Brain Neurotransmitters

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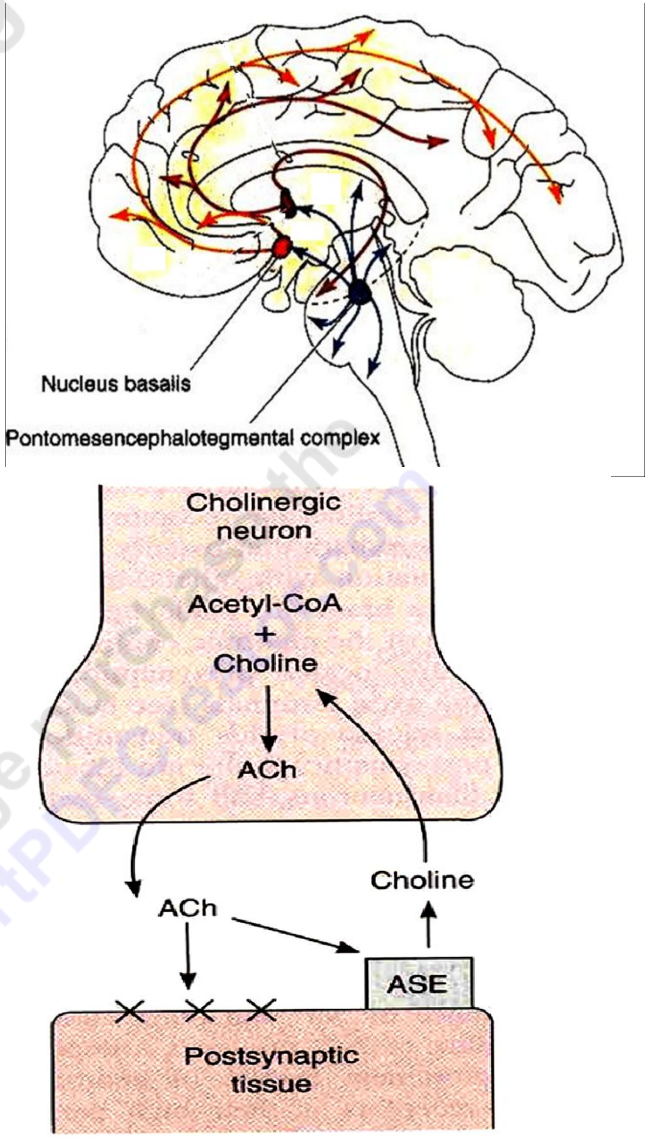
- **Objectives**

- At the end of this lecture the student should be able to describe the following brain neurotransmitter systems and their functions :
- Acetylcholine (Ach) .
- Norepinephrine (NE) .
- Glutamate .
- GABA .
- Serotonin .
- Dopamine (DA)

Acetylcholine (Ach)

- In the brain , ACh is found in →
- (1) the Basal Forebrain (mainly Nucleus Basalis) , and
- (2) Ponto-Mesencephalic Cholinergic Complex
- Functions : The brain Ach system (Cholinergic system) is concerned with
- (1) Consciousness ,wakefulness/sleep states
- (2) Learning & Memory
- Synthesis of Ach involves the reaction between Choline & Acetyl-CoA (active acetate)
- This reaction requires the enzyme Choline acetyltransferase
- After being released into the synaptic cleft , ACh opens Na channels to depolarize the postsynaptic membrane , and then is rapidly hydrolyzed into Choline and Acetate by the action of the enzyme Actylcholinesterase .
- ACh receptors of both types (i.e., nicotinic & muscarinic) are present in large numbers in the brain

