Physiology Team

LECTURE 24

Neurotransmitter

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OBJECTIVES

At the end of this lecture, student should be able to describe:

No objectives!

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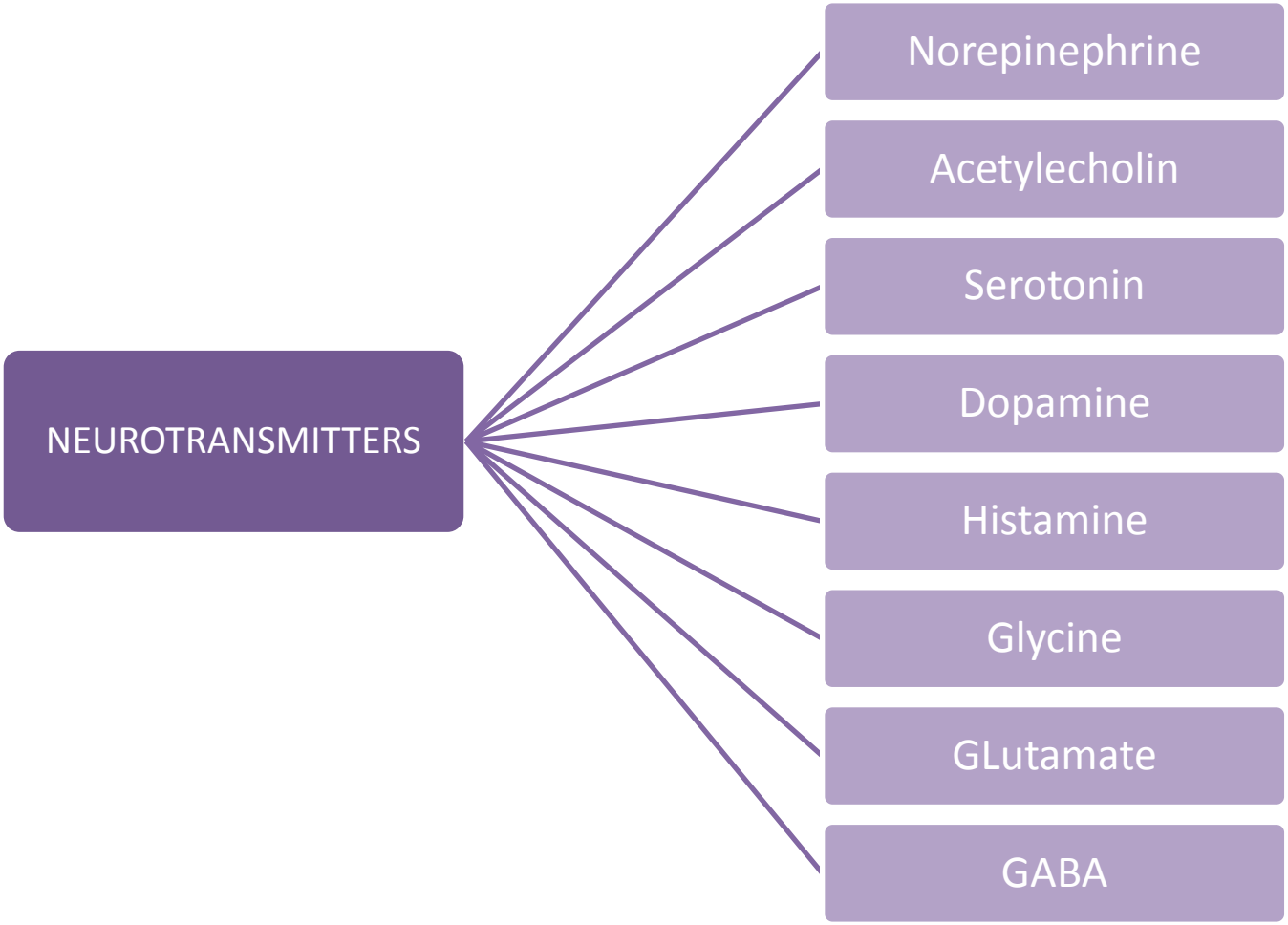
MIND MAP



