Physiology Team 439

MED439
KING SAUD UNIVERSITY

Revised & Approved

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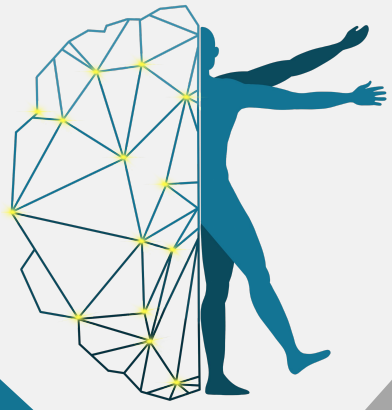


Brain Neurotransmitters

Objectives:

- Describe the functions of glutamergic system.
- Describe the functions of NTs of the brain (the noradrenergic & serotonergic cholinergic, dopaminergic, GABAergic systems).
- Appreciate that many drugs and CNS disorders affect function of brain neurotransmitters.

Male's doctor: The **Function of each Neurotransmitter** (& it's related system)
is the **Most Important Objective** of this Lecture*

Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

Brain Neurotransmitters:

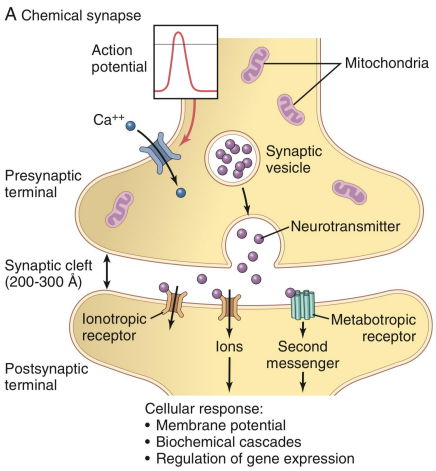
- Chemical substances released by electrical impulses into the synaptic cleft from synaptic vesicles of presynaptic membrane.
- Diffuses to the postsynaptic membrane.
- Binds to and activates the receptors.
- Leading to initiation of new electrical signals or inhibition of the postsynaptic neuron. EPSE or IPSP

Classification of Neurotransmitters			
Amines			
- Acetylcholine (ACh) - Dopamine (DA) - Norepinephrine (NE)		- Epinephrine - Serotonin (5-HT) - Histamine	
Amino Acids			
- Gamma-aminobutyric acid (GABA) - Glycine		- Aspartate - Glutamate	
Neuroactive Peptides - (Partial list!)			
- bradykinin - cholecystokinin - gastrin - secretin **- oxytocin** - Sleep peptides - Gonadotropin-releasing hormone	- beta-endorphin - enkephalin - Substance P - somatostatin - prolactin - galanin - Growth hormone-releasing hormone	- bombesin - dynorphin - neurotensin - motilin - thyrotropin **- Neuropeptide Y** - Vasoactive intestinal peptide	- calcitonin - insulin - glucagon - vasopressin - Angiotensin II - Thyrotropin-releasing hormone - Luteinizing hormone
Soluble Gases			
- Nitric Oxide (NO)		- Carbon Monoxide	

Classes of Receptors*

Guyton: Receptor activation controls the opening of ion channels in the postsynaptic cell in one of two ways:
(1) by gating **ion channels directly and allowing passage of specified types of ions** through the membrane.
(2) by **activating a "second messenger" that is not an ion channel** but instead is a molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron. These second messengers increase or decrease specific cellular functions.

Neurotransmitter receptors that **directly gate ion channels are often called ionotropic** receptors, whereas those that **act through second messenger systems are called metabotropic receptors.**



Classes of Receptors*

Ionotropic

Ligand gated ion channel.

Fast and short lived

Metatropic

Transmembrane receptor which acts through a secondary messenger.

important for memory

Hint: Read **Guyton** Unit IX, Chapter 46, Pages 582-584 (Actions of the transmitters on the Receptors) 13TH EDITION.

