CNS Block

23rd Lecture

Neurotransmitters

Physiology Team– 430

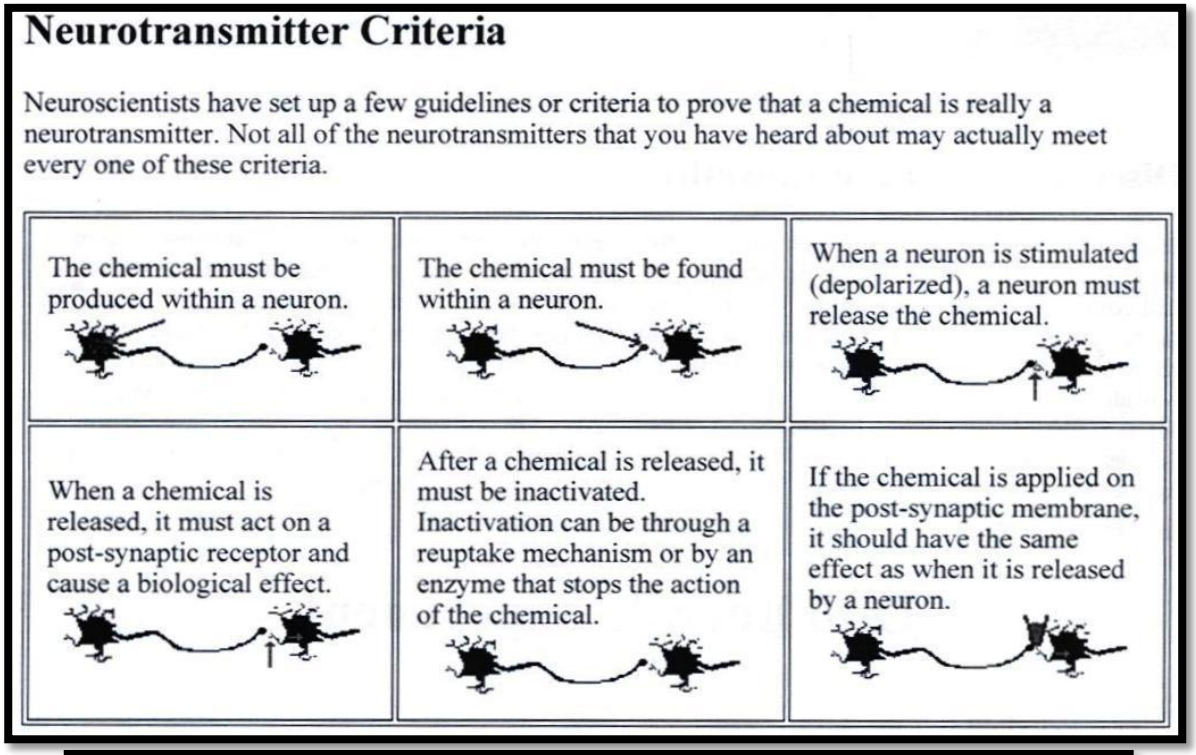
This Lecture is done by :

Hadeel Al-Sajjan

NEUROTRANSMITTERS

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.



Classification of Neurotransmitters

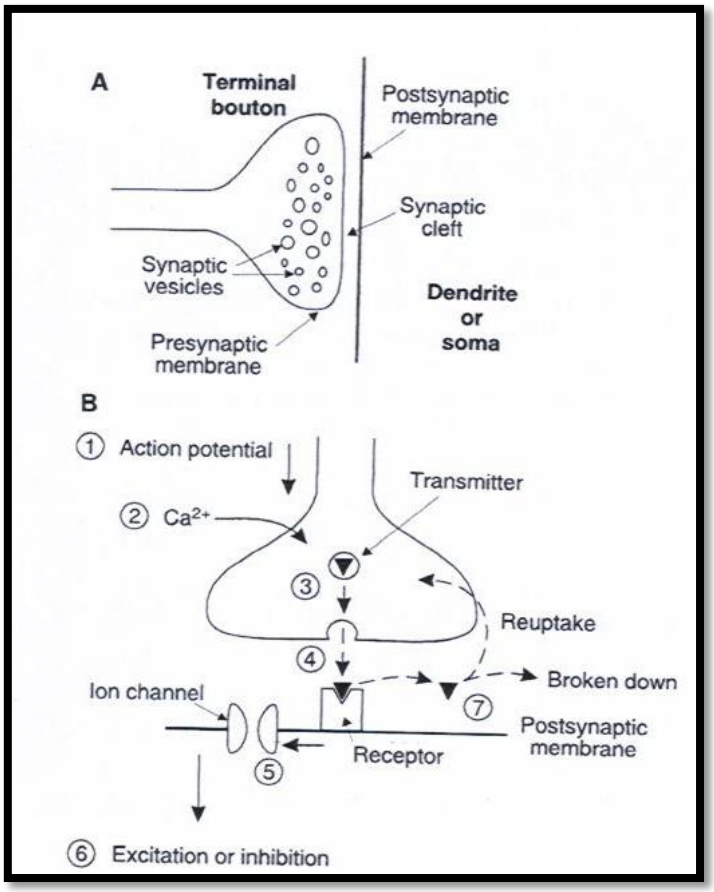
Amines		
Acetylcholine (ACh)	Dopamine (DA)	Norepinephrine (NE)
Serotonin (5-HT)	Histamine	Epinephrine

