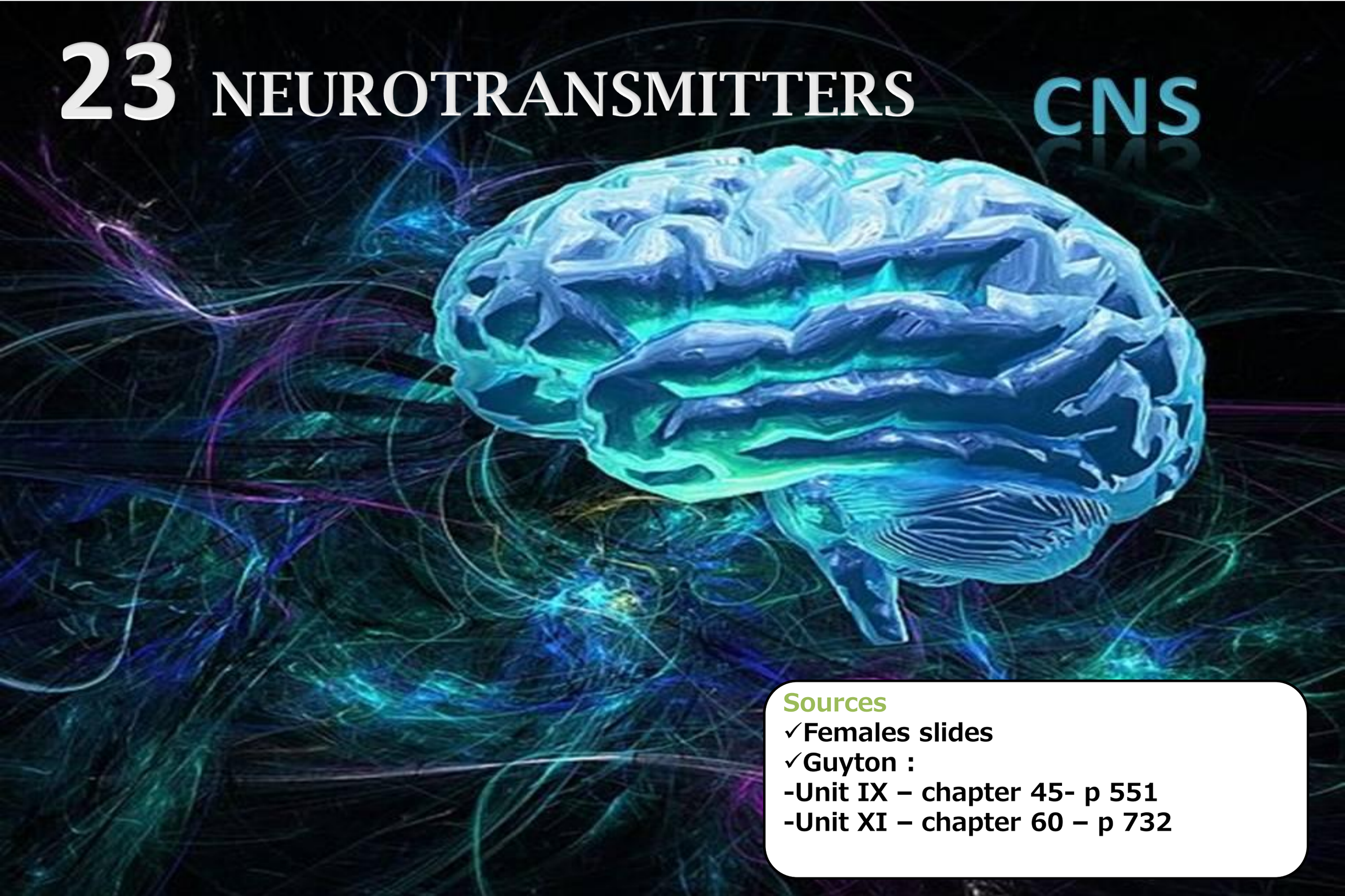
23 NEUROTRANSMITTERS



Sources

✓**Females slides**

✓**Guyton :**

-Unit IX – chapter 45- p 551

-Unit XI – chapter 60 – p 732

Definition

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.