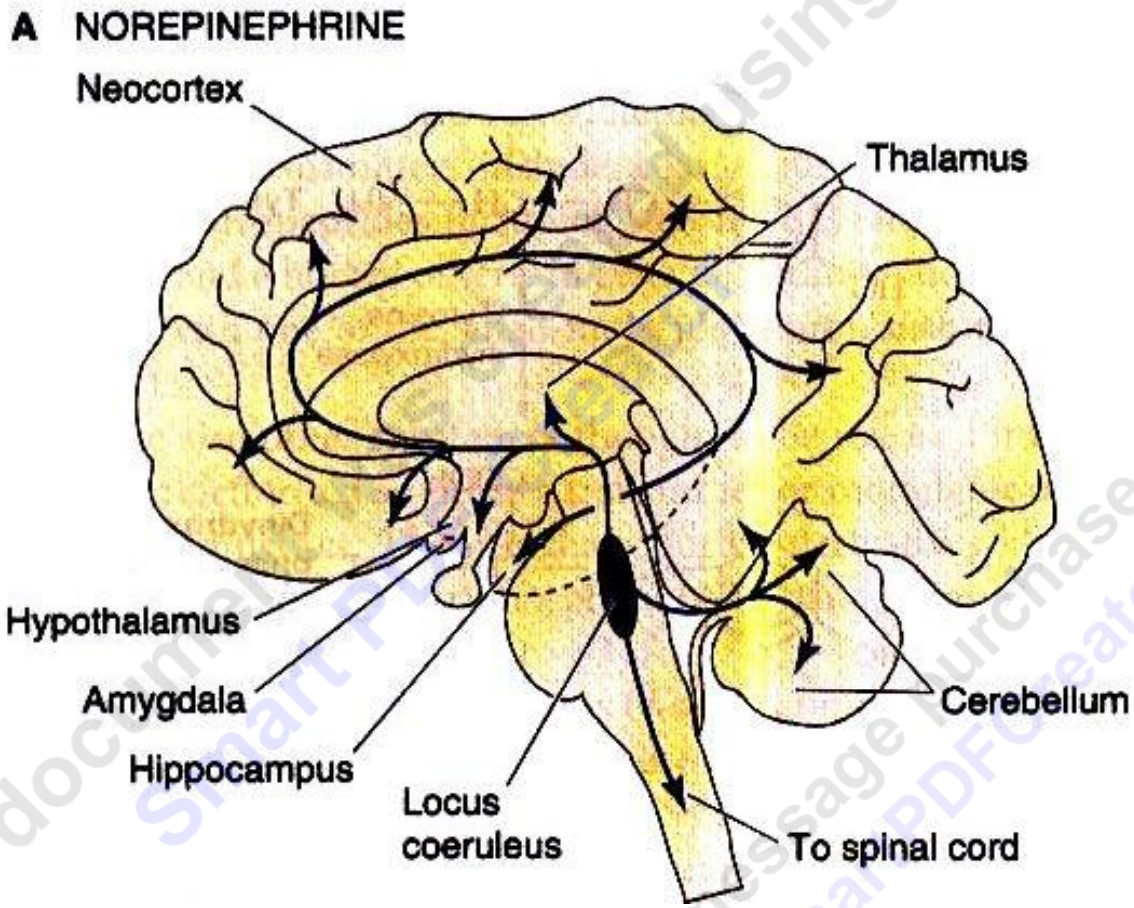


✓Defects in the brain cholinergic system interfere with learning and memory , such as in **Alzheimer's disease**