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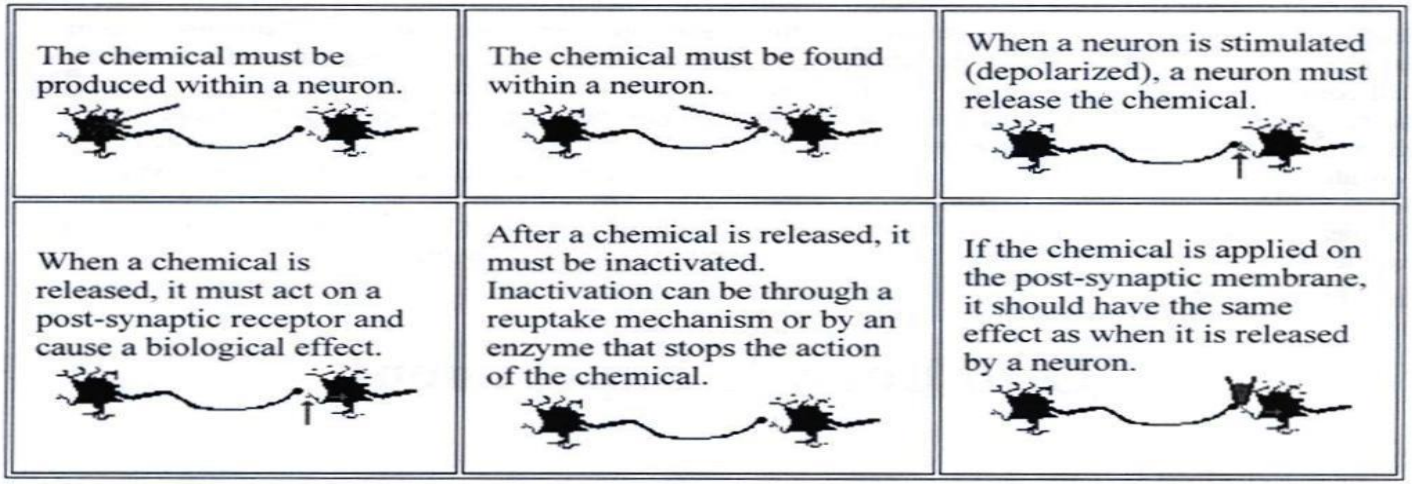
Definition of Neurotransmitters

- Are chemical substances released by electrical impulses into the synaptic cleft from synaptic vesicles of presynaptic membrane . It then diffuses to the postsynaptic membrane, binds to and activates the receptors present leading to initiation of new electrical signals or inhibition of the post-synaptic neuron.
- Function of neurotransmitters: **1.** Peripherally → Visceral (autonomic) + Muscular. **2.** Central → Storage and transmission of information.

Neurotransmitter Criteria

Neuroscientists have set up a few guidelines or criteria to prove that a chemical is really a neurotransmitter. Not all of the neurotransmitters that you have heard about may actually meet every one of these criteria.



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Classification of Neurotransmitters

Neurotransmitters have different chemical structures and therefore, different actions.

Amines		
Acetylcholine (ACh)	Dopamine (DA)	Norepinephrine (NE)
Serotonin (5-HT)	Histamine	Epinephrine

Amino Acids		
Gamma-aminobutyric acid (GABA)	Glycine	Glutamate
Aspartate		

Responsible for pain modulation

Neuroactive Peptides - partial list!!			
bradykinin	beta-endorphin	bombesin	calcitonin
cholecystokinin	enkephalin	dynorphin	insulin
gastrin	substance P	neurotensin	glucagon
secretin	somatostatin	motilin	vasopressin
oxytocin	prolactin	thyrotropin	angiotensin II
sleep peptides	galanin	neuropeptide Y	thyrotropin-releasing hormone
gonadotropnin-releasing hormone	growth hormone-releasing hormone	luteinizing hormone	vasoactive intestinal peptide

1. VSM relaxation → Blood flow.
2. Works at the level of CNS too.

Soluble Gases	
Nitric Oxide (NO)	Carbon Monoxide

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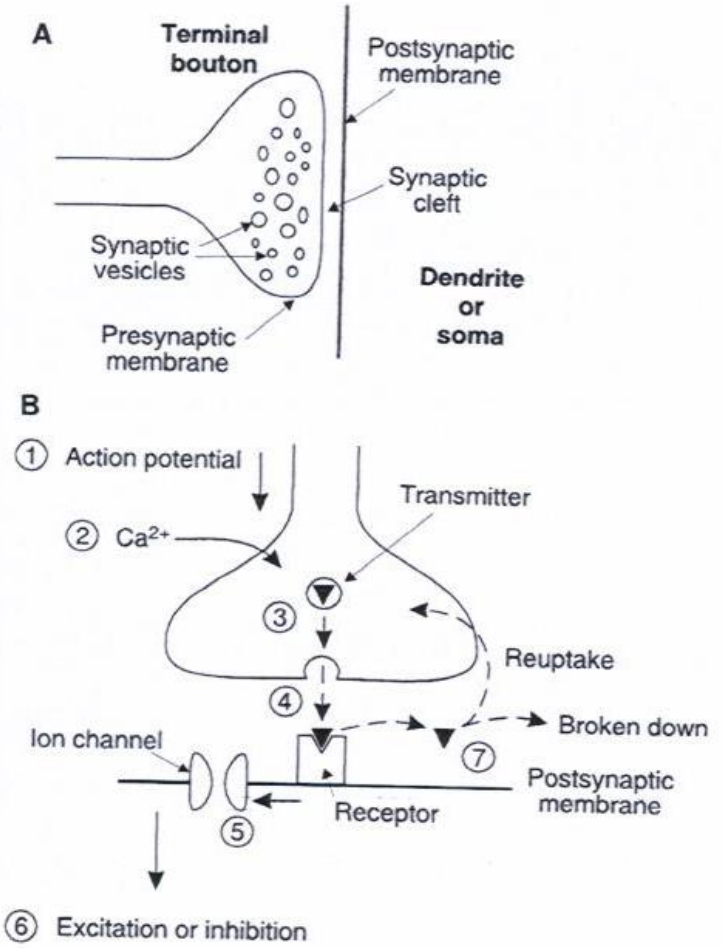
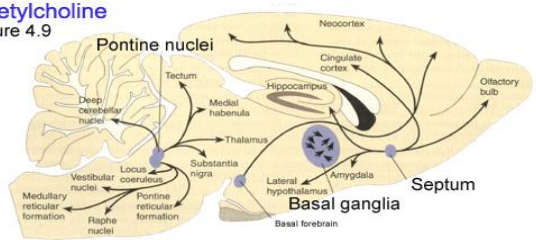
N.T. release & action