Neurotransmitters

- Norepinephrine
- achtycoline
- Serotonin
- Dopamine
- Histamine
- Glycine
- Glutamic acid
- GABA

Neurotransmitters criteria

1-the chemical must be produced within the neuron
2-the chemical must be found within the neuron
3-must release the chemical when it stimulated
4-the chemical must act on receptors on post synaptic and make an action
5-after that the chemical must be inactivated by the reuptake mechanism or by enzyme that stops it work
6-if the chemical is applied on the post synaptic membrane it should have the same effect as when it is released by a neuron

Classification of Neurotransmitters

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

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

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

Soluble Gases	
Nitric Oxide (NO)	Carbon Monoxide

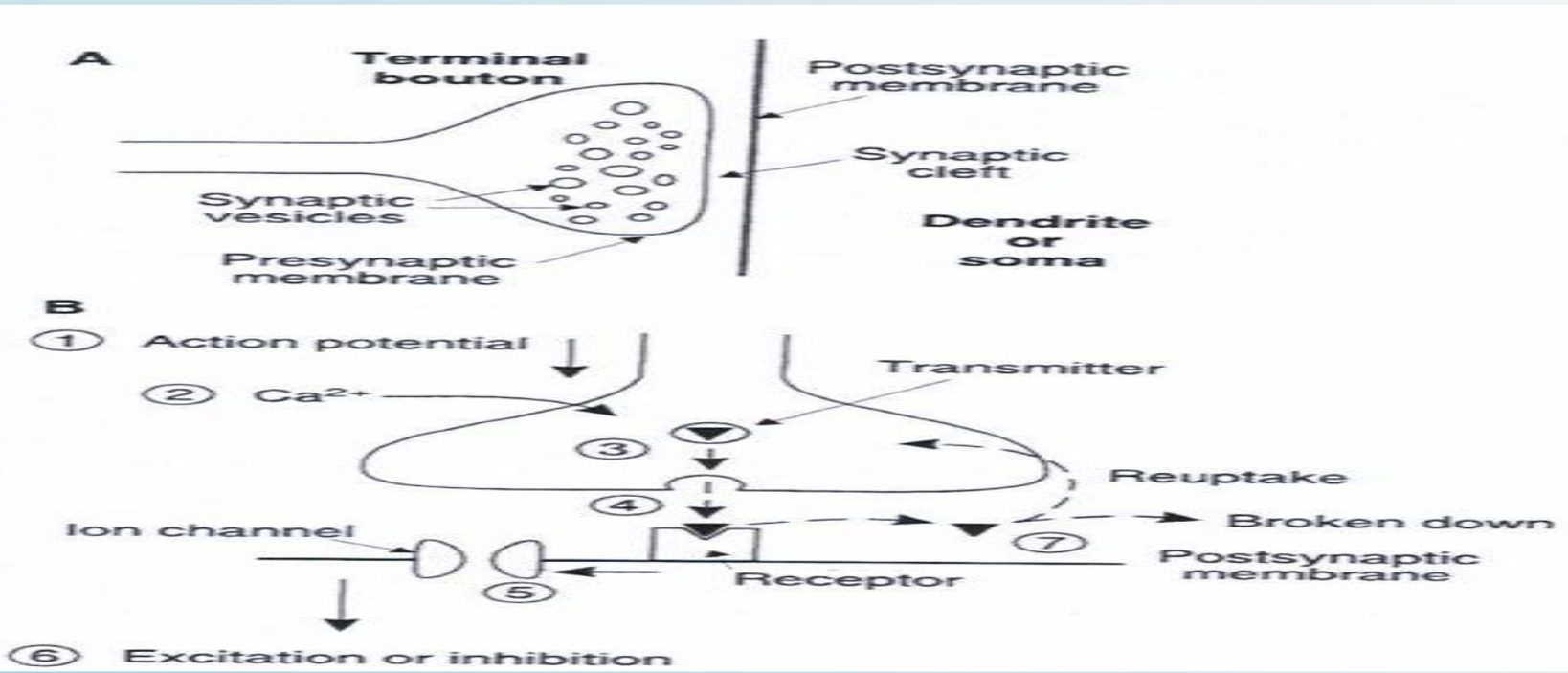
U have to remember it

Try to remember as much as u can

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.