Norepinephrine

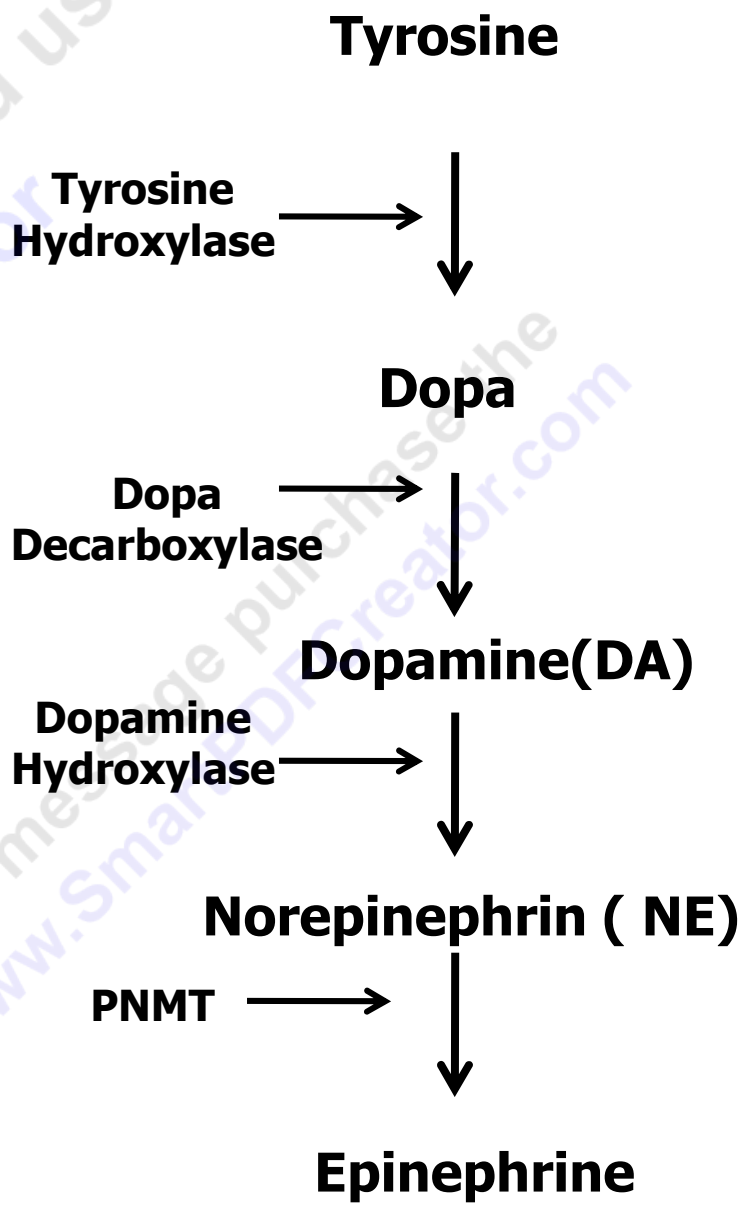
& Epinephrine

(Noradrenaline & Adrenaline)



- The cell-bodies of Noradrenergic neurons are located in mainly in the Locus Cereulus
- From the Locus Cereulus the axons of noradrenergic neurons arborize widely , constituting the Locus Cereulus System .

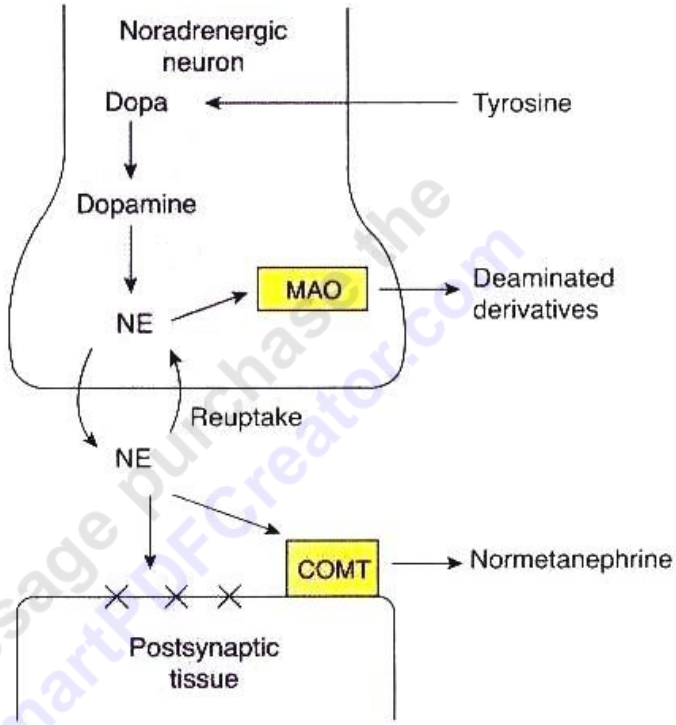
- The three Catecholamines (Norepinephrine , epinephrine and dopamine) are formed by hydroxylation and decarboxylation of the amino acid Tyrosine .
- Tyrosine Hydroxylase is the rate-limiting enzyme of synthesis , & it is subject to feed-back inhibition by dopamine and norepinephrine , thus prividing internal control of the synthesis process .
- Some brain neurons (and adrenal medullary cells) contain the their cytoplasm the enzyme PNMT which converts norepinephrine into epinephrine .



Catabolism of Catecholamines

- **NE is removed from the synaptic cleft by (1) binding to postsynaptic receptors , (2) binding to presynaptic receptors , (3) reuptake into presynaptic neurons , or (4) catabolism .**
- **Reuptake is a major mechanism**
- **NE and epinephrine are metabolized to inactive compounds by the enzymes MAO (Monoamine Oxidase) and COMT (Catechol-O-Methyl Transferase) .**
- **MAO is located in the cytoplasm of the nerve-endings at which catecholamines are secreted .**
- **In the brain , COMT is present in Glaial cells and small amonts are present in postsynaptic neurons , but not in presynaptic neurons (unlike MAO).**

- **Catabolism of Catecholamines**
- After binding to receptors , NE is
- (1) Re-uptaken into the presynaptic neuron → where degraded intracellularly by the enzyme Monoamine Oxidase (MAO) ; or
- (2) inactivated extracllularly by the enzyme Catechol-O-Methyl Transferase (COMT)
- NB : COMT , beside present on postsynaptic membrane , is present in larger amounts in Glial cells if taken into them .
- (However, COMT is not present in presynaptic neurons) .
- NB : Reuptake into presynaptic neurons & consequently degradation by MAO is the major mechanism of inactivation of NE .