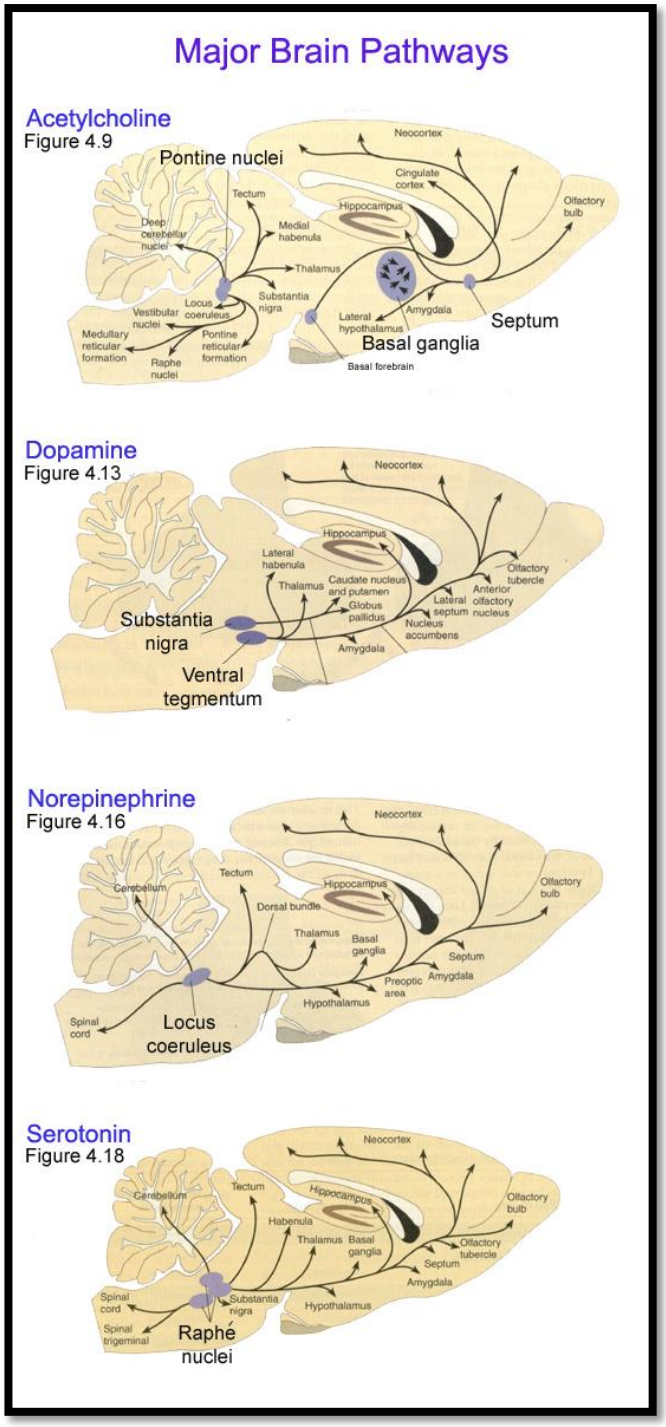
Amino Acids		
Gamma-aminobutyric acid (GABA)	Glycine	Glutamate
Aspartate		

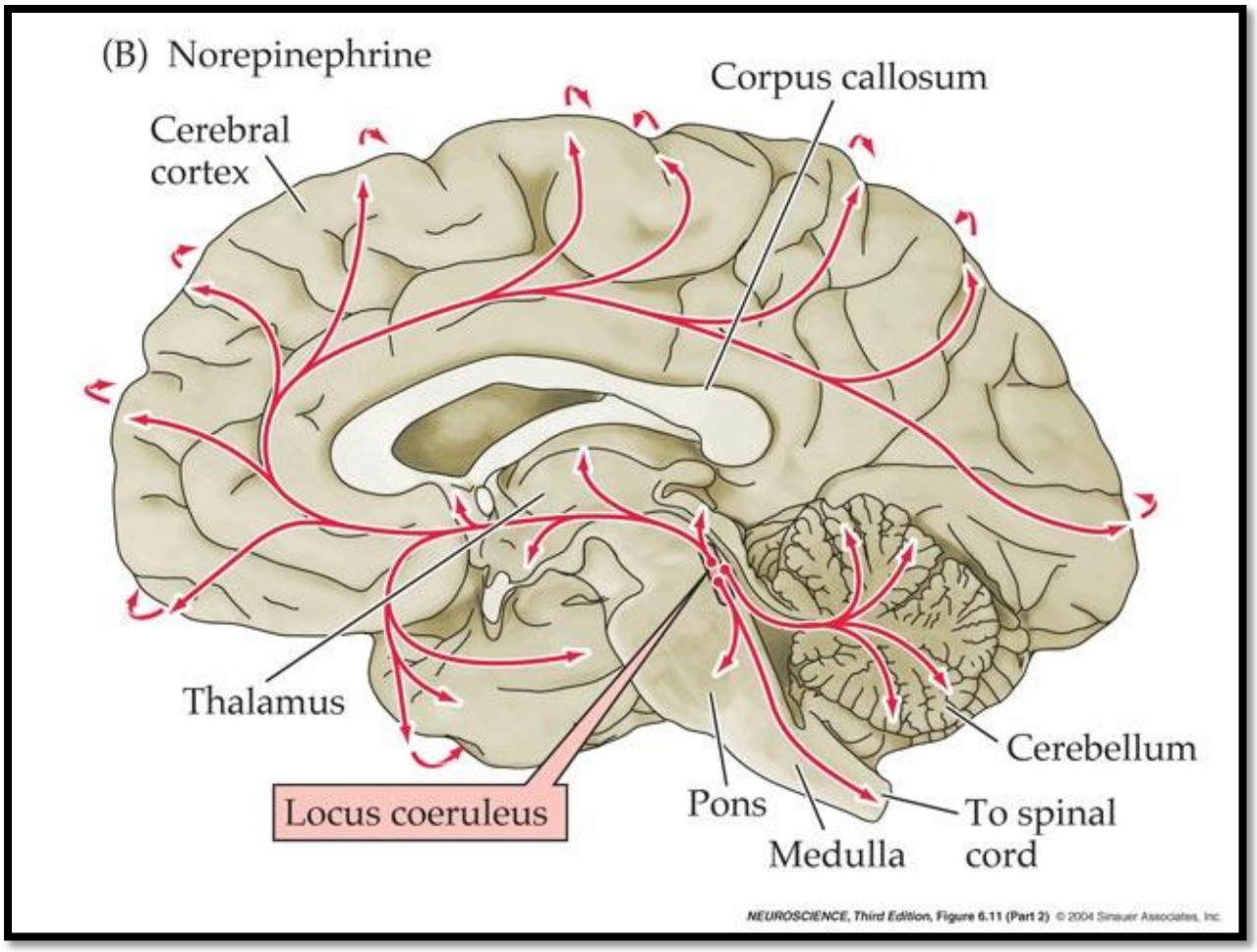
Neuroactive Peptides - partial list!!			
bradykinin	beta-endorphin	bombesin	calcitonin
cholecystokinin	enkephalin	dynorphin	insulin
gastrin	substance P	neurotensin	glucagon
secretin	somatostatin	motilin	vasopressin
oxytocin	prolactin	thyrotropin	angiotensin II
sleep peptides	galanin	neuropeptide Y	thyrotropin-releasing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