Neurotransmitters we gonna discuss:

1. **Ach (Acetylcholine).**
2. **Norepinephrine (NE)/ Epinephrine (Adrenaline).**
3. **Glutamate.**
4. **GABA (Gamma Aminobutyric acid).**
5. **Dopamine.**
6. **Serotonin.**

1. Cholinergic System:
Acetylcholine

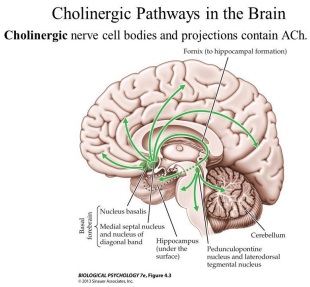
L24

Overview

- Acetylcholine is the major neurotransmitter in the peripheral nervous system. (Extensively collected in the brain & spinal cord).
- In the brain, cholinergic (ACh producing) neurons are present mainly in 2 areas:

limbic system

1) **Basal Forebrain** (namely Nucleus Basalis of Myenert and septal nuclei). It starts in the basal forebrain
2) **Mesopontine tegmental area** which is also called ponto-mesencephalic cholinergic complex.

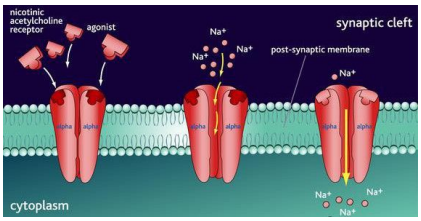


Receptors (boys slides only)

1- Nicotinic (ionotropic)
opens Na channels

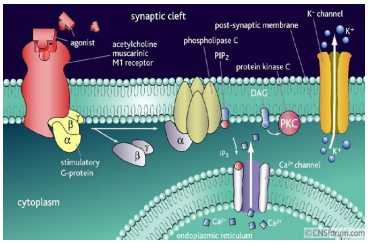
- 2 types:
1. The muscle-type: can be selectively blocked by curare.
2. The neuronal-type blocked by hexamethonium.

- Excitatory.



2- Muscarinic (metabotropic)
(antagonist-Atropine)

- Excitatory or inhibitory.
- Five subtypes (M1-M5): all are found in the brain but M1 is abundant.
- M1 receptors most involved in cognitive functioning (evidence from Knockout mice and pharmacologic human studies with M1 Blocking drugs).
- M2 blocking agents may facilitate cognition in animals (but these drugs are not being used in humans at this point).
- M3 receptors do not seem to play much of a role in cognition (animal studies).
- M4 and M5 functions in the brain are unknown.



Ach Functions & Disorders

Functions

- ACh is associated with, Thought, Memory, Muscular coordination, Speed of information processing in the brain and Production of myelin sheath.
- ACh influences mental processes such as: Learning, Memory, Alertness and sleep.
- ACh influences mental processes:

High levels during: Learning, Memory, and REM (rapid eye movement sleep).
Low levels during: Sleeping (Except REM).

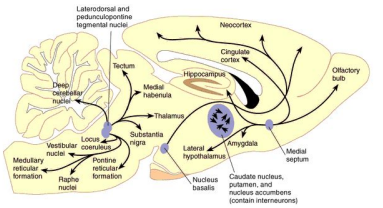
Disorders

- Alzheimer's Disease: the most common form of dementia. Associated with acetylcholine loss. Damage to Ach producing cells in the basal forebrain.
- Ach levels are disturbed in:
  1. Bipolar disorder.
  2. Mood swings.
  3. Depression.
  4. Mental attension.
- Inhibitors of acetylcholinesterase in the brain are the main drugs used to treat Alzheimer's disease.

2. Norepinephrine System:
Norepinephrine

Overview

- Norepinephrine(NE): is a catecholamine that is synthesized from Dopamine.
- It is released from sympathetic nerves, the adrenal medulla and brain stem neurons.
- NE is believed to play a role in both learning and memory.
- The Noradrenergic has Very wide-spread projection system.
- Extensively collected in the brain. Norepinephrine is secreted from locus coeruleus. It is widely distributed in the brain and it has a major role in stress.



It is highly associated with almost all parts of the brain

Receptors

- It acts on both α-and β- adrenergic receptors (G- protein-coupled receptors).