The chemical must be produced within a neuron. 	The chemical must be found within a neuron. 	When a neuron is stimulated (depolarized), a neuron must release the chemical. 
When a chemical is released, it must act on a post-synaptic receptor and cause a biological effect. 	After a chemical is released, it must be inactivated. Inactivation can be through a reuptake mechanism or by an enzyme that stops the action of the chemical. 	If the chemical is applied on the post-synaptic membrane, it should have the same effect as when it is released by a neuron. 



The release and action of neurotransmitters

Norepinephrine :

Locus coeruleus system (norepinephrine system) :

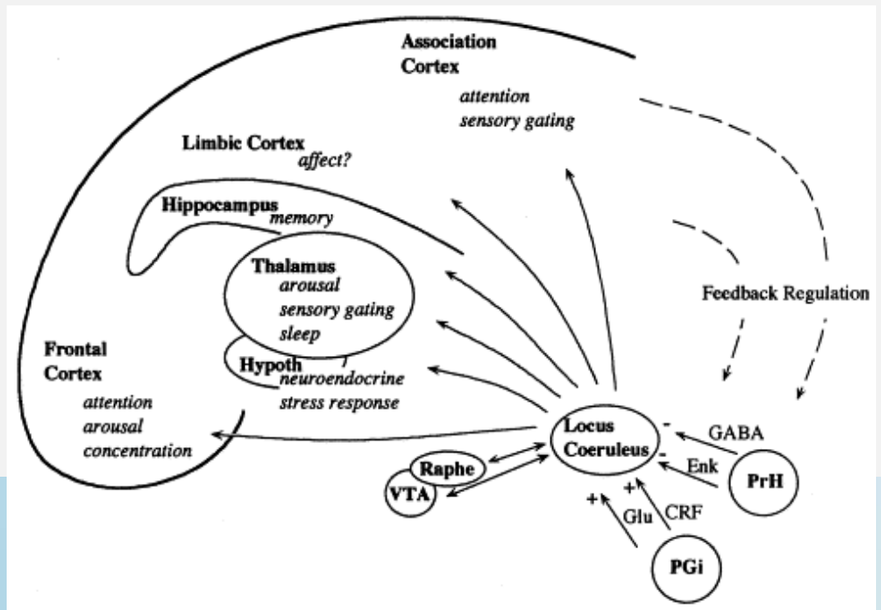
- **locus coeruleus neurons which located in pons secrete the norepinephrine.**
- **It projects to thalamus, cortex, hippocampus, amygdala, hypothalamus, autonomic brainstem centers & the spinal cord .**
- **Function : 1- activated by stress stimuli → changes in sleep/wake cycle .**

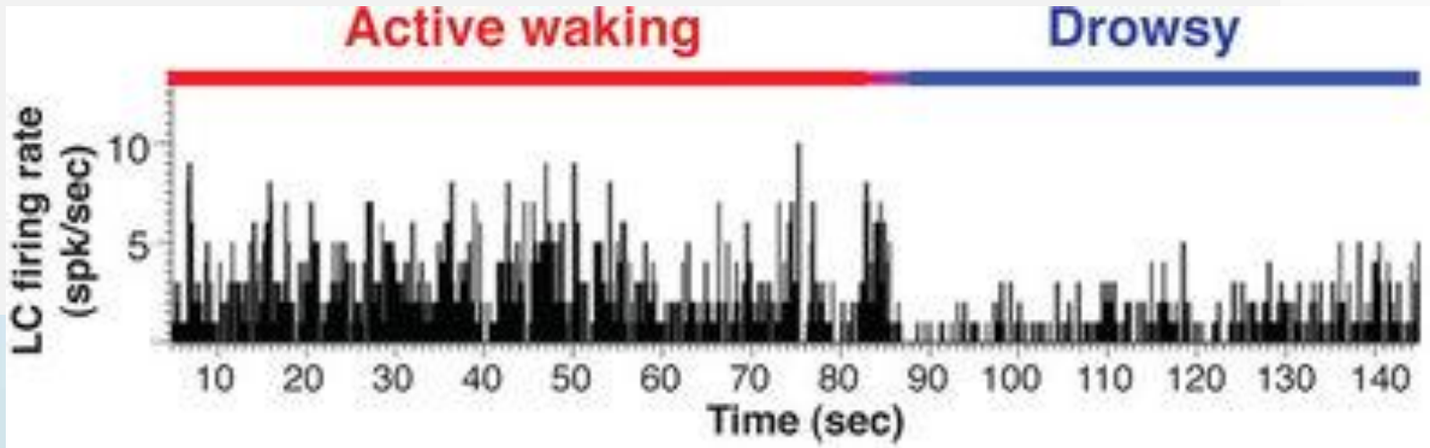
  2- activated by novel stimuli → attention/vigilance.
- **In EEG : locus coeruleus neurons fire in vigilance.**