Soluble Gases	
Nitric Oxide (NO)	Carbon Monoxide

Neurotransmitter: Release and Action







Note: Norepinephrine is an Amine

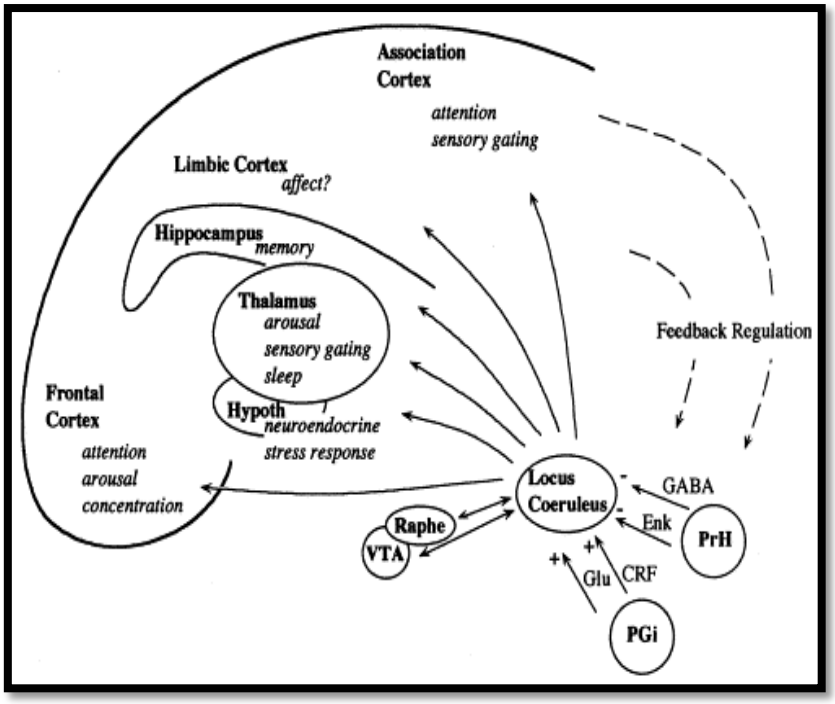
The Locus Coeruleus/Norepinephrine System:

- Very wide-spread projection system.
- LC is activated by: stress and co-ordinates responses via projections to thalamus, cortex, hippocampus, amygdala, hypothalamus, autonomic brainstem centers, and the spinal cord
- Sleep: LC activity predicts changes in sleep/wake cycle
- Attention/Vigilance: LC activated by novel stimuli, and LC activates EEG

Note: Most important Norepinephrine nucleus → The Locus Coeruleus

Norepinephrine (NE) Implicated in Stress-Related Disorders:

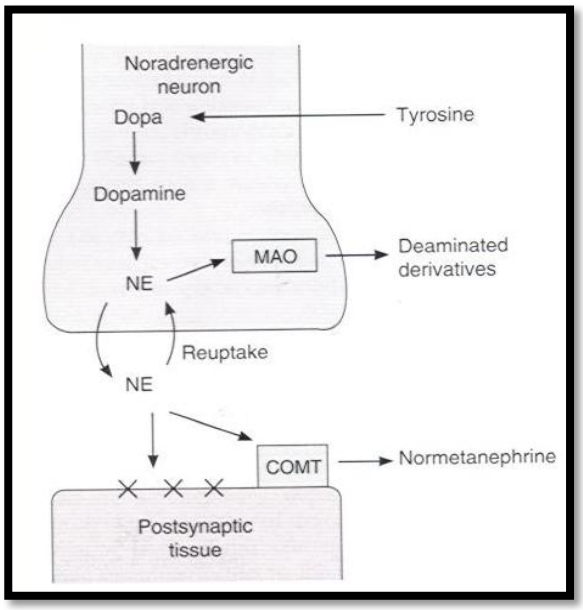
- Depression
- Withdrawal from some drugs of abuse
- Other stress-related disorders such as panic disorder