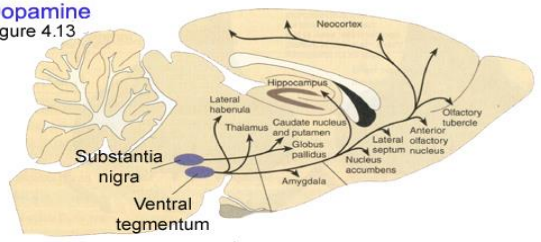


Major Brain Pathways

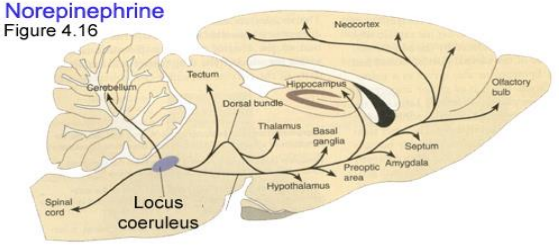
Acetylcholine
Figure 4.9



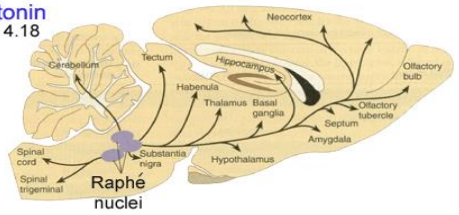
Dopamine
Figure 4.13



Norepinephrine
Figure 4.16



Serotonin
Figure 4.18



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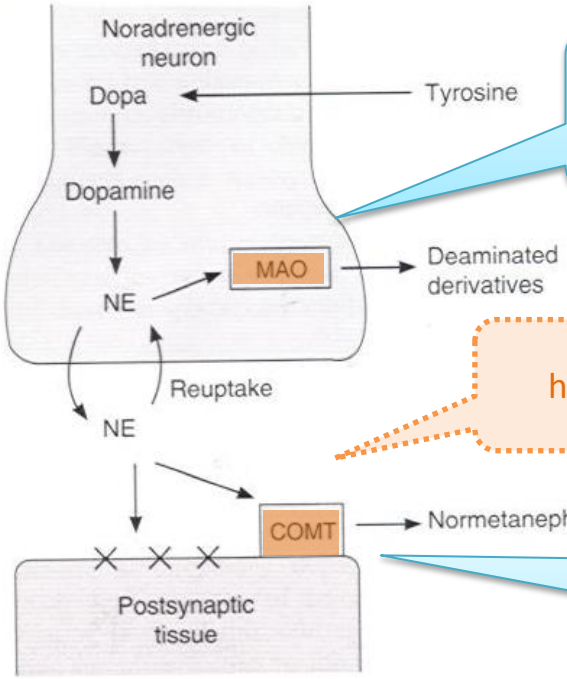
The Locus Coeruleus (Norepinephrine System)

Features	Sleep/wake cycle	Related disorders (LC activity)
Very wide-spread projection system	Locus coeruleus neurons fire as a function of vigilance and arousal. They display a slow irregular firing during quiet wakefulness and a sustained activation if the subject is stressed or excited. Their firing decreases markedly during slow-wave sleep and virtually disappears during REM sleep.	Some conditions of depression.
LC is activated by stress and co-ordinates responses via projections to thalamus, cortex, hippocampus, amygdala, hypothalamus, autonomic brainstem centers, and the spinal cord. When you're alert → all systems are activated because LC is sending impulses to all these areas.		Withdrawal from some drugs of abuse: When opioid consumption is stopped, the ↑ activity of the locus coeruleus contributes to the symptoms of opiate withdrawal. The alpha2 adrenoceptor agonist " Clonidine" is used to counteract this withdrawal effect by decreasing adrenergic neurotransmission from the locus coeruleus
Sleep: LC activity predicts changes in sleep/wake cycle.		Other stress related disorders such as panic disorders. Treatment: Anxiolytics
Attention/Vigilance: LC activated by novel stimuli, and LC activates EEG. High levels of activity of LC results in vigilance → treated by anxiolytic drugs		