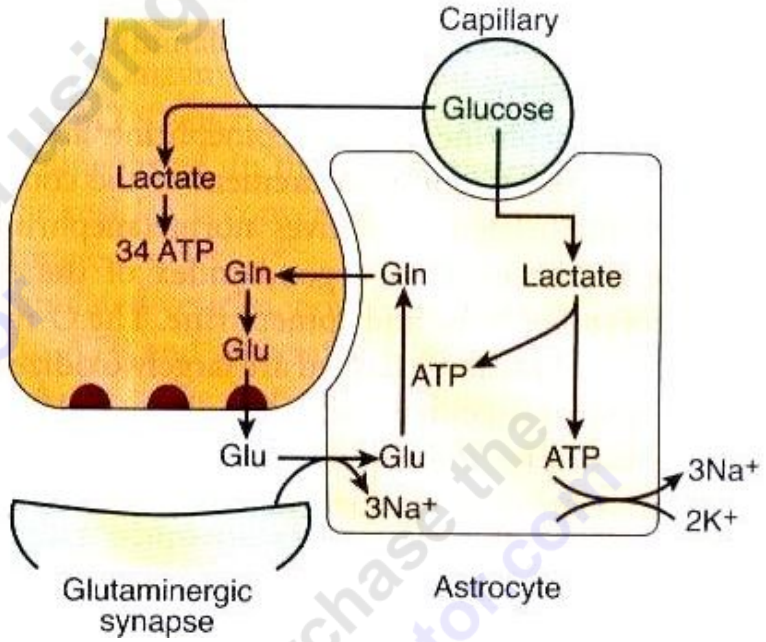


- Functions : of the Brain NE System

- (1) It constitutes part of the RAS (alertness) + plays role in →
- (2) fight-flight situations , including competitive athletic behavior , and aggressive behavior .
- (3) Norepinephrine and Serotonin deficiencies are implicated in pathogenesis of depression

Glutamate

- The excitatory amino acid Glutamate is believed to be responsible for 75% of excitatory transmission in the brain .
- It is formed in the Krebs cycle by reductive amination of alpha-ketoglutarate in the cytoplasm
  - Then , it is concentrated in synaptic vesicles by the vesicle-bound transporter BPN1 .
- When released , it is taken up by Astrocytes and converted to glutamine
- Then this glutamine passes back
- to the neurons and is converted back to Glutamate →



- which is again released as a synaptic transmitter
- Thus the main mechanism of removal of Glutamate from synapses is uptake into Astrocytes and neurons

Roles in Health & disease

- **In Health :**

- (1) Glutamic acid (and aspartic acid) : are major excitatory NTs in CNS.
- (2) Glutamate NMDA receptor involved in Long-Term Potentiation & memory storage .

- **In Disease :**

- (1) Excess Glutamate activity is implicated in some types of epileptic seizures
- (2) Under some pathological conditions , such Stroke , ALS (Amyotrophic Lateral Sclerosis) , and Alzheimer's diseases, it acts as an excitotoxin → producing exceesive influx of calcium into the neurons → causing neuronal death .

GABA

- GABA is a major inhibitory transmitter in the brain .
- Formation : GABA is formed by decarboxylation of Glutamate . The enzyme which caqtalyzes this reaction is Glutamate Decarboxylase (GAD , Glutamic Acid Decarboxylase) .
- GAD is present in the nerve ending.
- Inactivation : by 2 ways →
- (1) GABA is metabolized by the enzyme GABA Transaminase (GABA-T).
- (2) In addition , there is active reuptake of GABA
- GABA acts by (1) increasing Chloride influx , (2) increasing Potassium efflux and (3) decreasing Calcium influx → all these hyperpolarize the neuron and produce IPSP .