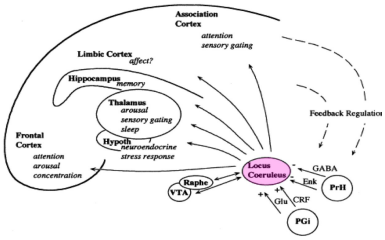
Nucleus & Its Function

Nucleus

- **Nucleus Coeruleus** is located in the pons, involved in physiological responses to stress and panic.

found bilaterally on the posterior surface of the junction between midbrain - pons

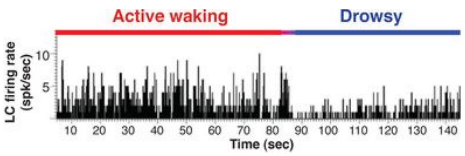
- LC (Locus ceruleus) is activated by stress and co-ordinates responses via projections to thalamus, cortex hippocampus, amygdala, hypothalamus, autonomic brainstem centers, and the spinal cord.



PGi: Nucleus paragigantocellularis PrH: Perirhinal Cortex

Function of the Nucleus

- Locus coeruleus neurons fire as a function of vigilance and arousal.
- Irregular firing during quiet wakefulness Sustained activation during stress.
- Their firing decreases markedly during slow-wave sleep and virtually disappears during REM sleep.



NE Functions & Disorders

Functions of NE
(the transmitter)

- It constitutes part of the RAS (Reticular Activating System Attention/Vigilance.
- Fight or flight response
- Learning
- Enhances formation and retrieval of memory
- Aggressive behaviour.

Norepinephrine (NE) Implicated in Stress-Related Disorders

- Reduced level in:
  1. Depression.
  2. Withdrawal from some drugs of abuse (NE imbalance + other NT).

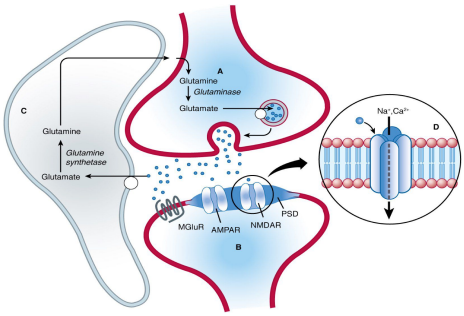
like alcohol and cocaine

- High level in anxiety panic disorder.

3. Glutaminergic System:
Glutamate

Overview

- Glutamate is the most commonly found neurotransmitter in the brain (king of NTs, ~50% neurons).
- Glutamate is the **major excitatory neurotransmitter of the brain and spinal cord,** responsible for 75% of the excitatory transmission in the brain.
- Glutamate (can cause excitotoxicity) is converted in astrocytes into glutamine (not toxic) and passed onto glutaminergic neurons.
- Wide spread, but high levels in hippocampus; hypofunction of NMDA receptors in this area and prefrontal cortex is associatedwith schizophrenia.
- Glutamate is synthesized from glutamine by the help of glutaminase enzyme present in the presynaptic vesicles. Upon stimulation, glutamate is released stimulating NMDAR receptors. The remaining unused glutamate will be reconverted to glutamine and the cycle repeats.