Norepinephrine synthesis & fate at synapse

Key Enzymes
th = tyrosine hydroxylase, rate limiting step
dd = dopa decarboxylase

Drugs can act on receptors or block the enzymes.
As a result → increased NE → Prolonged action



- (1) Re-uptake into the presynaptic neuron
- where it is degraded intracellularly MonoamineOxidase (MAO) enzyme;

Norepinephrine is hydrolyzed by MAO & COMT

- (2) Extracellular inactivation by Catechol-O-Methyl Transferase (COMT)

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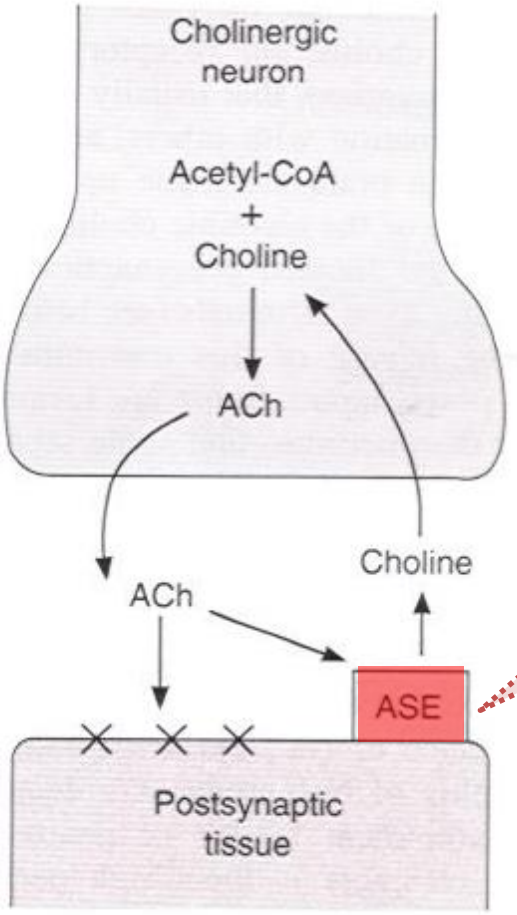
- The three Catecholamines (dopamine , NE and epinephrine) are formed by hydroxylation and decarboxylation of the amino acid Tyrosine .
- Tyrosine is converted to Dopa and then Dopamine in the cytoplasm of cells by Tyrosine Hydroxylase and Dopa Decarboxylase
- The Dopamine then enters the granulated vesicles , and inside them it is converted to Norepinephrine by the enzyme Dopamine Hydroxylase (Dopamine beta-Hydroxylase , DBH)
- L-Dopa is the isomer of Dopamine .
- Tyrosine Hydroxylase is the rate-limiting enzyme of synthesis , & it is subject to feed-back inhibition by dopamine and norepinephrine , thus prividing internal control of the synthesis process .
- Some brain neurons and adrenal medullary cells (but not postgqanglionic sympathetic nerves) contain the their cytoplasm the enzyme PNMT (Phenylthanolamine-N-Methyl Transferase) , which converts norepinephrine into epinephrine .
- In these epinephrine-secreting neurons , norepinephrine leaves the vesicles to the cytoplasm , where it is converted by PNMT into epinephrine , and then enters other storage vesicles .

Cholinergic Pathways

Important

- Basal ganglia contains **"caudate nucleus"** which is one of the main cholinergic systems in the CNS → it controls muscle tone.
- Muscle tone needs to be balanced by two opposing factors i.e. a factor that enhances it and another that reduces it. Thus, if one of them is absent, the other will take the upper hand in controlling muscle tone → imbalance.
- Ach secreted by caudate nucleus is excitatory → increases muscle tone. On the other hand, substantia nigra "Dopaminergic system" has an inhibitory effect → decreases muscle tone.
- Imbalance between the two as in cases of decreased activity of substantia nigra → activity of caudate nucleus will not be opposed → increased Ach → excessive increase in muscle tone → rigidity of muscles → Parkinson's Disease.
- In addition, cholinergic system is connected to hippocampus → participates in memory. Consequently, degeneration of cholinergic system may result in Alzheimer's disease.
- In the brain , cholinergic (ACh producing) neurons are present mainly in 2 areas: 1. Basal Forebrain (namely Nucleus Basalis of Myenert) 2. Ponto-Mesencephalic Cholinergic Complex
- Functions :The brain Cholinergic system is concerned with:
- (1) Consciousness/wakefulness alertness (see Brainstem Bulboreticular Facilitatory Area in Consciousness & Sleep lectures) .
- (2) Memory & learning .