1- they display a slow irregular firing during wakefulness.

2- the firing decreases during slow-wave sleep (Non-REM sleep).

3- the firing disappears during REM sleep.





Norepinephrine :

- **Synthesization :** tyrosine $\xrightarrow{\text{Hydroxylation}}$ Dopa $\xrightarrow{\text{Decarboxylation}}$ Dopamine $\xrightarrow{\text{Hydroxylation}}$ Norepinephrine $\xrightarrow{\text{Methylation}}$ Epinephrine

- **Fate at synapses :**

  1- reuptake it into adrenergic nerve endings.

  2- destruction by MAO (monoamine oxidase) .

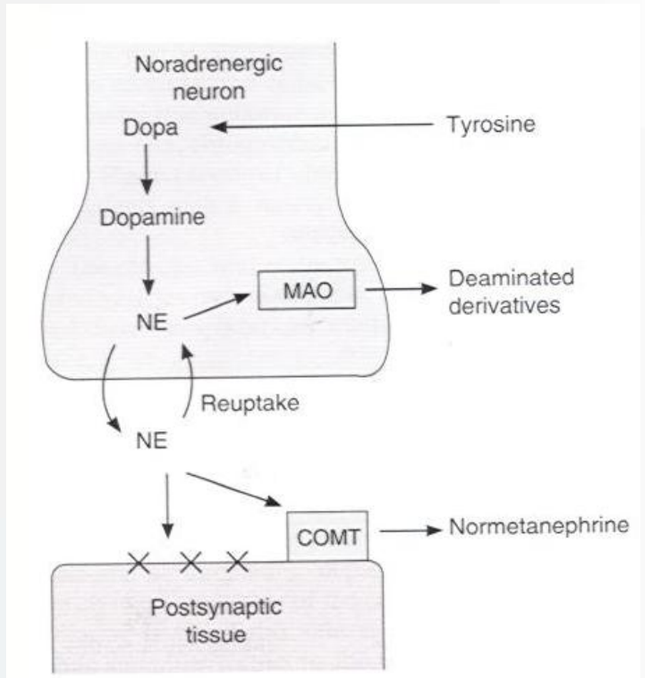
  3- diffuse away from nerve endings into body fluid then into the blood where they remain active until they are destructed by COMT (catechol-O-methyl transferase).

- **Norepinephrine involved in stress related disorders such as :**

  1- depression

  2- withdrawal from drug abuse “treated by clonidine”