Functions of GABA & Medical Uses of its Agonists

- The increase in chloride conductance produced by GABAa receptors is potentiated by members of the Benzodiazepinethe family of drugs such as Diazepam (Valium) .
- Medical uses of Benzodiazepines include →

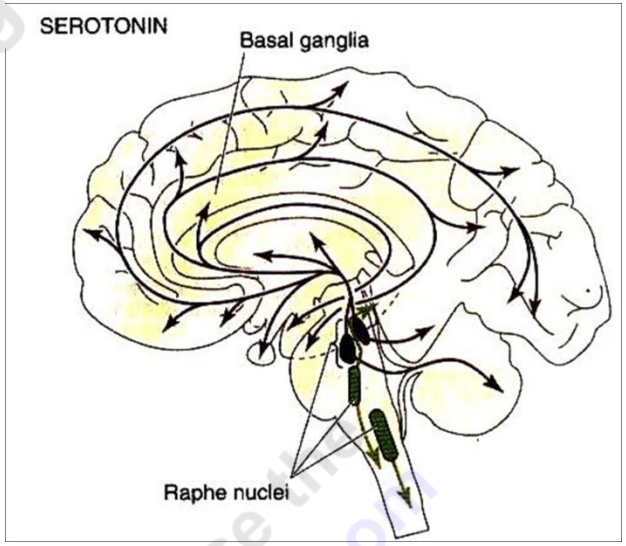
(1) Anxiolytic (anti-anxiety) /sedatives

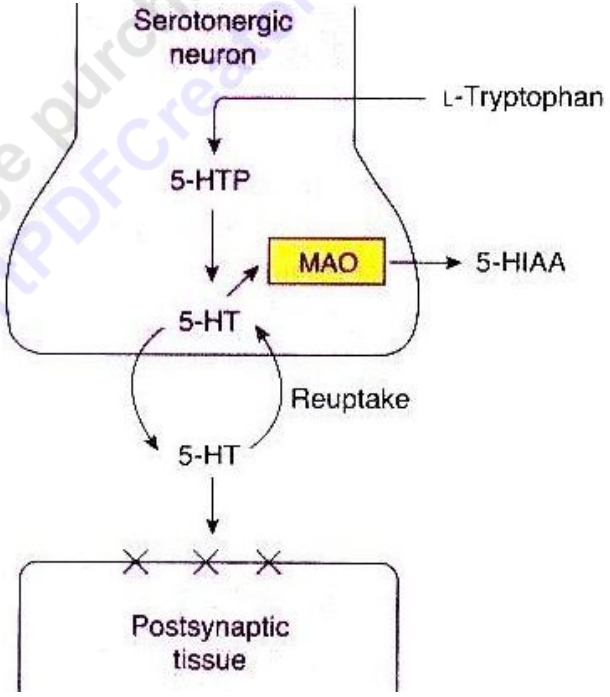
(2) Muscle relaxants , and

(3) Anticonvulsants

Serotonin

- Brain Serotonin is present in the **Raphe Nuclei**
- Serotonin is formed by the hydroxylation & decarboxylation of tryptophan
- After release , it is recaptured by an active , reuptake mechanism and inactivated by **Monoamino Oxidase (MAO) enzyme .**
- As mentioned before , it is believed that decreased synaptic activity of Serotonin & Norepinephrine can cause depression
- **MAOI (Monoamine Oxidase Inhibitor drugs)** block MAO enzyme → increase synaptic Serotonin & Norepinephrine

