Physiology 435 team

BRAIN NEUROTRANSMITTERS

Objectives:

- Be able to describe the **main location** in the brain of the following transmitters, as well as their physiological functions; and give examples of clinical conditions associated with their imbalance:
  - **Acetylcholine (Ach)**
  - **Norepinephrine (NE).**
  - **Glutamate.**
  - **GABA.**
  - **Serotonin.**
  - **Dopamine.**

Done by:

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Color index: Important - Further explanation - Doctors Notes - Numbers.

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*Please check out this link before viewing the file to know if there are any additions or changes.

Brain Neurotransmitters

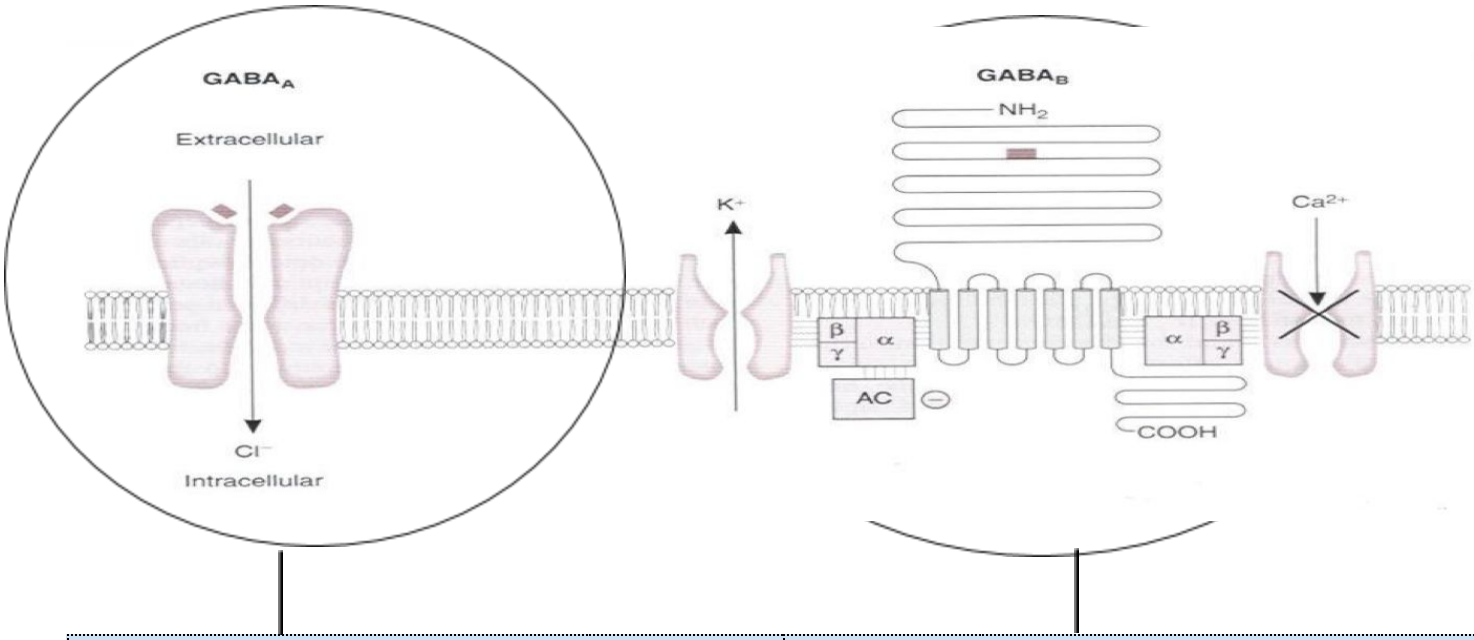
They are **Chemical substances** released by electrical impulses into the synaptic cleft from synaptic vesicles of presynaptic membrane (by exocytosis), then they diffuses to the **postsynaptic membrane** by Binding to **receptors** and activating them. Leading to initiation of new electrical signals (activation) or inhibition of the postsynaptic neuron.

Classification of neurotransmitters

All the NT are proteins and the widely spread NTs in the brain are the amine.