Acetylecholine synthesis & fate at synapse



Most important way to get rid of Ach at the level of neurons → acetylecholinesterase

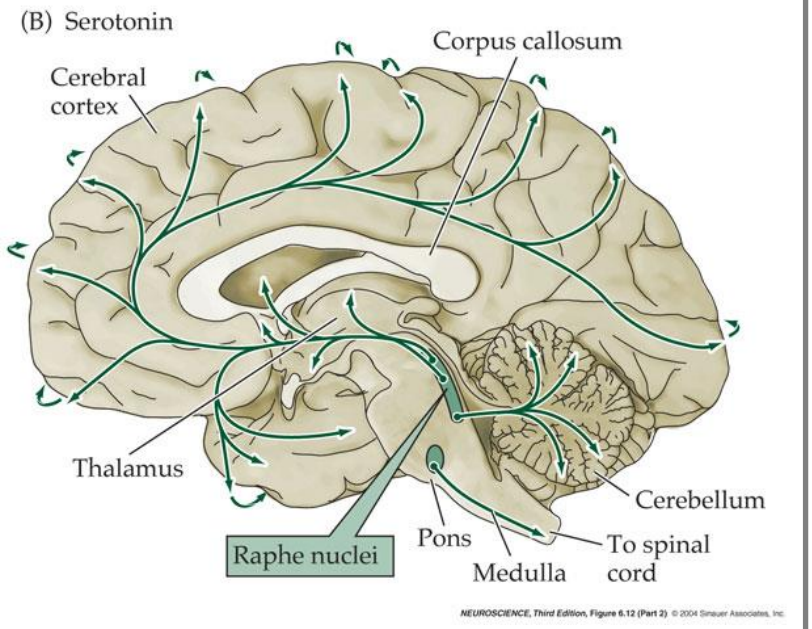
Serotonin

- Sertonergic neurons project to many parts in CNS (in brain & spinal cord).
- Importance of serotonin:

1. Pain modulation through its connection with spinal cord → decreases severity of pain.
2. Participates in mood elevation. (Tryptophan "precursor of 5-HT" is presents richly in chocolate, and that's why it uplifts one's mood.) :D

- **Disorders associated with 5-HT:**

1. Depression .
2. Anxiety.



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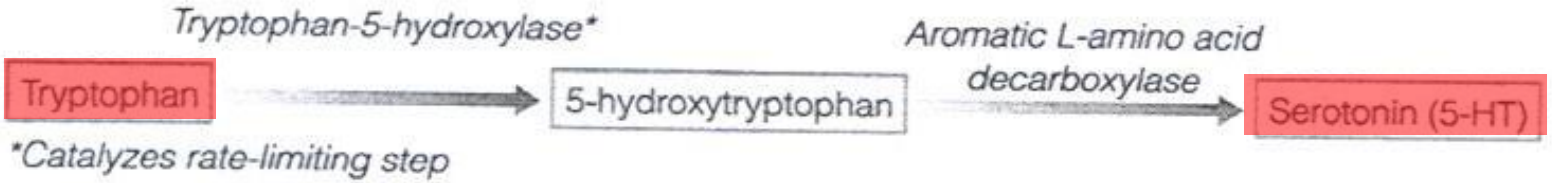
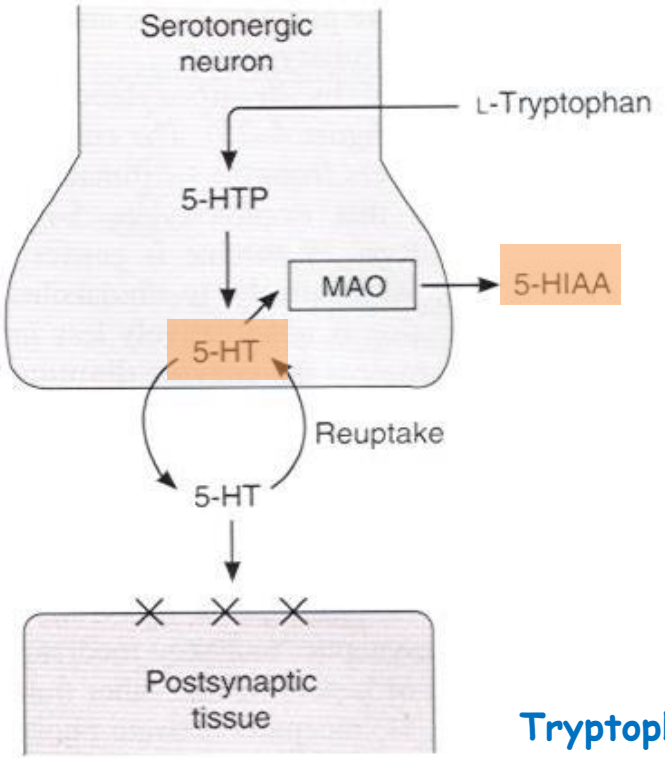
Serotonin synthesis & fate at synapse





5-HT = Hydroxy tryptamine
HIAA= hydroxyindoleacetic acid

Tryptophan neuronal cell bodies are present in Raphe Nuclei

Dopaminergic Pathway

Dopamine is transmitted via three major pathways

Important

Origin	Termination	Function	Notes
Substantia nigra Nigrostriatal System	Caudate nucleus-putamen (neostriatum)	Sensory stimuli and movement	Inhibition of caudate nucleus → decreases muscle tone
Ventral tegmentum Mesocortical System	Mesolimbic forebrain	Cognitive, reward and emotional behavior.	-
Tubero-infundibular system		Neuronal control of hypothalamic-pituitary endocrine system.	Dopamine inhibits prolactin. (Prolactine is a hormone that may lead to infertility) Thus, we can treat infertility by a prolactin antagonist i.e. dopamine.