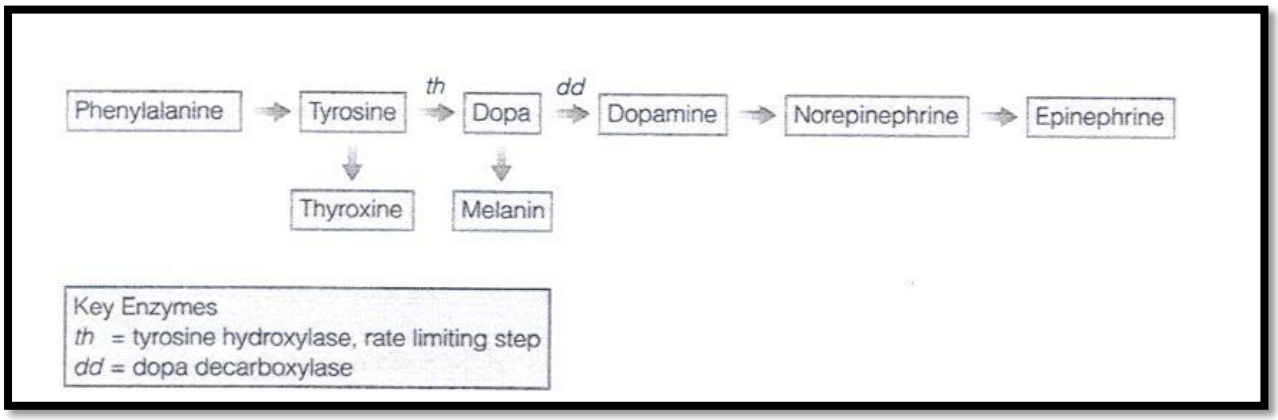
PGi: Nucleus paragigantocellularis

PrH: Perirhinal Cortex

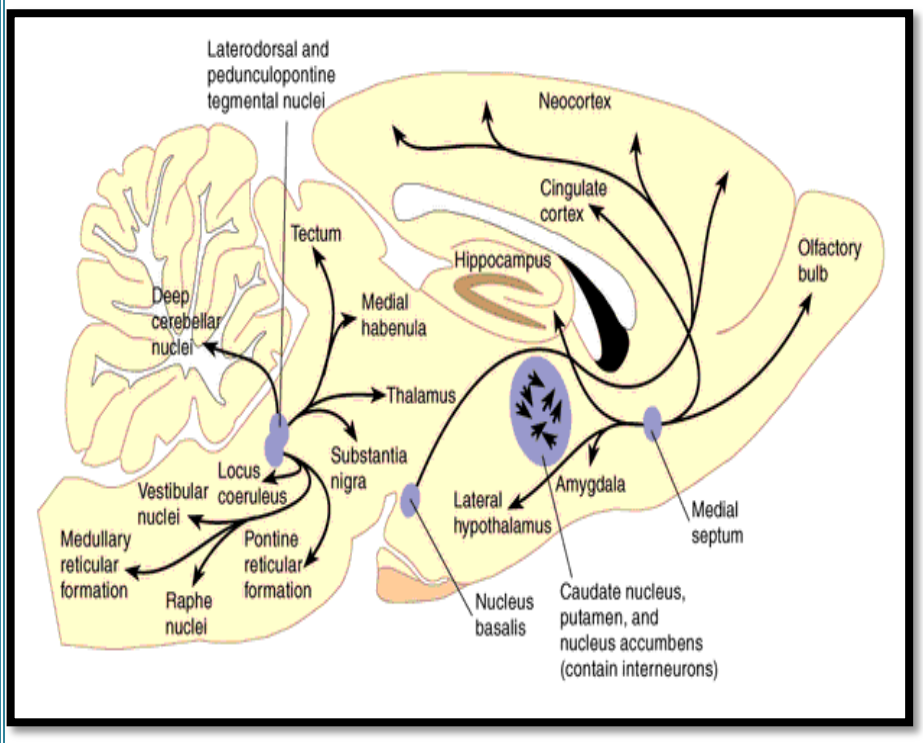
Norepinephrine synthesis and fate at synapses