AMINES		
Acetylcholine (ACh)	**Dopamine (DA)**	**Norepinephrine (NE)**
Serotonin (5-HT)	**Histamine**	**Epinephrine**
AMINO ACIDS		
Gamma-aminobutyric acid (GABA)		**Glutamate**
Glycine		**Aspartate**
NEUROACTIVE PEPTIDES		
Bradykinin	Substance P	Thyrotropin
Cholecystokinin	Somatostatin	Neuropeptide Y
Gastrin	Prolactin	Luteinizing hormone
Secretin	Galanin	Calcitonin
Oxytocin	Growth hormone- releasing hormone	Glucagon
Sleep peptides	Bombesin	Vasopressin
gonadotropin-releasing hormone	Dynorphin	Angiotensin 2
Beta- endorphin	Neurotensin	thyrotropin - releasing hormone
Enkephalin	Motilin	Vasoactive intestinal peptide
Soluble gases		
Nitric oxide (NO)	**Carbon monoxide**	

Classes of Receptors



Metabotropic	Ionotropic
transmembrane receptor acts through a **secondary messenger.**	**Ligand gated ion channel**

Norepinephrine System

Nucleus Coeruleus:

❖ What is nucleus coeruleus?

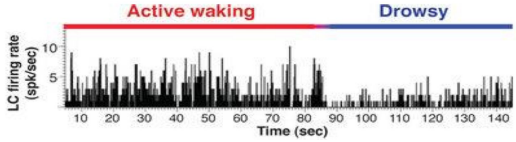
- It is a nucleus in the pons involved with physiological responses to **stress**, **panic** and coordinate responses.
- It is the site at which **norepinephrine** is formed and distributed to almost all brain structures.
- **Gives projection to: thalamus, cortex, hippocampus, amygdala, hypothalamus, autonomic brainstem centers, and the spinal cord. "Very wide spread"**

it's the main hormone that is produced during stress " it's most production" ,wakefulness and activities + it has excitation function in both the periphery and the CNS.

❖ Activated during: Sleep \ Attention \ Vigilance. "Irregular firing during wakefulness"

❖ Unactivated during:

- Their firing **decreases** markedly during **slow-wave sleep**
- virtually **disappears** during **REM sleep.**

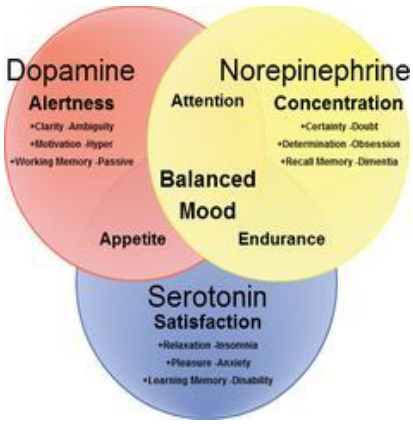


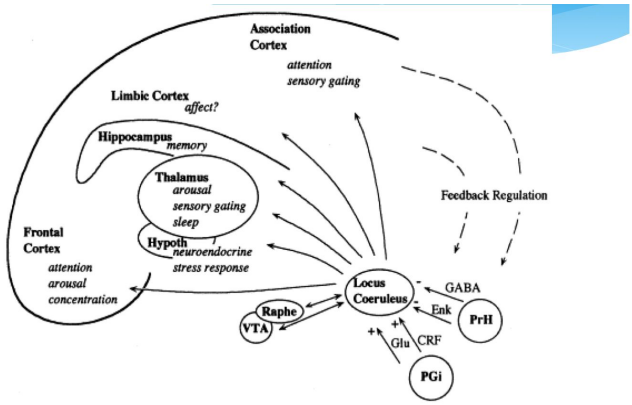
❖ Implicated in (stress-related disorder):

- **Depression.**
- **Withdrawal** from some drugs of abuse.
- **Other stress-related disorders** such as panic disorder.

❖ Norepinephrine pathway:

1. The feedback from all the areas that are affected by the NE is going to help in maintaining the equilibrium.
2. We have to know that these NTs are NOT working alone instead they provide their function as a one unite, so they're all related to each other and all of them are found in the pathway of each other .





