but *some* antidepressants that ↑ serotonin may result in rebound increase in appetite/weight.
- It can be either *excitatory* or *inhibitory* based on the receptor

Location

- Cell bodies lie in **Raphe nuclei**, mainly in the pons & midbrain.
- Project to many parts of the cortex, hippocampus , basal ganglia, limbic system, hypothalamus, cerebellum , medulla & spinal cord.



Disorders

Diseases influenced by changes in 5-HT brain content:

1. Depression: ↓ 5-HT
2. Social phobia
3. Obsessive compulsive disorders (OCD)
4. Generalized anxiety
5. **Schizophrenia**
6. Vomiting

Glutamic Acid

Overview

- An *excitatory* neurotransmitter.
- ↑ Glutamic acid levels predispose to: epilepsy.

Potential therapeutic effect of glutamate antagonists:

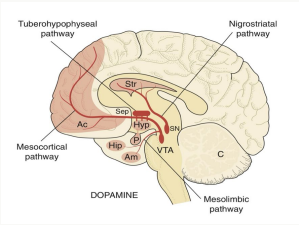
- Treatment of epilepsy
- Reduction of brain damage following strokes & head injury
  - Head injury causes ↑ glutamate release (over-excitation).
- Drug dependence
- Schizophrenia

consider as the main reason for parkinson

Dopamine

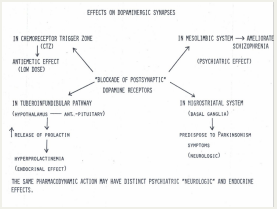
Definition

- Dopamine is mainly *inhibitory* in function but it depends on the receptor subtype.
- Cell bodies in all levels of brain



Pathways

Pathway	Synthesis	Projects to	Function	Effect of Dopamine Antagonists
Mesolimbic (reward pathway)	Tegmental area	Limbic system via nucleus accumbens	Cognitive & emotional	**Psychiatric effect:** ameliorates (improves) schizophrenia
Mesocortical		Frontal cortex	Memory, motivation & emotions	
Nigrostriatal (basal ganglia)	Substantia nigra	Striatum	Controls Movement	**Neurologic effect:** predispose to Parkinsonism symptoms
Tuberoinfundibular (tuberohypophyseal)	Hypothalamus	Anterior pituitary	Regulation of prolactin secretion	**Endocrine effect:** ↑ prolactin release
Chemoreceptor Trigger Zone (CTZ)			Nausea & vomiting	**Antiemetic effect** (low dose) (e.g. Metoclopramide)



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

Diseases

1. **Parkinson's disease:** ↓ DA
2. Attention deficit hyperactivity disorder (ADHD)
3. **Schizophrenia:** ↑ DA
4. Depression
5. **Drug addiction** by the inhibition of dopamine re-uptake

Gamma-Aminobutyric Acid (GABA)

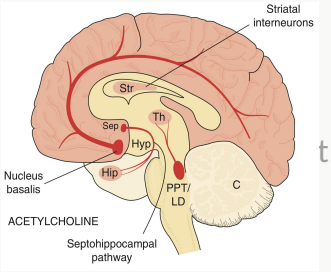
Definition

- The main inhibitory neurotransmitter in the brain.
- Present throughout the brain (CNS).
- There is very little in peripheral tissues (PNS).

Diseases

- Decreased GABA is associated with:
  - Epilepsy.
  - Anxiety.
  - Convulsions.
  - Insomnia.

Acetylcholine

Definition	• Ach is the first neurotransmitter discovered.
Functions	1. Inside the brain Ach acts as a neuromodulator (modifies the activity) -neuromodulator : a chemical that alters the way other brain structure process information -Neurotransmitter : a chemical that transmits information from point to point. 2. Thought to be involved in cognitive functions as : memory , arousal & attention. 3. Also found in the peripheral NS (neuromuscular junction). • **Is Ach an Excitatory or inhibitory neurotransmitter?** **Both, depending on receptor subtype: nicotinic & M1 are excitatory while M2 is inhibitory .**
Main nuclei & projections	1) Brainstem: mesopontine tegmental area 2) Basal forebrain: nucleus basalis; projects to the cortex. 3) Septohippocampal nucleus:provides the main to the hippocampus for memory 4) Corpus striatum 
Disorders	• **Parkinson's:** predisposed by ↑ Ach in the brain. Rx: anticholiergics • **Alzheimer's:** damage to cholinergic **(muscarinic)** receptors is associated with the memory deficits. Rx: cholinomimetis • **Amnesia:** may be caused by **muscarinic** antagonists (e.g. Hyoscine). • **Depression:** may be a manifestation of a central cholinergic predominance. Variable findings among studies, but most have found ↑ Ach. • **Schizophrenia:** may be due to imbalance between Ach & dopamine brain levels.

Summary

Doctor: for Each NT you should know
1- Whether it is excitatory, inhibitory or both.
2- Receptors types & subtypes → receptor mechanisms/drugs mentioned are not important.
3- Location (in general).