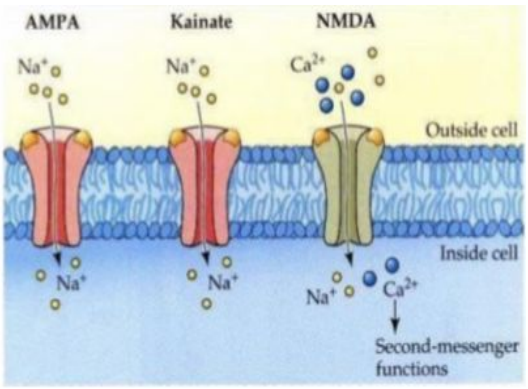


Glutamate Functions & Disorders

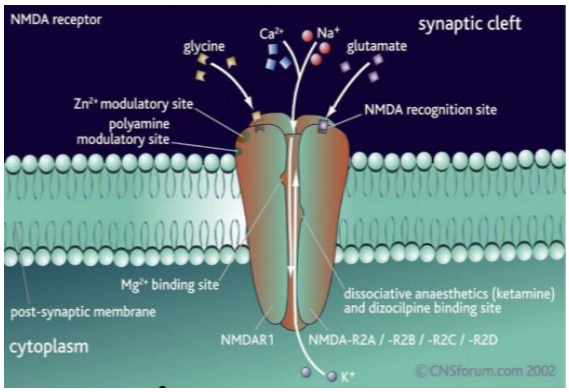
Functions	❖ Glutamic acid (and aspartic acid): are major excitatory NTs in CNS. ❖ Glutamate NMDA receptor involved in Long-Term Potentiation & memory storage. ❖ Important role in Learning and memory.
Disorders	❖ Excess Glutamate activity is implicated in some types of epileptic seizures. ❖ Under some pathological conditions, such Stroke, ALS (Amyotrophic Lateral Sclerosis), autism, and Alzheimer's disease, it acts as an excitotoxin, producing excessive influx of calcium into the neurons and causing neuronal death. ❖ **Reduced level in:** Stroke, Autism, Intellectual disability, Motor neuron disease, Huntington's disease, Parkinson's disease and Alzheimer's disease.

3. Glutaminergic System: cont.
Glutamate

Receptors (boys slides only): Are widely distributed in the brain; they are of two types:		
1- Metabotropic receptors:		❖ (G protein- coupled receptors): mGluR. ❖ Found in hippocampus, cerebellum and the cerebral cortex. ❖ Act through second messengers which activate biochemical cascades, leading to modification of other proteins such as ion channels.
2- Ionotropic ligand-gated ion channels Three types:	**AMPA**	(α-amino-3-hydroxy-5-methyl isoxazole- 4-propionate).
	Kainate	Kainate receptors (kainite is an acid isolated from seaweed).
	NMDA	(for N-methyl D-aspartate); play a role in long term potentiation so they are involved in learning and memory storage. Permits passage of Na+ and large amounts of Ca2+. They are unique: ❖ Glycine is essential for their normal response to glutamate. ❖ The channel is blocked by Mg2+ ion at normal membrane potentials. ❖ This blockade is removed by depolarization (caused by AMPA). ❖ Excitatory postsynaptic potential induced by activation of NMDA receptor is slower than that elicited by activation of AMPA and kainate receptors.



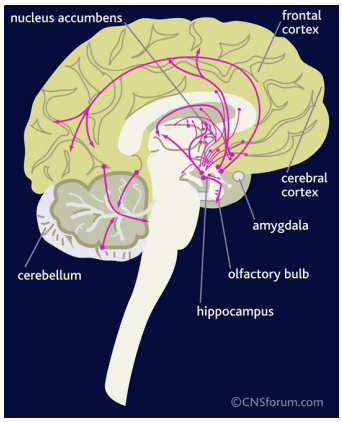
NMDA



4. GABA-ergic System:
Gamma Aminobutyric acid (GABA)

Overview

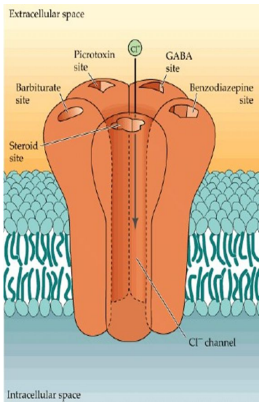
- GABA is the main inhibitory neurotransmitter in the central nervous system (CNS).
- GABAergic inhibition is seen at all levels of the CNS (Hypothalamus, hippocampus cerebral cortex and cerebellar cortex).
- GABA interneurons are abundant in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated.
- Formed by decarboxylation of glutamate.



Receptors (boys slides only)

Three types of GABA receptors: GABA A ,B & C.

- GABA A & B receptors are widely distributed in CNS.
- GABA C are found in retina only.
- GABA B are metabotropic (G-protein) in function.
- GABA A and C receptors (ionotropic) have multiple binding sides (for benzodiazepine and barbiturates).
- The channel is a Cl-channel (not Na).



GABA Functions & Disorders (boys slides only)

Functions

- Presynaptic inhibition.
- GABA receptors in CNS are chronically stimulated to regulate neuronal excitability.

Disorders

- under activity of GABA leads to seizures.

Alcohol, barbiturates, progesterone and deoxycorticosterone also in part work by increasing GABA activity.