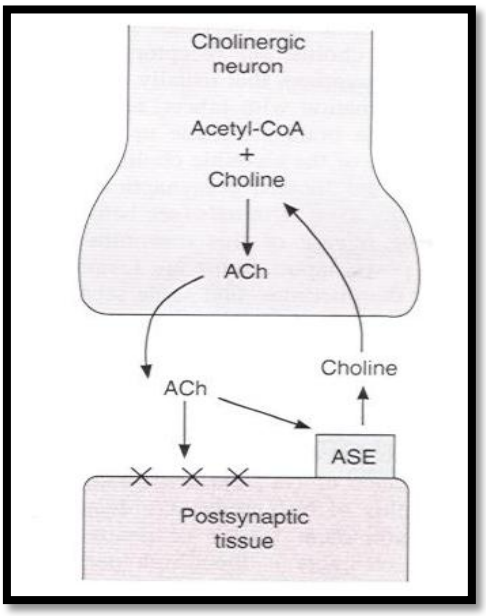


Epinephrine & Norepinephrine



Cholinergic Pathways



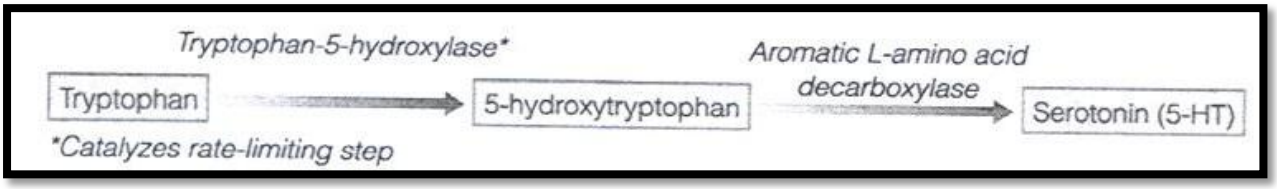


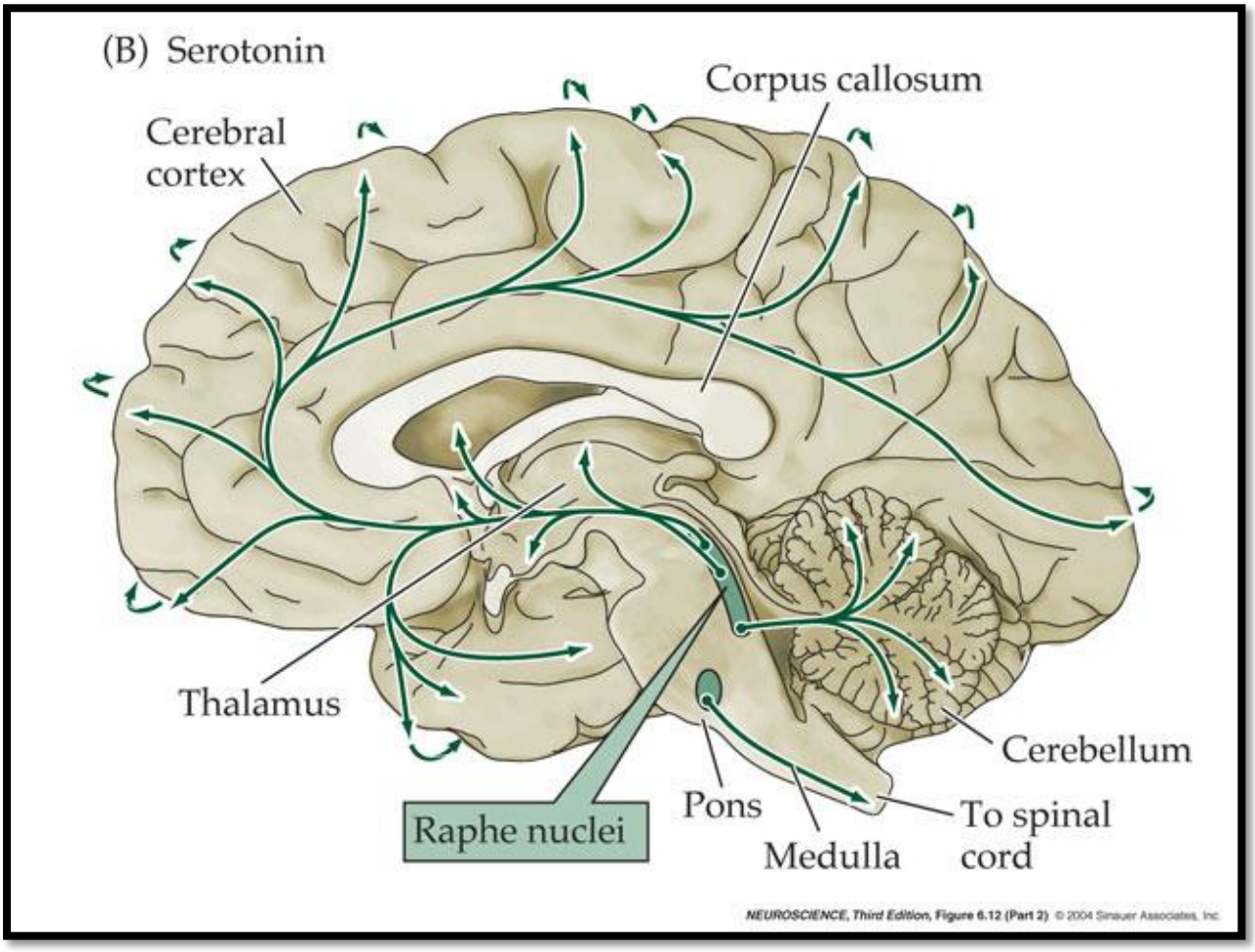
Acetyl Choline Receptors

	Nicotinic	Muscarinic
1 Located at:	• Neuromuscular junction of skeletal muscle • Postganglionic neurons of parasympathetic nervous system. • Ventral tegmental area.	• Glands • Neuromuscular junctions of cardiac and smooth muscle. • Postganglionic neurons of sympathetic nervous system.
2 Agonist	• Nicotine	• Muscarine (a toxin produced by certain mushroom)
3 Antagonist	• Curare (paralyses skeletal muscle)	• Atropine

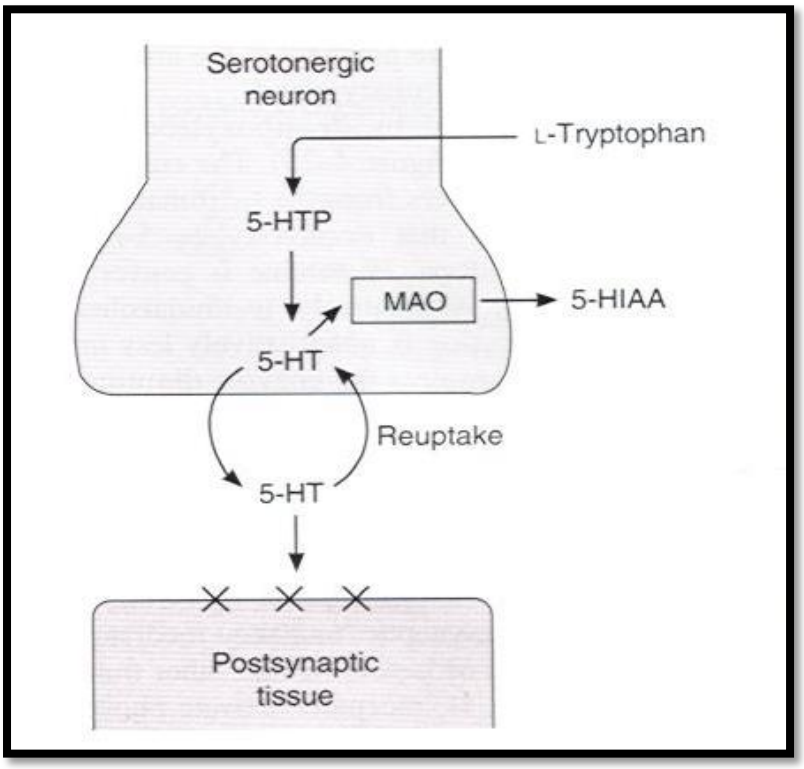
Note: Acytilecholine (Ach)is an Amine

Serotonin





Note: Serotonin (5-HT) is an Amine



Formation of serotonin =5-HT

- Hydroxy tryptamine
- HIAA=Hydroxyindoleacetic acid

Serotonin (5-HT) Disorders:

- Depression
- Anxiety

Antidepressants

- **Tricyclics:** Block re-uptake of NE and 5HT
- **MAO inhibitors:** Inhibit enzymatic degradation of the monoamine by monoamine oxidase (MAO)
- **Selective 5-HT and NE re-uptake inhibitors: The popular SSRIs**