PGi: Nucleus paragigantocellularis
PrH: Perirhinal Cortex

Acetylcholine

- Acetylcholine is the Major neurotransmitter in the **peripheral nervous system**.
- Produced by the neurons in the **parietal lobes** (basal forebrain and ponto-mesencephalic cholinergic complex) of the brain.

❖ Associated with:

Thought, Memory, Muscular coordination, Speed of information processing in the brain and Production of myelin sheath.

❖ Mental processes influenced by Ach:

- **Learning.**
- **Memory.**
- **Sleeping.**
- **Dreaming.**

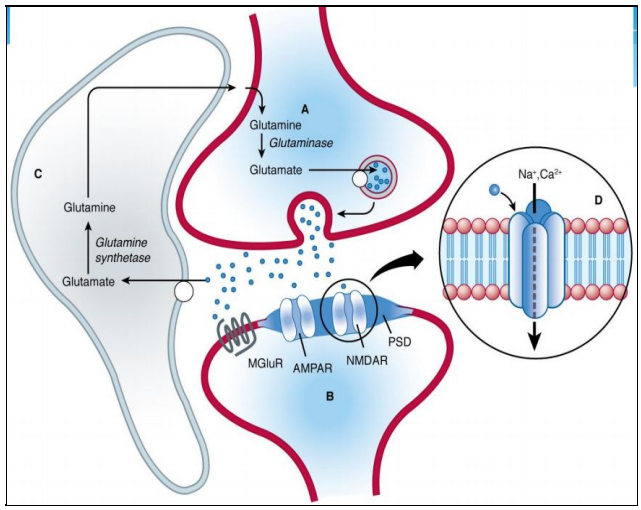
❖ Disorders of Ach system include:

- **Alzheimer's Disease:** the most common form of **dementia** that is associated with acetylcholine. It caused by damage to **Ach producing cells in the basal forebrain.** " because of that they lose their ability to learn and memorize and they will have a sleep disorder."
- **Bipolar disorder** " manic depressive disorder ".
- **Mood swings.**
- **Depression** " like the NE ".
- **Mental attention.**

Glutamate Guyton 12th edition page (551)

Facts:

- It is the **most commonly** found neurotransmitter in the brain.
- It is always **excitatory**.



Formation:

(for better understanding, please follow with the picture above)

- Glutamate is formed (alpha keto regulation) **Kreb's cycle** → carried into **astrocytes** → converted to **glutamine** → passed on to **glutaminergic neurons**

Prof. Laylea explanation: Glutamate is produced by kreb's cycle in the synaptic cleft then → glutamate enters astrocytes then → it is converted to glutamine by enzymes then (from the astrocytes) → it will be transferred into the nerve terminal as glutamine then → there it will be converted to glutamate (which is the neurotransmitter) → it will be stored in the vesicles ready for action potential and release process.

Function: **Learning** and **memory**

Adrenaline, noradrenaline, acetylcholine and glutamate are ALL important for learning and memory.

Reduced level in: *(glutamate is **reduced** in these disorders; they have found low glutamate in these disorders that means that glutamate is associated in the pathophysiology of these disorders)*:

- **Stroke.**
- **Autism.**

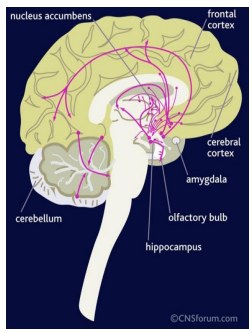
مو شرط كل اللي عندهم توحد يكون عندهم intellectual disability لأن ال autism له spectrum فيه اللي عنده توحد و هم very intellectual و فيه ال middle و فيه ال low IQ فهو على حسب الحالة، هم شافوا أن ال glutamate له تأثير و يلعب دور في أنواع من ال autism مو كلها.

- **Intellectual disability.**
- **Alzheimer's disease.**

YouTube **2-Minute Neuroscience: Glutamate** (Duration:2:00)

Gamma Aminobutyric acid (GABA) Guyton 12th edition page (551)

GABAergic neurons



Facts:

- **Main Inhibitory neurotransmitter** of CNS and is found in retina.
- GABAergic inhibition is seen at all levels of the CNC (**Hypothalamus**, **hippocampus**, **cerebral cortex** and **cerebellar cortex**.)
- GABA interneurons are **abundant in the brain**, with 50% of the inhibitory synapses in the brain being GABA mediated.