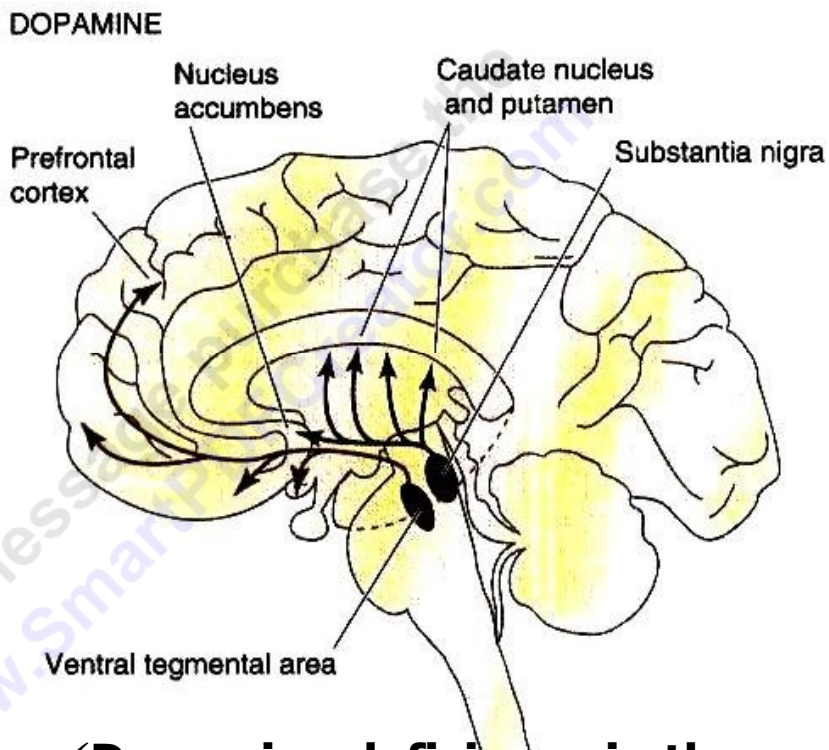




- MAOIs are some of the most effective Antidepressant Drugs .
- Drugs that inhibit serotonin uptake such as Fluoxetine (Prozac) are also effective antidepressants .
- Whereas decreased serotonin activity causes depression , increased serotonin activity can induce hallucinations .
- The hallucinogenic drug Lysergic Acid Diethylamide **(LSD)** is a serotonin agonist that produces its effect by activating 5-HT2 receptors in the brain .

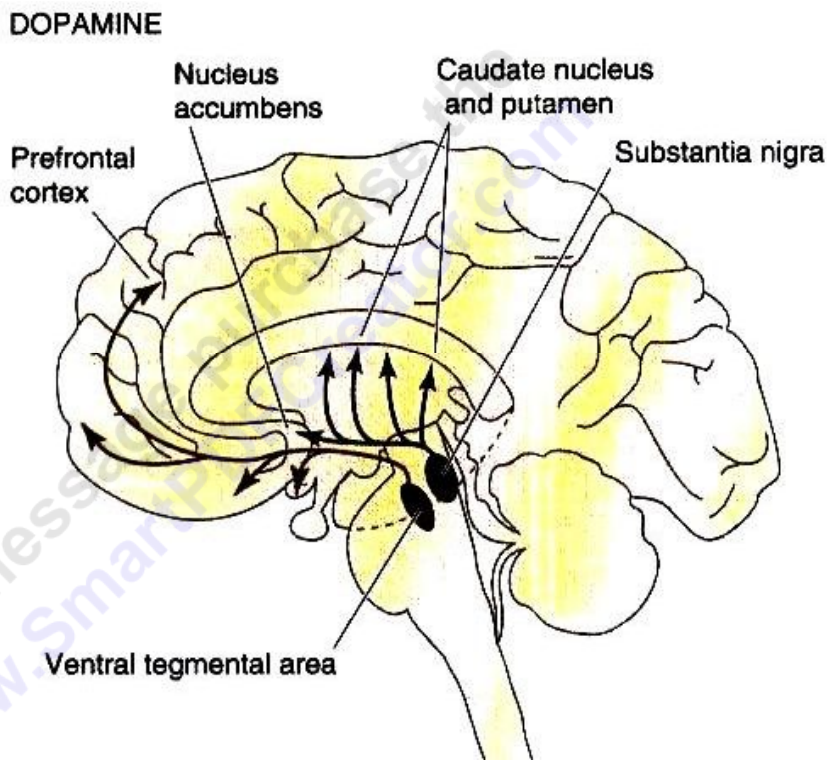
Dopamine (DA)

- In certain parts of the brain , catecholamine synthesis stops at dopamine (DA) .
- After being secreted into the synaptic cleft , reuptake takes place via a Na+ and Cl- dependent dopamine transporter .
- DA is metabolized by MAO and COMT .
- In the brain , dopaminergic neurons comprise →
- <u>(A) Nigrostriatal System</u> :
- Dopaminergic fibers originate in Substantia Nigra and project to the Striatum .
- This system is involved in motor control



✓**Dopamine deficiency in the Basal Ganglia can lead to Parkinsonism**

- **(B) Mesocortical System :**
- **Dopaminegic fibers arises from the Ventral Tegmental Area (VTA) , and projects to Nucleus Accumbens and Limbic System .**
- **The Mesocortical System is involved in behaviors of Pleasure , Reward , and Addiction .**
- **Defect in the Mesocortical System could be responsible for the psychotic symptoms of Schizophrenia .**
- **Overstimulation of Dopaminergic receptors leads to Schizophrenia-like psychotic symptoms .**



- Thank you !