Dopaminergic Pathways

*Dopamine is transmitted via three major pathways:

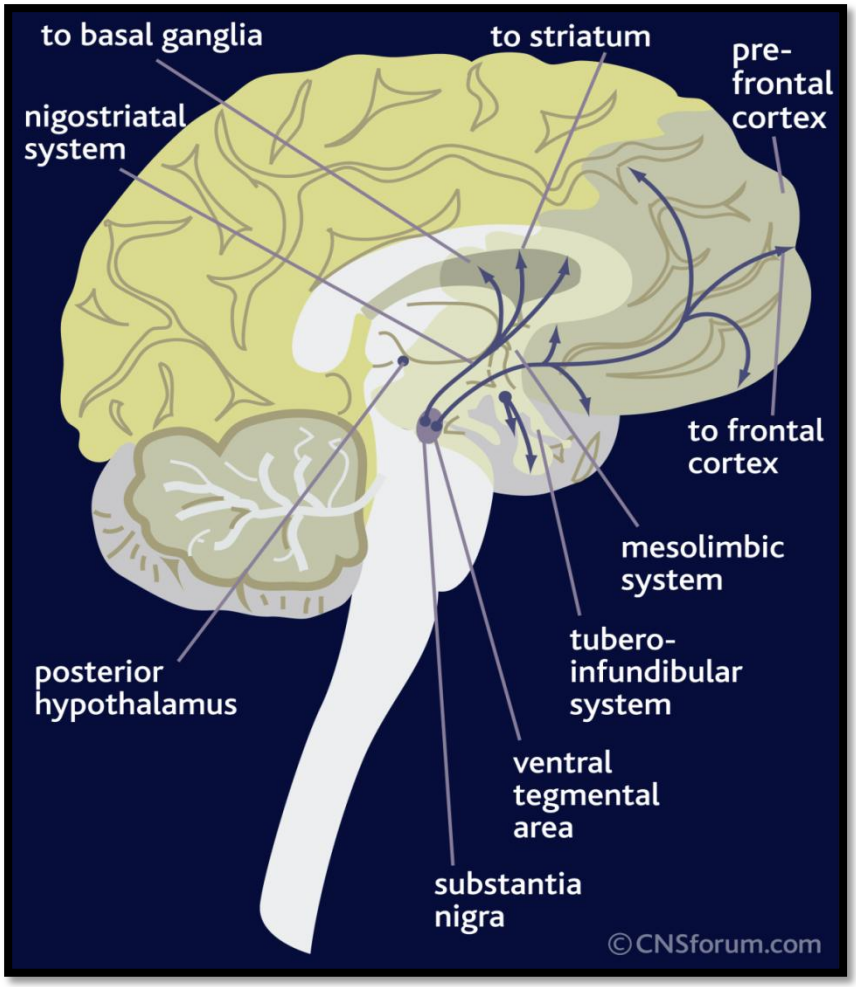
1. The first extends from the **substantia nigra** to the **caudate nucleus-putamen (neostriatum)** and is concerned with **sensory stimuli and movement.**

2. The second pathway projects from the **ventral tegmentum** to the **mesolimbic forebrain** and is thought to be associated with **cognitive, reward and emotional behavior.**

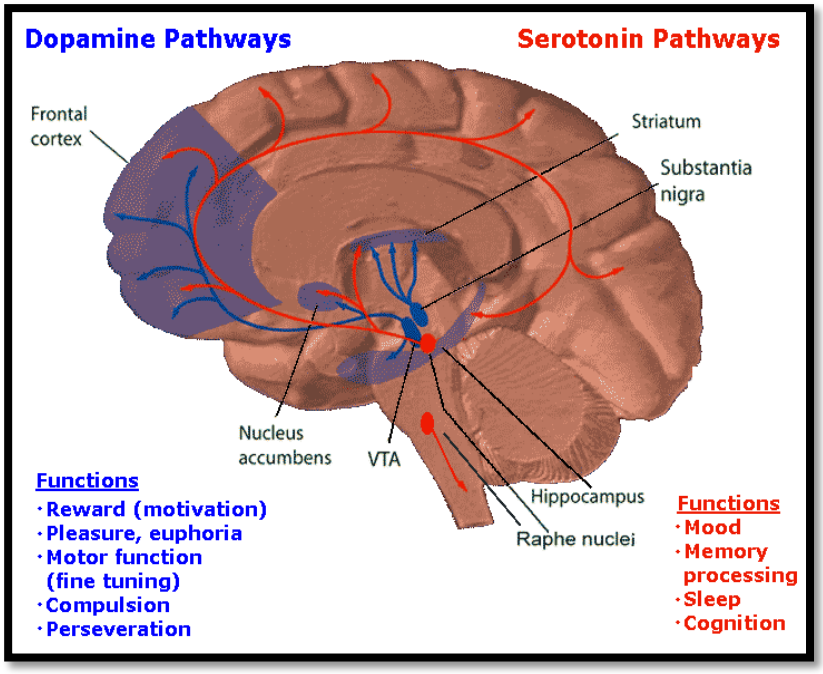
3. The third pathway, known as the **tubero-infundibular system**, is concerned with neuronal control of the **hypothalmic-pituatory endocrine system.**

Note: Dopamine (DA) is an Amine

Dopaminergic Pathways



Dopaminergic Pathways/Functions



Dopaminergic neurons disorders:

- Schezophrenia.
- Parkinson's Disease.

Histamine

- Histamine forming cells are in **posterior hypothalamus** also found in **gastric mucosa and in mast cells.**
- Formed by **decarboxylation** of **amino acid histidine** with the **help** of **enzyme histaminase**.
- Three known types of histamine receptors in found e.g. **H_1**, **H_2**, **H_3**.
- **H_3 receptors** are **presynaptic**. Its function in brain is not very certain. Its **main function** is that it is **excitatory**.