Formed by: **decarboxylation of glutamate.**

Types: **Three** types of GABA receptors e.g. GABA **A, B** & **C**. (GABA **A** , GABA **B**, GABA **C**).

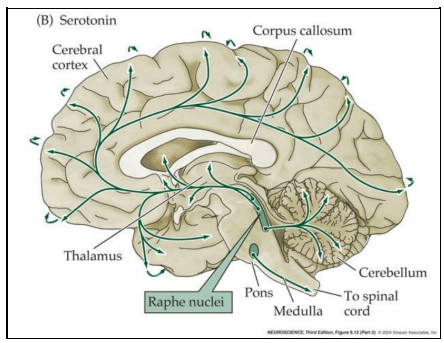
GABA A	Widely distributed in **CNS** كل ال GABA الموجودة في ال brain تكون على ال A + B	-
GABA B		metabotropic[1] (G-protein) in function.
GABA C	Found in **retina** only	-

YouTube 2-Minute Neuroscience: GABA (Duration:2:00)

Serotonin Guyton 12th edition page (551)

Serotonin pathways in the brain:

- **The principal centers for serotonergic neurons are:** the rostral and caudal raphe nuclei →
- **Projection:**
  - Axons **ascend** to the cerebral cortex, limbic and basal ganglia Serotonergic nuclei in the brainstem)
  - **Descending** axons (terminate in the medulla & spinal cord)



★ Serotonin is mainly produced from the caudal part of the raphe nuclei (reticular formation).

★ Serotonin produced from the raphe nuclei either connect to the higher brain centers (whatever above like thalamus, cerebral cortex and cerebellum) and it is connected to any centers or important structures below the raphe nucleus (the rest of the brain stem structures and the spinal cord)

Serotonin (5-HT[2]) Disorders

- **Depression**
- **Anxiety**

★ Serotonin has an important role in depression and anxiety (with adrenaline, noradrenaline and acetylcholine) because serotonin is connected to the thalamus, basal ganglia, limbic system, cerebral cortex (above) and (termination of serotonin) producing neurons from raphe nuclei to the brainstem and descending tract to medulla then spinal cord.

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YouTube Neurotransmitter Pathways Serotonin (Duration:2:09)

Dopaminergic Pathways Guyton 12th edition page (713)

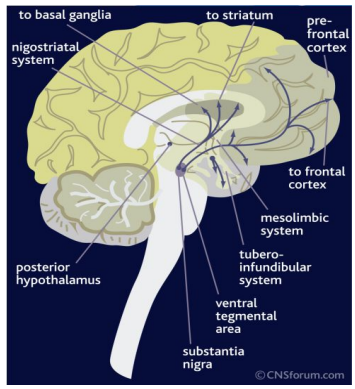
Dopaminergic Pathways:

[1] Ionotropic receptors form an ion channel pore. In contrast, **metabotropic** receptors are indirectly linked with ion channels on the plasma membrane of the cell through signal transduction mechanisms, often G proteins. Hence, G protein-coupled receptors are inherently **metabotropic.**

[2] The serotonin receptors, also known as 5-hydroxytryptamine receptors or 5-HT receptors, are a group of G protein-coupled receptors and ligand-gated ion channels found in the central and peripheral nervous systems.

Dopamine is transmitted via t**hree** major pathways:

1st pathway	From the substantia nigra to the **caudate nucleus-putamen** (neostriatum) (substantia nigra (basal ganglia)→ neostriatum)	concerned with sensory stimuli and movement.
2nd pathway	Project to the **mesolimbic forebrain** (substantia nigra (basal ganglia) → mesolimbic system)	Related to cognitive, reward and emotional behavio
3rd pathway	known as the **tuberoinfundibular system** (substantia nigra (basal ganglia) → tuberoinfundibular system)	Related to neuronal control of the hypothalamic-pituitary endocrine system. "Part of neuroendocrine function"



Dopamine pathways, antipsychotics and schizophrenia (Duration:5:00)

Neurotransmitter Pathways Dopamine (Duration:4:27)

Dopaminergic Pathways Functions:

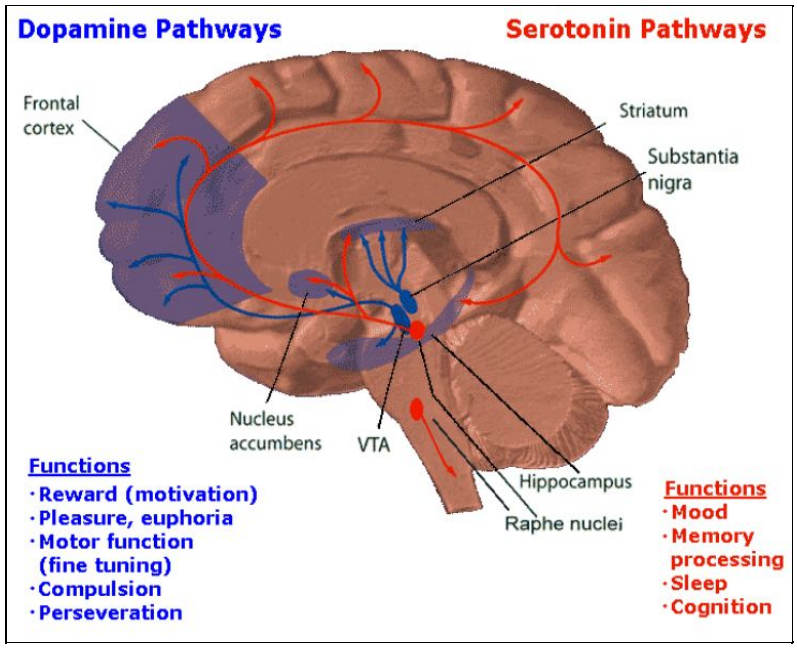
Note that the functions written in blue are for dopamine and the ones written in red are the functions of serotonin

★ **Prof. Layla's explanation:**

- We can conclude the function according to the part connected to it.
- For dopamine:

The **"reward (motivation)"** function → **reward system** *which can be explained by this example*:

التعليم بالتشجيع، مثل الأطفال الصغار لما يحصلوا على "نجمة" في المدرسة أو في الروضة، تكون هذه "النجمة" شيء مهم جدًّا بالنسبة للطفل و يفرح فيها جدًّا و بالتالي يتحفز هذا الجزء من الدماغ (stimulating learning, memory and cognition) و يتضح في مثال آخر لما الأم تحط لوحة إذا الأطفال أنجزوا شيء تحط لهم (علامة صح ✓) و إذا سووا شيء غلط تحط لهم (علامة خطأ X) و هنا ممكن نسأل أنفسنا ما هو تأثير ال ✓ و ال X ؟؟ تأثر تأثير كبير، فبعض الأطفال يطلبون أن تُكتب علامة الصح بالحبر و علامة الخطأ بالرصاص عشان ال X تتمسح لما يسوون شي كويس بينما ال ✓ بالحبر فما تتمسح،، الفكرة جدًّا بسيطة لكن : it is very rewarding



Activating reward system → dopamine system is working → we are stimulating sensory and sensory processing , we are also stimulating the mesolimbic and maintaining balance in neuroendocrine → that's why those kids grow normal

أما الطفل الي grows neglected ما له اهتمام بالبيئة حوله، كل ال systems ما فيها توازن فما عنده reward ، فلما يكبر مثلًا المدرسة في الثانوي تضع لوحة بأسماء المتفوقين و هذا بالنسبة له لا يعني شيء ،،

بينما في الطفل الثاني الي عنده reward system تطور -> يحفز extra learning and cognitive behavior

2-Minute Neuroscience: Reward System (Duration:2:00)

Reward pathway in the brain | Processing the Environment | MCAT | Khan Academy (Duration:8:25)

Dopaminergic neurons disorders:

- **Schizophrenia.**
- **Parkinson's Disease.**

What Is Schizophrenia? (Duration:4:06) What is Parkinson's disease? (Duration:8:53)

Brain Nuerotransmitters "summary from the slides"