NT	Anatomic Distribution	Receptor Subtypes	Receptor Mechanisms
Ach	Cell bodies at **all levels**; short & long axons	M_1 blocked by Pirenzepine & Atropine	↓ K^+ conductance; ↑ IP_3 & DAG
		M_2 blocked by Atropine	↑ K^+ conductance; ↓ cAMP
	Motoneuron; Renshaw cell synapse (presynaptic)	Nicotinic (N)	↑ Cation conductance
DA	Cell bodies at **all levels**; short, medium & long axons	D_1 blocked by Phenothiazines	↑ cAMP
		D_2 blocked by Phenothiazines & Haloperidol	**Presynaptic:** ↓ Ca^{2+} conductance **Postsynaptic:** ↑ K^+ conductance; ↓cAMP
NE	Cell bodies in **pons & brain stem**; project to all levels	α_1 blocked by Prazosin	↓ K^+ conductance; ↑ IP_3 & DAG
		α_2 activated by Clonidine	**Presynaptic:** ↓ Ca^{2+} conductance **Postsynaptic:** ↑ K^+ conductance; ↓ cAMP
		β_1 blocked by Propranolol	↓ K^+ conductance; ↑ cAMP
		β_2 blocked by Propranolol	↑ Electrogenic Na^+ pump; ↑ cAMP
5-HT	Cell bodies in **midbrain & pons** project to all levels	5-HT_{1A} → Buspirone is a partial agonist	↑ K^+ conductance; ↓ cAMP
		$5HT_{2A}$ blocked by Clozapine, Risperidone & Olanzapine	↓ K^+ conductance; ↑ IP_3 & DAG
		$5HT_3$ blocked by Ondansetron (antiemetic in chemotherapy)	↑ Cation conductance
		$5HT_4$	↓ K^+ conductance

Summary

NT	Anatomic Distribution	Receptor Subtypes	Receptor Mechanisms
GABA	Supraspinal & spinal interneurons involved in presynaptic inhibition	$GABA_A$ facilitated by Benzodiazepines & Zolpidem	↑ Cl^- conductance
Glutamate (you should know the type of receptor)	Relay neurons at all levels	4 Subtypes: **NMDA** subtype blocked by Phencyclidine	↑ Ca^{2+} or cation conductance
		Metabotropic subtypes	**Presynaptic:** ↓ Ca^{2+} conductance; ↓ cAMP
			↓ K^+ conductance; ↑ IP_3 & DAG
Glycine (Inhibitory)	Interneurons in spinal cord & brainstem	1 Subtype; blocked by Strychnine	↑Cl^- conductance
Opioid peptide (Inhibitory)	Cell bodies at all levels	3 Major subtypes: **μ** (mu) **δ** (delta) **κ** (kappa)	**Presynaptic:** ↓ Ca^{2+} conductance; ↓ cAMP
			Postsynaptic: ↑ K^+ conductance; ↓ cAMP

Important Questions From Female Doctor

1. Which NT is responsible for feeling of well-being & happiness?
2. Which NT is responsible for cognitive function (memory & attention)?
3. **T or F:** ↓ GABA brain content is associated with epilepsy.
4. **T or F:** ↑ Glutamic acid in the brain is associated with epilepsy.

Answers
1- Serotonin
2- Ach
3- T
4- T

Extra First Aid Summary

	LOCATION OF SYNTHESIS	ANXIETY	DEPRESSION	SCHIZOPHRENIA	ALZHEIMER DISEASE	HUNTINGTON DISEASE	PARKINSON DISEASE
Acetylcholine	Basal nucleus of Meynert (forebrain)				↓	↓	↑
Dopamine	Ventral tegmentum, SNc (midbrain)		↓	↑		↑	↓
GABA	Nucleus accumbens (basal ganglia)	↓				↓	
Norepinephrine	Locus ceruleus (pons)	↑	↓				
Serotonin	Raphe nuclei (brain stem)	↓	↓				↓

MCQ

1. What is the main inhibitory neurotransmitter in the brain			
A. serotonin	B. GABA	C. Glutamic acid	D. Ach
2. Primarily found in the CNS, GIT, and platelet			
A. serotonin	B. GABA	C. Glutamic acid	D. Ach
3. An increase in Glutamic acid level predispose to			
A. epilepsy	B. Parkinson's	C. OCD	D. insomnia
4. decreased levels of GABA is associated with which of the following			
A. Alzheimer	B. Parkinson's	C. insomnia	D. none of the above
5. increased levels of norepinephrine lead to			
A. Mania	B. depression	C. Parkinson's	D. Alzheimer

1:B ,2:A ,3:A ,4:C ,5:A

SAQ

01

What are the CNS diseases that linked to Ach derangement ?

1. Alzheimer
2. amnesia
3. Parkinson's
4. Schizophrenia
5. Depression

02

What are the diseases that influenced by dopamine level ?

1. Parkinson's disease.
2. Attention Deficit Hyperactivity disorder.
3. Schizophrenia.
4. Depression.
5. Drug addiction.

03

What are the diseases that are influenced by changes in 5-HT brain content

1. Depression.
2. Social phobia.
3. Obsessive Compulsive Disorders.
4. Generalized Anxiety.
5. Schizophrenia.
6. Vomiting.

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Special thanks to norah almania for the amazing logo