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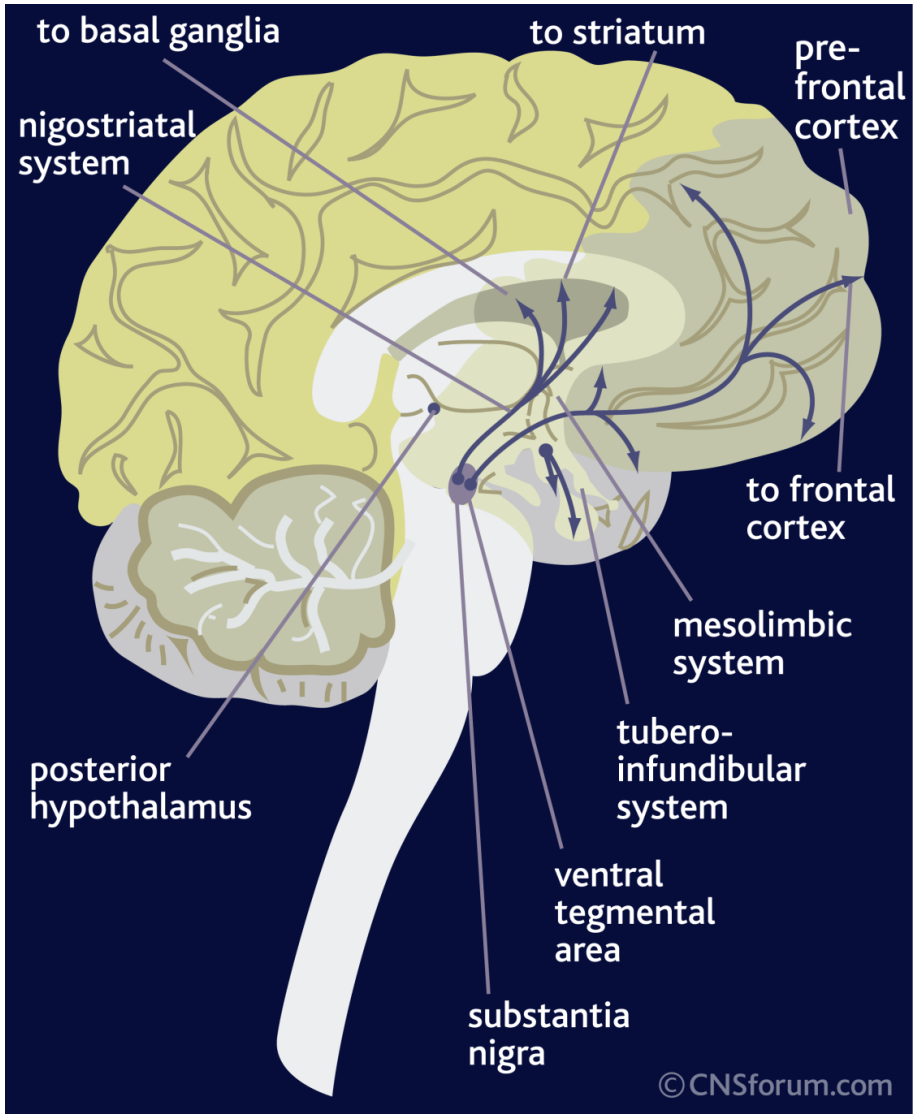
Dopamine cannot cross blood brain barrier, however L-Dopa (AKA Levo-Dopa) can.