  3- panic disorders

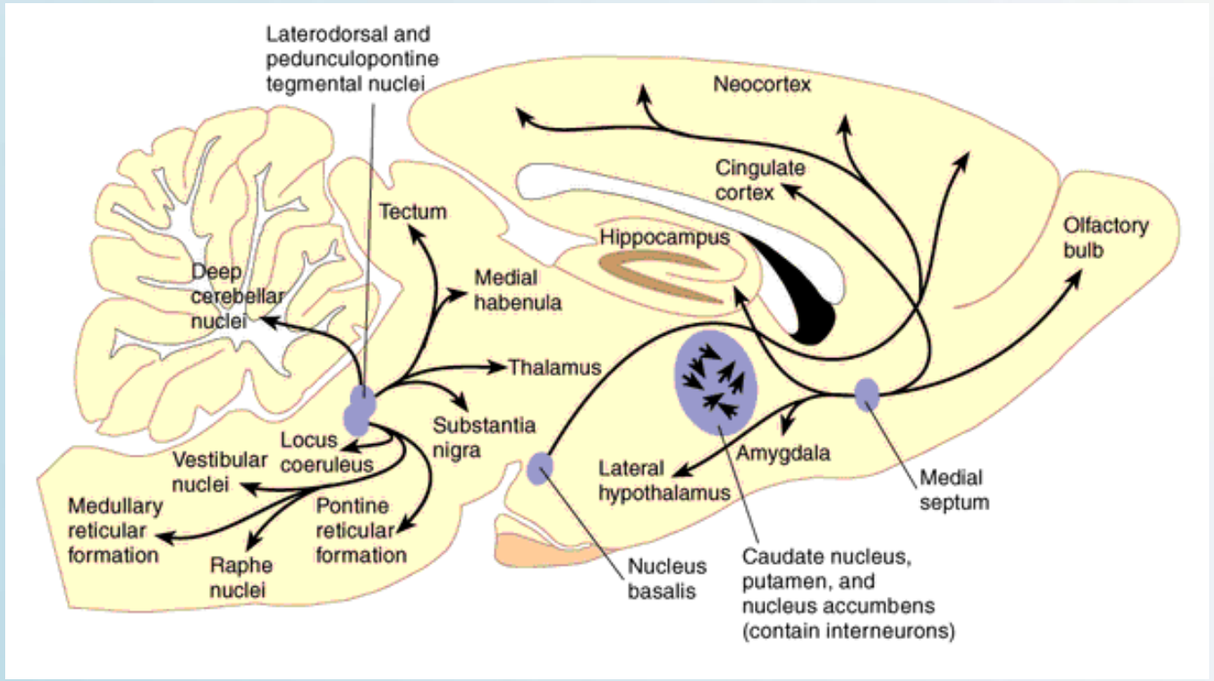


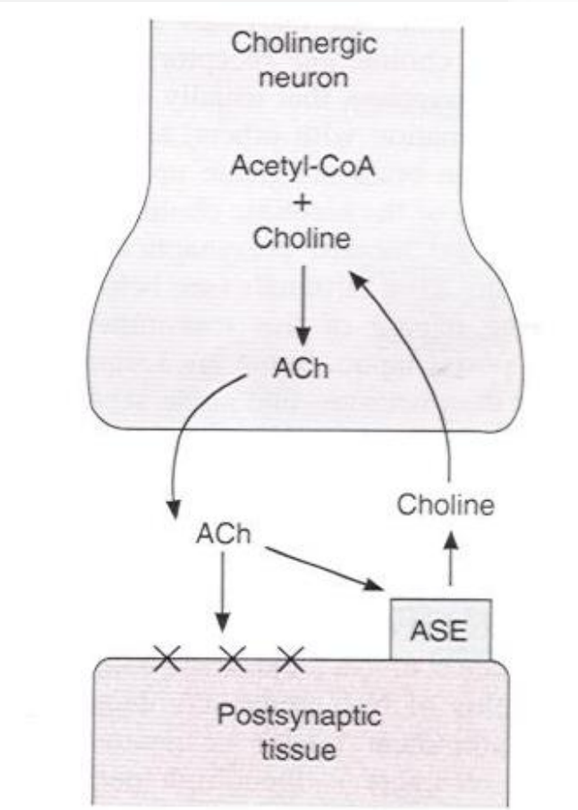
Acetylcholine

- **Produced by :** basal forebrain & ponto-mesencephalic cholinergic complex.
- **Functions :** 1- conciousness & wakefullness.

  2- memory & learning.
- **Synthesization :** acetyl CoA + Choline → acetylcholine.

  (acetate is activated to be acetyl CoA)
- **Fate at synapses :** once acetylcholine secreted from cholinergic nerve endings for a few seconds they are catalyzed by Acetylcholinestrase into acetate and choline
- **Disorders :** alzheimer's disease .