Neuro-transmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
1.Acetyl-choline (Ach)	Excitatory	Acetyl coA + Choline	**Cholinergic** nerve endings Cholinergic pathways of brainstem	1.Nicotinic 2.Muscarinic	Broken by **acetylcholinesterase**	Cognitive functions e.g. memory Peripheral action e.g. cardiovascular system
2.Catechol-amines i. Epinephrine (adrenaline)	Excitatory in some but inhibitory in other	**Tyrosine** produced in liver from phenylalanine	**Adrenal medulla** and some CNS cells	Excites both alpha α & beta β receptors	**1.Catabolized** to inactive product through COMT & MAO in liver. **2.Reuptake** into adrenergic nerve endings. **3.Diffusion** away from nerve endings to body fluid	For details refer ANS. e.g. fight or flight, on heart, BP, gastrointestinal activity etc. Norepinephrine controls attention & arousal, sleep/wake cycle.
2.Catechol-amines ii.Norepinephrine	Excitatory	**Tyrosine**, found in pons. Reticular formation, locus coeruleus, thalamus, midbrain	Begins inside axoplasm of **adrenergic** nerve ending is completed inside the secretory vesicles	$\alpha 1$ $\alpha 2$ $\beta 1$ $\beta 2$		
2.Catechol-a	Excitatory	**Tyrosine**	CNS, concentrated in basal ganglia	D1 to D5 receptor	Same as above	Sensory motor Cognitive/emotional behavior Endocrine

mines iii. Dopamine			and dopamine pathways e.g. nigrostriatal, mesocorticolimbic and			Hypothalamic Decreased dopamine in
3. serotonin (5HT)	Excitatory	**Tryptophan**	**CNS, Gut** (chromaffin cells) **Platelets** & **retina**	5-HT1 to 5-HT 7 5-HT 2 A receptor mediate platelet aggregation & smooth muscle contraction	**Inactivated** by MAO to form 5-hydroxyindoleacetic acid(5-HIAA) in pineal body it is converted to melatonin	Mood control, sleep, pain feeling, temperature, BP, & hormonal activity
4. Histamine	Excitatory	**Histidine**	**Hypothalamus**	Three types H1, H2 ,H3 receptors found in peripheral tissues & the brain	**Enzyme diamine oxidase (histaminase) cause breakdown**	Arousal, pain threshold, blood pressure, blood flow control, gut secretion, allergic reaction (involved in sensation of itch)
5. Glutamate	Excitatory 75% of excitatory transmission in the brain	By **reductive amination** of Kreb's cycle intermediate α – ketoglutarate .	**Brain** & **spinal cord** e.g. hippocampus	Ionotropic and metabotropic receptors. Three types of ionotropic receptors e.g. NMDA, AMPA and kainate receptors.	It is **cleared from the brain ECF** by Na + dependent uptake system in neurons and neuroglia.	Long term potentiation involved in memory and learning by causing Ca++ influx.
6. Aspartate	Excitatory	**Acidic amines**	**Spinal cord**	Spinal cord	Aspartate & Glycine form an excitatory / inhibitory pair in the ventral spinal cord	
7. Gamma amino-butyric acid (GABA)	Major inhibitory mediator	**Decarboxylation** of glutamate by glutamate decarboxylase (GAD) by GABAergic neuron.	**CNS**	GABA – A increases the Cl - conductance, GABA – B is metabotropic works with G – protein GABA transaminase catalyzes. GABA – C found exclusively	**Metabolized** by transamination to succinate in the citric acid cycle.	GABA – A causes hyperpolarization (inhibition) Anxiolytic drugs like benzodiazepine cause increase in Cl- entry into the cell & cause soothing effects. GABA – B cause increase conductance of K+ into the cell.

				in the retina.		
8. Glycine	Inhibitory	Is **simple amino acid** having amino group and a carboxyl group attached to a carbon atom	**Spinal cord**	Glycine receptor makes postsynaptic membrane more permeable to Cl- ion.	**Deactivated in the synapse** by simple process of reabsorption by active **transport back** into the presynaptic membrane	Glycine is inhibitory transmitted found in the ventral spinal cord. It is inhibitory transmitter to Renshaw cells.

★ References:

- 435 girls slides and notes.
- Guyton and Hall Textbook of Medical Physiology, 12th edition