Note: Histamine is an Amine

Glycine

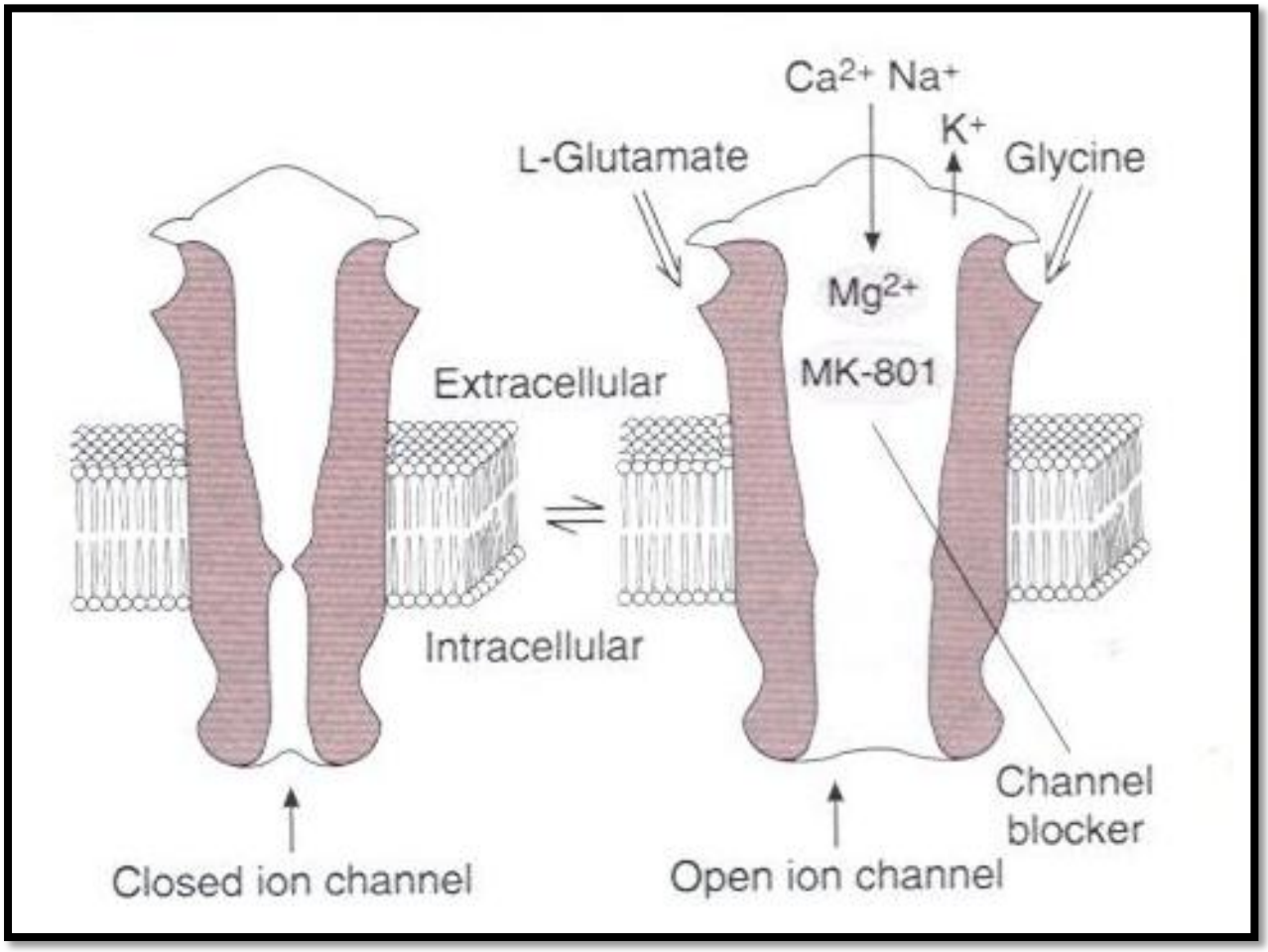
- It is **simplest** of all **aminoacids**, consisting of amino group and a carboxyl group attached to a carbon atom
- Its an **inhibitory neurotransmitter**.
- It binds to a receptor which makes the post synaptic membrane **more permeable** to **Cl^- Ion** and cause **hyperpolarization** (**inhibition**).
- The glycine **receptor** is primarily **found** in the **ventral part of the spinal cord**.
- **Strychnine** is **glycine antagonist**.

Note: Glycine is an Amino Acid

Glutamic acid

- It is the **most commonly found neurotransmitter** in the **brain**.
- It is **always excitatory**.
- Glutamate is **formed during Kreb's cycle** for **α – ketoglutarate**.
- Glutamate is **carried** into **astrocytes** where it is **converted** to **glutamine** and **passed on to glutaminergic neurones**.
- **Glutamate** is **neurotoxic** while **glutamine** is **not**.
- There are **two** types of **receptors** e.g. **metabotropic** and **iontropic** receptors.