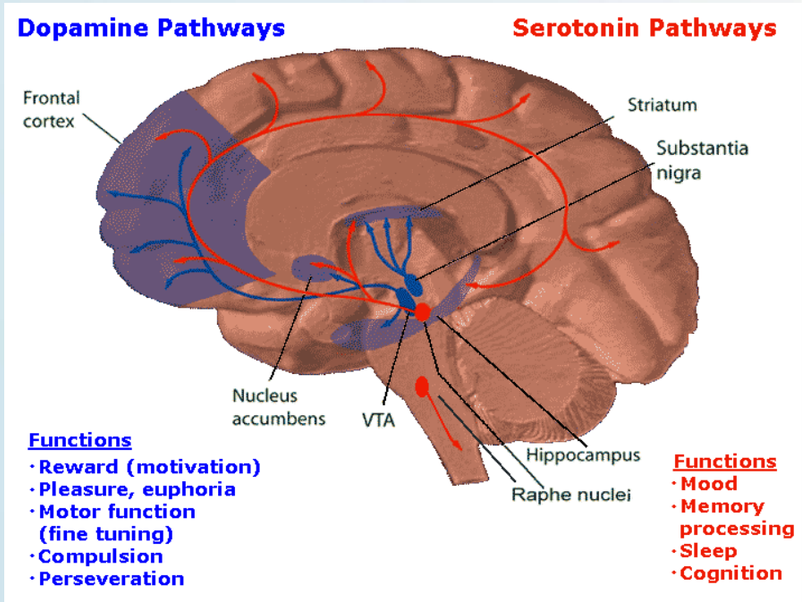
Dopamine :

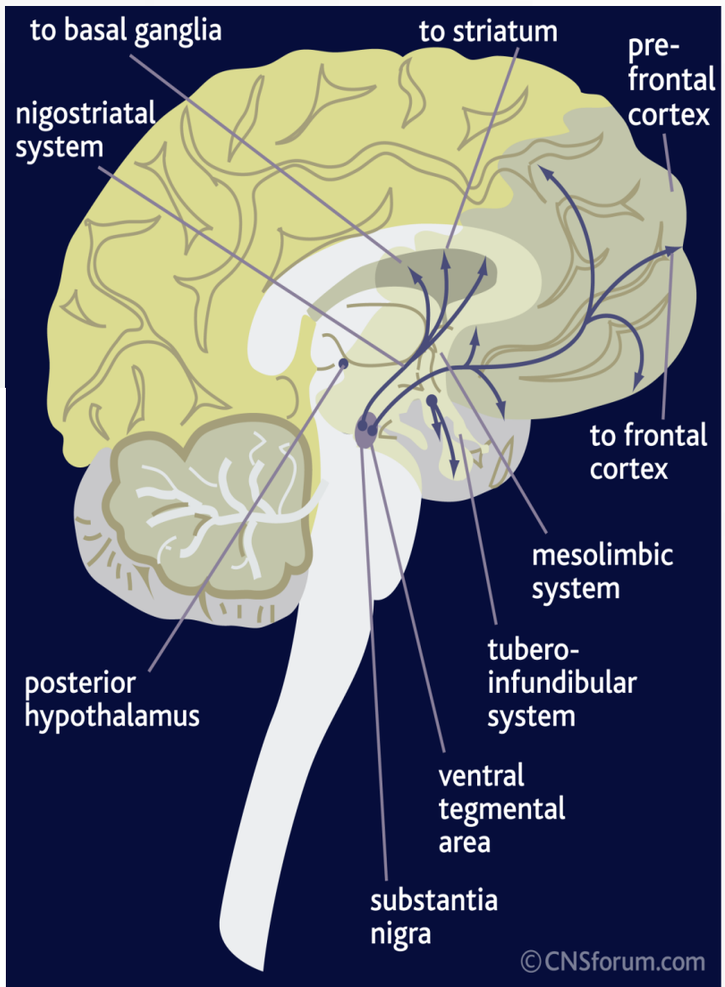
3 pathways of dopamine transmission :

	from	to	Concerned with
1	substantia nigra	caudate nucleus-putamen (neostriatum)	sensory stimuli and movement
2	the ventral tegmentum	mesolimbic forebrain	cognitive, reward and emotional behavior
3	the tubero-infundibular system		neuronal control of the hypothalmic-pituatory endocrine system

Dopaminergic neurons disorders :

- Schizophrenia.
- Parkinson’s Disease.