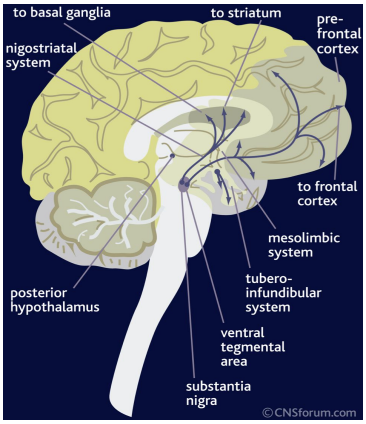
5. Dopamine System:
Dopamine

Overview

- Dopamine is a catecholamine that is synthesized from tyrosine
- Five dopaminergic receptors (D1-D5).
- Overstimulation of D2 receptors is thought to be related to schizophrenia.
- Dopamine is transmitted via three major pathways:

Pathways

1	The first (nigro striatal system) extends from the substantia nigra to the caudate nucleus-putamen (neostriatum) and is involved in motor control and concerned with sensory stimuli and movement.
2	The second pathway project to the mesolimbic forebrain and Related to cognitive, reward and emotional behavior in reward and emotional behavior and addiction. Dysfunction is connected to hallucinations and schizophrenia.
3	The third pathway, known as the tuberoinfundibular system It is concerned with: - Regulation of secretion of prolactin from the anterior pituitary endocrine systems. - Maternal behavior (nurturing).



Dopamine Functions & Disorders

Functions	❖ Reward ❖ Pleasure, euphoria ❖ Motor function (fine tuning) ❖ Compulsion ❖ Perseveration
Disorders	❖ Schizophrenia ❖ Parkinson's Disease. Cocaine elevate activity at dopaminergic synapses.

6. Serotonin System:
Serotonin

Overview (boys slides only)

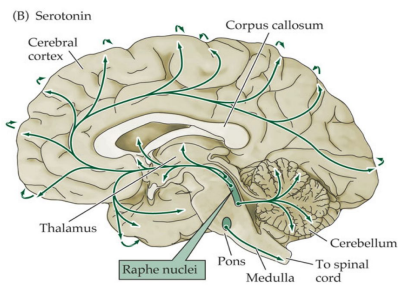
- Serotonin is synthesized from the amino acid tryptophan, which is abundant in meat.
- Our bodies cannot make tryptophan (must get from diet).
- Tryptophan deprivation alters brain chemistry and mood.
- There is only a few 100,000`s of 5-HT neurons in human brain.
- There is 7 classes serotonin receptors in different parts of CNS (most are metabotropic, except 5-HT3).
- Mice in which the gene for 5-HT2 C receptors has been knocked out are obese.

Serotonergic Centers & Nuclei

- The principal centers for serotonergic neurons are the rostral and caudal **raphe nuclei.**