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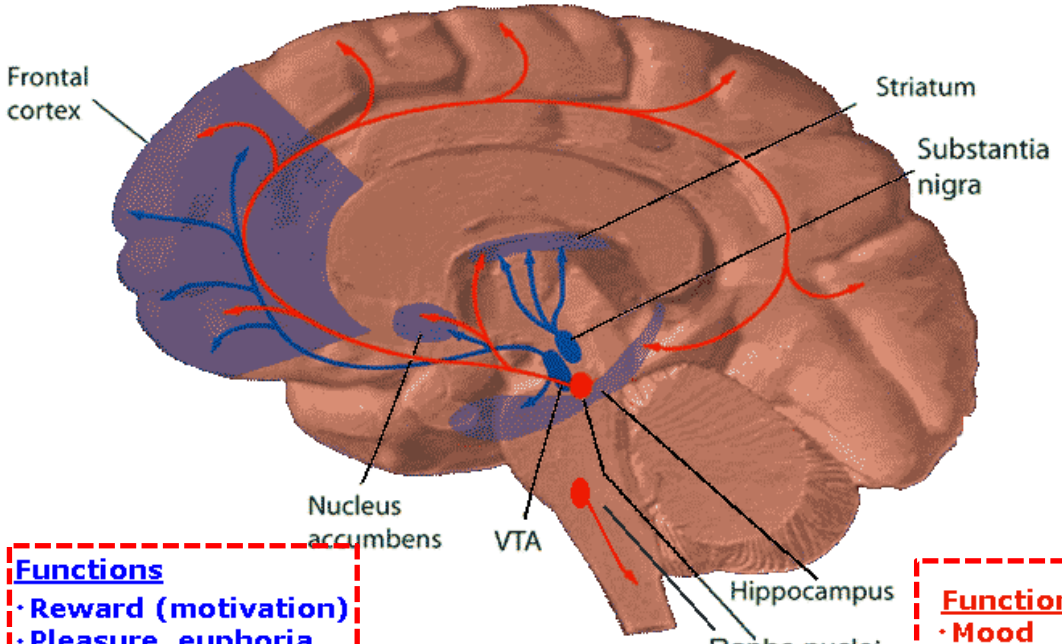
Dopamine Pathways

Serotonin Pathways



Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions
- Mood
- Memory processing
- Sleep
- Cognition

Dopaminergeic neuron disorders:
Schizophrenia.
Parkinson's disease.

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Histamine

- **Location of forming cells:**

1. Posterior hypothalamus.

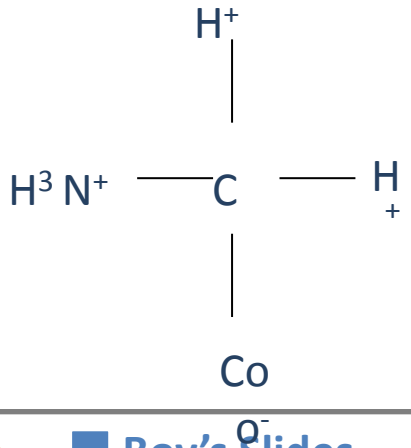
2.Gastric mucosa. Histamine increases HCL → gastric ulcer. Treatment: by blocking peripheral H receptors.

3.Mast cells.

- **Formation:** Histidine (amino acid) —Decarboxylation by Histaminase→ Histamine
- **Receptors:** H1 & H2 (peripheral) H3 (central)
- H3 Receptors are presynaptic. It is an excitatory neurotransmitter but with an uncertain function in the brain (centrally).

Glycine

- It is simplest of all aminoacids, consisting of amino group and a carboxyl group attached to a carbon atom
- **Type:** Inhibitory.
- **Action:** Binds to a receptor → makes postsynaptic membrane more permeable to Cl ions → Hyperpolarization (inhibition).
- **Location of receptor:** Ventral part of spinal cord. It blocks pain in spinal cord.
- Strychnine is a glycine antagonist. Strychnine can cause poisoning.



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Glutamic Acid

- It is the most commonly found neurotransmitter in the brain.
- **Type:** Always excitatory.
- **Formation:** during Kreb's cycle for α – ketoglutarate.
- Glutamate is carried into astrocytes where it is converted to glutamine and passed on to glutaminergic neurones.
- **Types of receptors**: metabotropic and iontropic receptors.

Gamma Aminobutyric acid (GABA)