Neurotransmitters

Neurotransmitters	Post synaptic effect	pathways in the brain And where it's found	formation	Receptors types and place	Disorders
Serotonin*	excitatory	1)The principal centers for serotonergic is raphe nuclei 2) **axons ascend** to the cerebral cortex, limbic regions and specifically to the basal ganglia. 3)Serotonergic nuclei in the **brain stem** give rise to **descending axons**, some of which terminate in the medulla, while others descend the spinal cord.	Tryptophan gives 5-HT Hydroxy tryptamine If it degredeted by MAO it gives HIAA=hydroxyindoleacetic acid	————————	#Depression #Anxiety
Histamine	excitatory	Histamine forming cells are in posterior hypothalamus also found in gastric mucosa and in mast cells	Histidine decarboxylation → histaminase	H_1, H_2, H_3 H_3 receptors are presynaptic in brain	————————
Glycine*	Inhibitory	It binds to a receptor which makes the post synaptic membrane more permeable to Cl^- Ion and cause hyperpolarization (inhibition).	————————	The glycine receptor is primarily found in the ventral part of the spinal cord	————————
Glutamic acid*	excitatory	. Glutamate is carried into astrocytes where it is converted to glutamine and passed on to glutaminergic neurones.	By reductive amination of Kreb's cycle intermediate α –ketoglutarate.	There are two types of receptors e.g. metabotropic and iontropic receptors.	————————
Gamma Aminobutyric acid (GABA)	Inhibitory	GABA is the main inhibitory neurotransmitter in the central nervous system (CNS). GABAergic inhibition is seen at all levels of the CNS, including the hypothalamus, hippocampus, cerebral cortex and cerebellar cortex. As well as the large well-established GABA pathways, GABA interneurons are abundant in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated	Glutamate decarboxylation → glutamate decarboxylase(GAD)	Three types of GABA receptors e.g. $GABA_{A\ B\ \&\ C}$ $GABA_{A\ \&\ B}$ In CNS $GABA_B$ are metabotropic (G-protein) $GABA_C$ are found in retina only	————————

Neurotransmitters

Serotonin*

1)Pain modulation

2)Participates in mood elevation.

Glycine *

1)It is simplest of all aminoacids, consisting of amino group and a carboxyl group attached to a carbon atom

2) Strychnine is glycine antagonist

3) Play role in controlling pain

Glutamic acid*

1)It is the **most commonly found neurotransmitter** in the brain.

2)Glutamate is neurotoxic while glutamine is not.

Summary

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
1.Acetyl choline (Ach)	Excitatory	Acetyl co-A + Choline	Cholinergic nerve endings Cholinergic pathways of brainstem	1.Nicotinic 2.Muscarinic	Broken by acetyl cholinesterase	Cognitive functions e.g. memory Peripheral action e.g. cardiovascular system
2. Catecholamines 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. Norepinehrine controls attention & arousal, sleep/wake cycle.
ii.Norepinephrine	Excitatory	Tyrosine, found in pons. Reticular formation, locus coerules, thalamus, mid-brain	Begins inside axoplasm of adrenergic nerve ending is completed inside the secretary vesicles	α_1 α_2 β_1 β_2		
iii. Dopamine	Excitatory	Tyrosine	CNS, concentrated in basal ganglia and dopamine pathways e.g. nigrostriatal, mesocorticolimbic and tubero-hypophyseal pathway	D_1 to D_5 receptor	Same as above	Sensory motor Cognetive/emotional behavior Endocrine Hypothalamic Decreased dopamine in parkinson's disease. Increased dopamine concentration causes schizophrenia

Summary

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
3. serotonin (5HT)	Excitatory	Tryptophan	CNS, Gut (chromaffin cells) Platelets & retina	5-HT_1 to 5-HT_7 5-HT_2A 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 H_1, H_2, H_3 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.

Summary

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
6. Aspartate	Excitatory	Acidic amines	Spinal cord	Spinal cord	Aspartate & Glycine form an excitatory / inhibitory pair in the ventral spinal cord	
7. Gama 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 in the retina.	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.
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 reabsorbtion 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.

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CNS Block