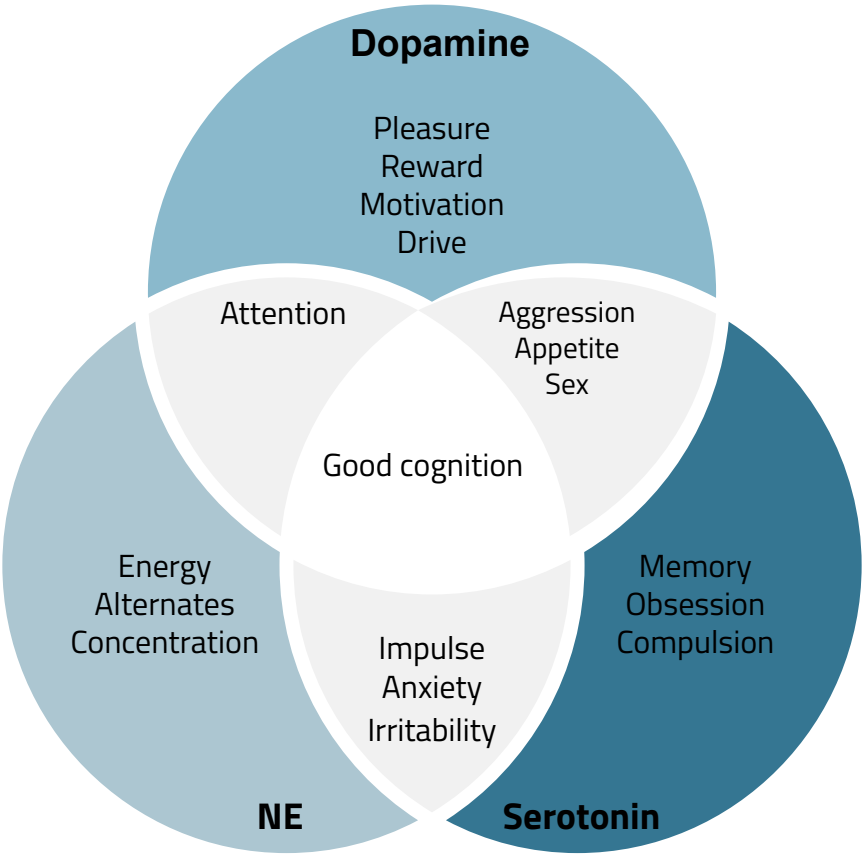
Pathways

1- ascending..	axons ascend to the cerebral cortex, limbic & basal ganglia.
2- descending..	Serotonergic nuclei in the Brainstem >>>> descending axons (terminate in the medulla & spinal cord. (blocks pain)



Serotonin Functions & Disorders

Functions	❖ Improved mood. ❖ Decrease appetite . ❖ Sleep.
Disorders	Low level in: ❖ Depression. (we use drugs like SSRIs to inhibit the reuptake of serotonin for depression and other disorders) ❖ Anxiety. ❖ Irritability. ❖ Low self-esteem. ❖ Poor appetite. ❖ Poor memory. Drugs (e.g.Prozac) that prolong serotonin actions relieve symptoms of depression & obsessive disorders

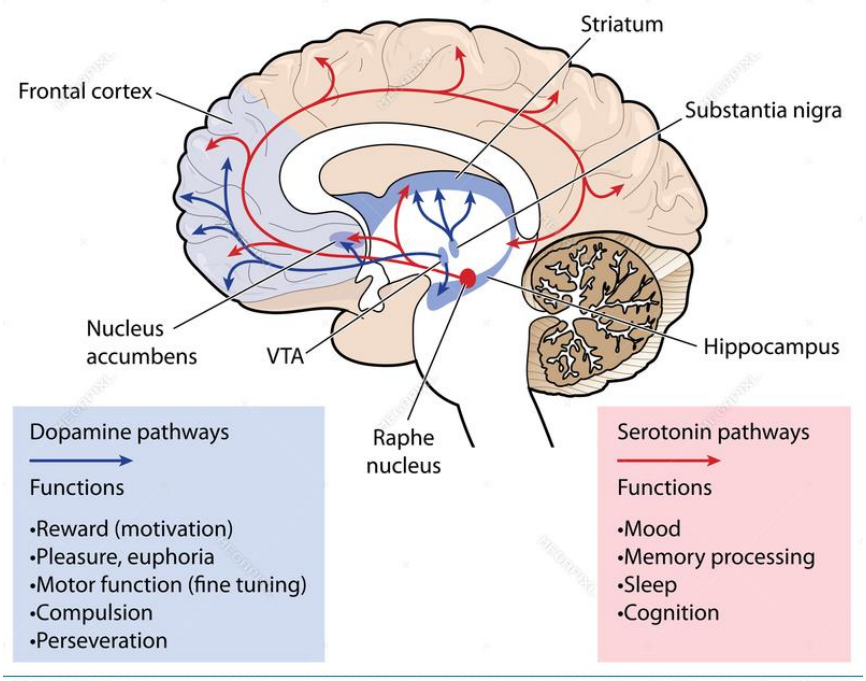


Aim is to show that
1- neurotransmitters work together to produce multiple functions
2- deficit in 1 neurotransmitter will cause multiple disorders