Note: Glutamic Acid (Glutamate) is an Amino Acid

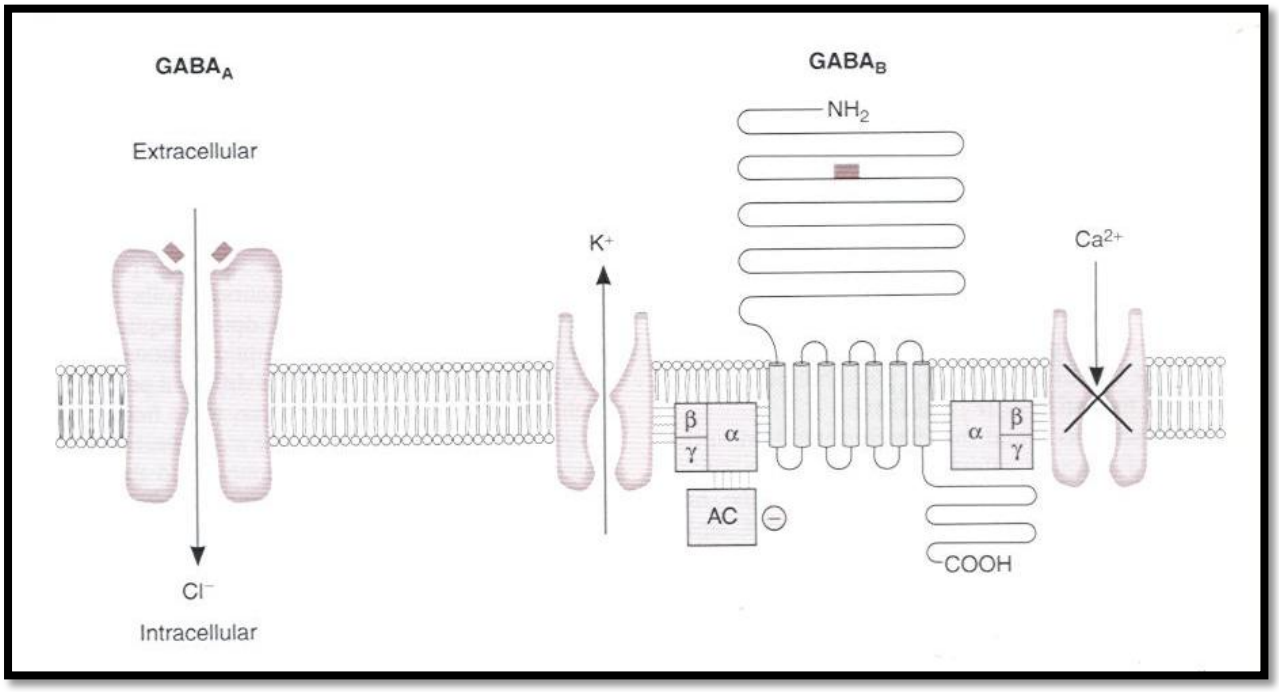


- **NMDA** =N methyl-D-aspartate receptors,
- When glutamate & glycine bind to receptor **ion** channels **open**,
- **Mg block channels**

Gamma Amino butyric acid (GABA)

- **Inhibitory** neurotransmitter of **CNS** and is **also found** in **retina**.
- Formed by **decarboxylation** of **glutamate**.
- The enzyme that **catalyzes** this reaction is **glutamate decarboxylase**(**GAD**)
- **Three types** of GABA receptors e.g. **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**.

Note: Gamma Amino butyric acid (GABA) is an Amino Acid



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.
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	Decreased dopamine in parkinson's disease. Increased dopamine concentration causes schizophrenia

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.

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.

Neuro-transmitters	Precursor, enzymes	Receptors	Areas of concentration	Related disorders
Acetylcholine (Ach)	Choline, Choline-*O*-acetyltransferase	Nicotinic Muscarinic	Basal nucleus of Meynert, Limbic system, NM junctions, Parasympathetic neurons, Autonomic ganglia	Alzheimer disease, Myasthenia gravis, Botulism

Neuro-transmitters	Precursor, enzymes	Receptors	Areas of concentration	Related disorders
Dopamine	Phenylalanine, Tyrosine hydroxylase DOPA decarboxylase	D1 D2 (main receptors) D3, D4, D5	Nigrostriatal pathway, Hypothalamus	Parkinson disease, Prolactinoma, Schizophrenia
Norepinephrine (NE)	Phenylalanine, Tyrosine hydroxylase Dopamine-β-hydroxylase	α-receptor β-receptor	Locus coeruleus, Lateral tegmental nuclei, Sympathetic ganglia	Sleep-wake cycle
Glutamate	α-Ketoglutarate, Glutamate dehydrogenase	NMDA, Kainate, AMPA	Cerebral cortex, Brainstem, Spinal cord, Hippocampus	Epilepsy, Migraine, Stroke
Gamma-aminobutyric acid (GABA)	Glutamate, Glutamic acid decarboxylase (GAD)	$GABA_A$ $GABA_B$	Striatonigral system, Cerebellum, Hippocampus, Cerebral cortex	Sleep, Epilepsy Anxiety
Glycine	Serine		Spinal cord, Brainstem	Tetanus, Strychnine poisoning
Serotonin	Tryptophan, Tryptophan hydroxylase		Raphe nuclei	Levels of arousal, Pain modulation, Migraine, Depression

RECEPTORS DYSFUNCTION

1- Presynaptic effect

- **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.

2- Effects at Postsynaptic level:

- **Curare** binds to the acetylcholine receptor (AchR) and prevents Ach from acting on it and so that it induces paralysis.
- **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.

22.1 NEUROTRANSMITTERS

Neurotransmitter	Effect	Clinical relevance
Acetylcholine	Excitatory	Alzheimer's disease Myasthenia gravis Parkinson's disease Huntington's chorea Motion sickness Bladder control Vomiting
Noradrenaline/adrenaline	Excitatory	Migraine Mood disorders Cardiovascular control Bladder control Appetite Sleep disorders
Glutamate **Aspartate**	Excitatory	Cerebral ischaemia Epilepsy Memory Degenerative diseases (motor neuron disease)
Dopamine	Excitatory	Parkinson's disease Schizophrenia Vomiting
5-hydroxytryptamine (5-HT, serotonin)	Excitatory	Migraine Depression Pain Sleep
Gamma-aminobutyric acid (GABA) **Glycine**	Inhibitory	Epilepsy Spasticity
Histamine	Inhibitory	Uncertain
Neuropeptides Vasopressin Adrenocorticotrophic hormone (ACTH) Melanocyte-stimulating hormone (MSH) Substance P Opioid peptides (> 20) Endorphins Enkephalins Dynorphins	Excitatory and inhibitory	Memory Uncertain Pain
Purines Adenosine triphosphate/ diphosphate (ATP/ADP) Adenosine monophosphate (AMP) Adenosine	Excitatory and modulation of neurotransmission	Uncertain
Nitric oxide	Modulation of neurotransmission	Memory Cerebral ischaemia