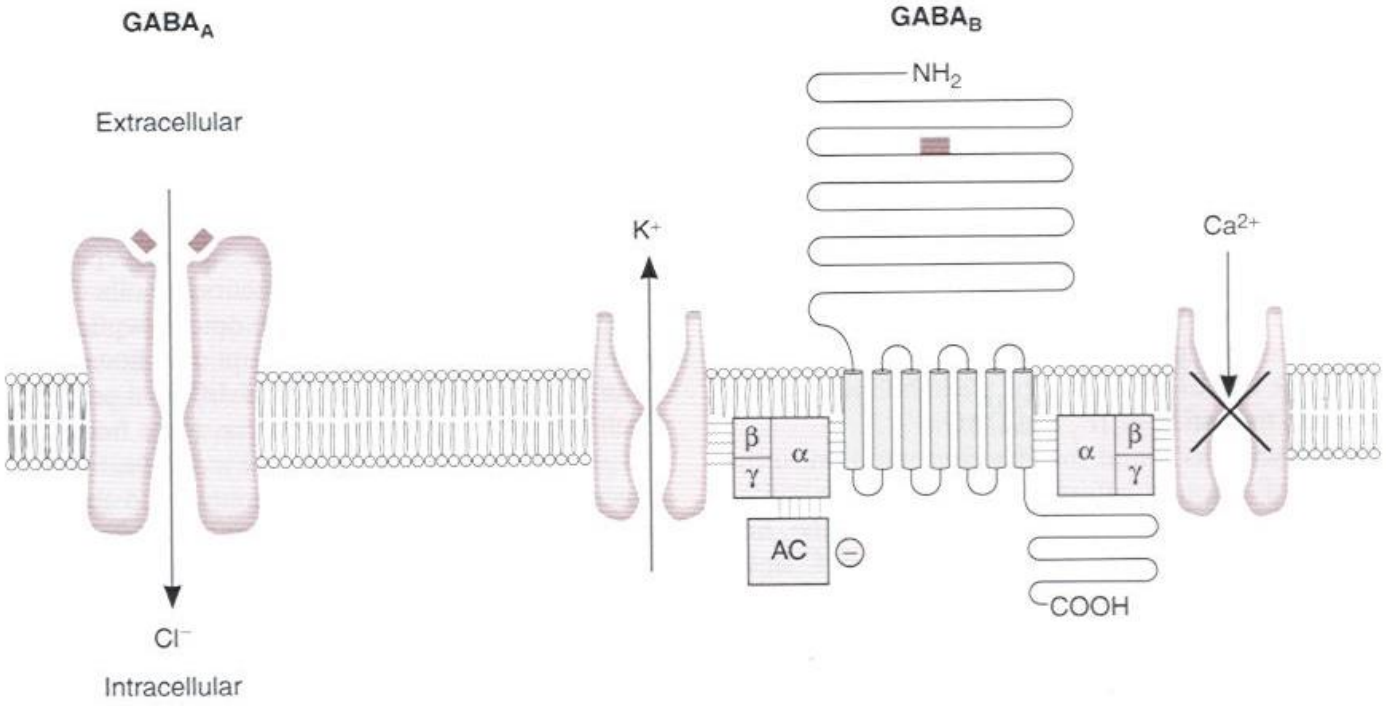
- **Type**: Inhibitory
- **Location:** CNS and retina.

- **Formation:** Glutamate —(Decarboxylation by GAD)→ GABA

- **Types of GABA receptors: $GABA_{A\ B\ \&\ C.}$**

1. $GABA_{A\ \&\ B}$ receptors are widely distributed in CNS.
2. $GABA_C$ are found in retina only.
3. $GABA_B$ are metabotropic (G-protein) in function.

- including being responsible for presynaptic inhibition



GABA causes inhibtion "hyperpolarization" by one of these mechanisms:

1. Opening Cl channels → influx.
2. Opening of K channels → leakage.
3. Blocking Ca channels.

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RECEPTORS DYSFUNCTION

Clinical application

- **Presynaptic effect**

1. **Botulinum toxin:** Its an exotoxin that binds to the presynaptic membrane and prevents the release of Ach resulting in weakness and reduction of tone. It is used to control dystonia in which body shows overactive muscular activity.

   Botox used in cosmetic surgery is actually a derivative of botulinm toxin.

- **Effects at Postsynaptic level:**

1. **Curare:** binds to the acetylcholine receptor (AchR) and prevents Ach from acting on it and so that it induces paralysis. Curare is used as a muscle relaxant in anesthesia.
2. **Myasthenia gravis:** is caused by an antibody against the Ach receptors and Ach receptors are reduced hence the Ach released has few Ach receptor available to work and patients complain of weakness that increases with exercise.

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SUMMARY

- **Neurotransmitters** are chemical substances released by electrical impulses into the synaptic cleft from synaptic vesicles of presynaptic membrane . It then diffuses to the postsynaptic membrane, binds to and activates the receptors present leading to initiation of new electrical signals or inhibition of the post-synaptic neuron.
- **Major brain pathways are:** Ach, NE, Dopamine and serotonin.
- **Inhibitory neurotransmitters mentioned in this lecture are:** Glycine ,GABA and sometimes NE.
- **Disorders related to:**

1. NE → Depression, withdrawal from some drugs and panic disorders.
2. Serotonin → Depression & anxiety.
3. Ach → Dementia and Parkinson's disease.
4. Dopamine → schizophrenia & Parkinson's disease.

- Check out female slides for a summery of neurotransmitters arranged in a table!

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QUESTIONS

Answers:
1 = c
2 = b
3 = d
4 = a

1. Norepinephrine system is involved in:

a) Memory.
b) Motor activity.
c) Sleep/wake cycle.
d) Pain modulation.

2. Which one of the following is a function of Ach:

a) Inhibition of muscle tone.
b) Enhancement of muscle tone.
c) Mood improvement.
d) Neural control of endocrine system.

3. Which one of the following is the most commonly found neurotransmitter in brain:

a) Histamine.
b) Ach.
c) Norepinephrine.
d) Glutamic acid.

4. Glycine causes inhibition by:

a) Increasing membrane permeability of Cl.
b) Decreasing membrane permeability of Cl.
c) Increasing membrane permeability of Ca.

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THE END

If there are any Problems or Suggestions,
Feel free to contact:

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THANK YOU