The difference between dopamine and serotonin

Very important

They overlap and complement each other



Summary

NT	Ach	Glutamate	GABA	serotonin (5HT)
Postsynaptic effect	Excitation	Excitatory 75% of excitatory transmission in the brain.	Major inhibitory mediator	Excitatory
From	Acetyl co-A + choline	By reductive amination of kreb's cycle intermediate α-ketoglutarate.	Decarboxylation of glutamate by glutamate decarboxylase (GAD) by GABAergic neuron.	Tryptophan
Site of Synthesis	Cholinergic nerve endings Cholinergic pathways of brainstem.	Brain & spinal cord e.g. hippocampus.	CNS	CNS, Gut (chromaffin cells) Platelets & retina.
Postsynaptic Receptor	1.Nicotinic. 2.Muscarinic.	Ionotropic and metabotropic receptors. Three types of ionotropic receptors e.g. NMDA, AMPA and kainate receptors.	GABA – A increases the Cl - conductance, GABA – B is metabotropic works with G – protein GABA transaminase catalyzes. GABA – C found exclusively in the retina.	5-HT1 to 5-HT 7 5-HT 2 A receptor mediate platelet aggregation & smooth muscle contraction.
Fate	Broken by acetyl cholinesterase.	It is cleared from the brain ECF by Na + dependent uptake system in neurons and neuroglia.	Metabolized by transamination to succinate in the citric acid cycle.	Inactivated by MAO to form 5-hydroxyindoleacetic acid(5-HIAA) in pineal body it is converted to melatonin.
Function	Cognitive functions e.g. -memor -peripheral action e.g. cardiovascular system.	Long term potentiation involved in memory and learning by causing Ca^{++} influx.	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.	Mood control, sleep, pain feeling, temperature, BP, & hormonal activity.

Summary

Catecholamines			
NT	**Epinephrine (adrenaline)**	**Norepinephrine**	**Dopamine**
Postsynaptic effect	Excitatory in some but inhibitory in other	Excitatory	Excitatory
From	Tyrosine produced in liver fromphenylalanine	Tyrosine, found in pons. Reticular formation, Locus coeruleus, Thalamus, Midbrain	Tyrosine
Site of Synthesis	Adrenal medulla and some CNS cells	Begins inside axoplasm of adrenergic nerve ending is completed inside the secretory vesicles	CNS, concentrated in basal ganglia and dopamine pathways e.g. -nigrostriatal -mesocorticolim bic and tubero-hypophyseal pathway
Postsynaptic Receptor	Excites both alpha α and beta β receptors	α1 α2 β1 β2	D1 to D5 receptor
Fate	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.		
Function	For details refer ANS. e.g. fight or flight, on heart, BP, gastrointestinal activity etc. Norepinephrine controls attention & arousal, sleep/wake cycle.		Sensory motor Cognitive/emotional behavior Endocrine Hypothalamic Decreased dopamine in Parkinson's disease. Increased dopamine 36 concentration.

MCQ & SAQ:

Q1: which of the following is major excitatory neurotransmitter of the brain?

A. GABA.
B. Glycine.
C. dopamine.
D. glutamate.

Q2: which of the following statement is correct about acetylcholine

A. High levels during non REM Sleeping.
B. Low levels during Memory, and REM.
C. Ach levels are disturbed in Bipolar disorder.
D. ACh producing neurons are present mainly in 1 areas.

Q3: which of the following statement is not correct about GABA receptor?

A. GABA A & B receptors are widely distributed in CNS.
B. GABA B are ionotropic in function.
C. GABA A and C receptors (metabotropic).
D. Both B,C.

Q4: A disorders related to having a low level of dopamine:

A. Temporal lobe epilepsy.
B. Schizophrenia.
C. Parkinson's Disease.
D.Anterograde amnesia.

Q5: Raphe nuclei is the center of:

A. serotonin.
B. Ach.
C. NE.
D. GABA.

Q6: Dysfunction of which of the following dopaminergic pathways can lead to schizophrenia and hallucinations?

A. Tuberoinfundibular system.
B. Project to the mesolimbic forebrain.
C. Nigro-striatal system.

answer key:
1: D
2: C
3: D
4: C
5: A
6: B

1- Where acetylcholine produced ?

2- What is the function of GABA and what is the disorder if it's level low?

3- list the Dopamine functions.

4- What is the post-synaptic effect of Glutamate?

A1: 1) Basal Forebrain. 2) Mesopontine tegmental area.

A2: Presynaptic inhibition, seizures.

A3: Reward / Pleasure, euphoria /Motor function (fine tuning) / Compulsion / Perseveration.

A4: Excitatory 75% of excitatory transmission in the brain.

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- Ibraheem Altamimi.
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- Khalid Almutlaq.
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- Norah Alsalem.
- Norah Aldakhil.
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