

# **Brain Neurotransmitters**

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# objectives

By the end of this lecture you are expected to:

- 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

# 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 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
gonadotropin-releasing hormone	growth hormone-releasing hormone	luteinizing hormone	vasoactive intestinal peptide

## Soluble Gases

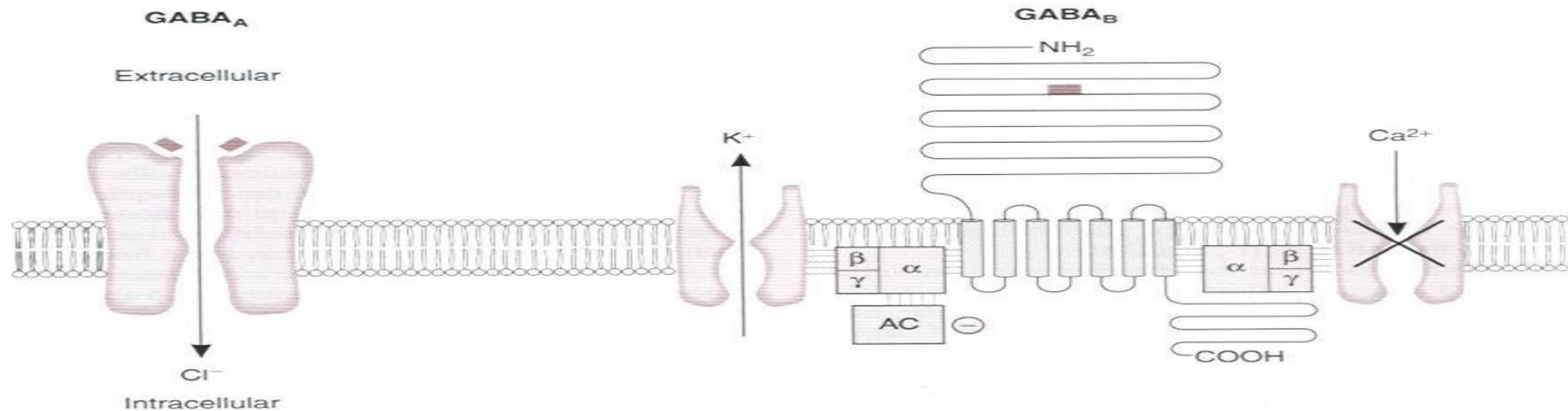
Nitric Oxide (NO)	Carbon Monoxide
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## Some of the Brain Neurotransmitters

1. Ach
2. Glutamate
3. GABA
4. Norepinephrine (NE)/Epinephrine
5. Serotonin
6. Dopamine

# Classes of Receptors

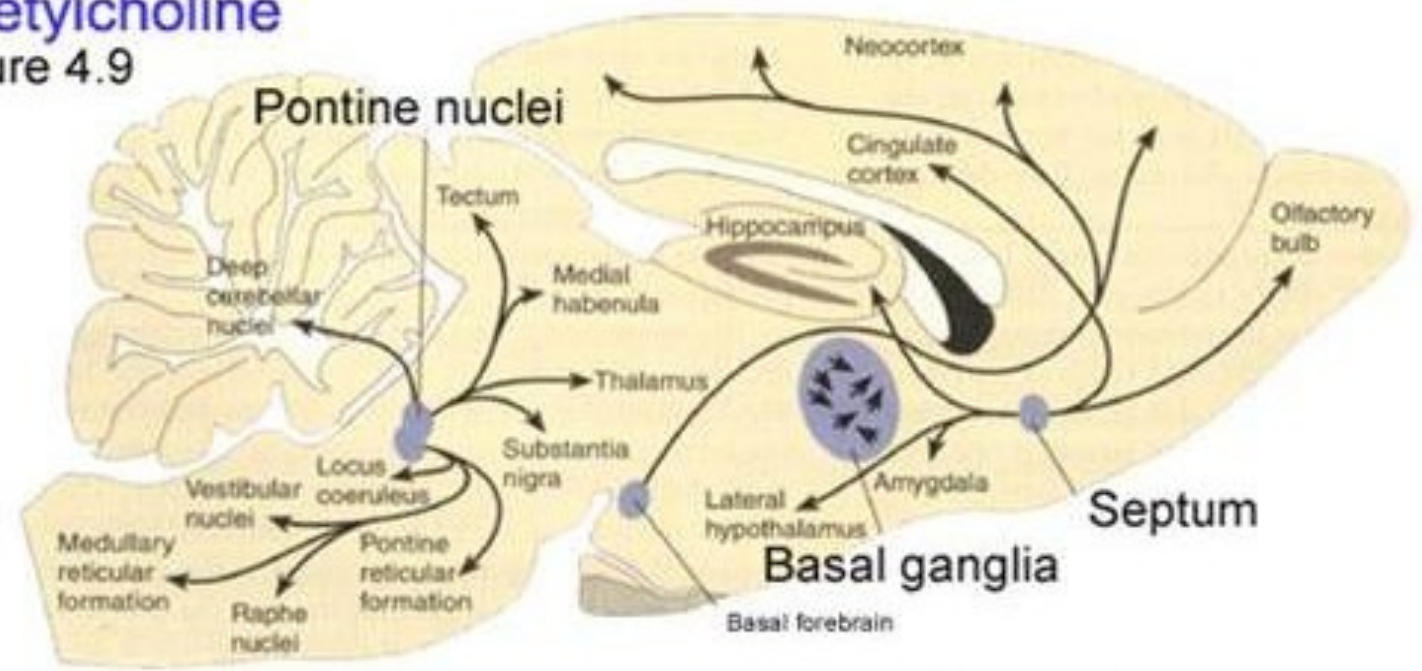
- **Metabotropic** = trans membrane receptor acts through a second messenger
- **Iontropic** = Ligand gated ion channel





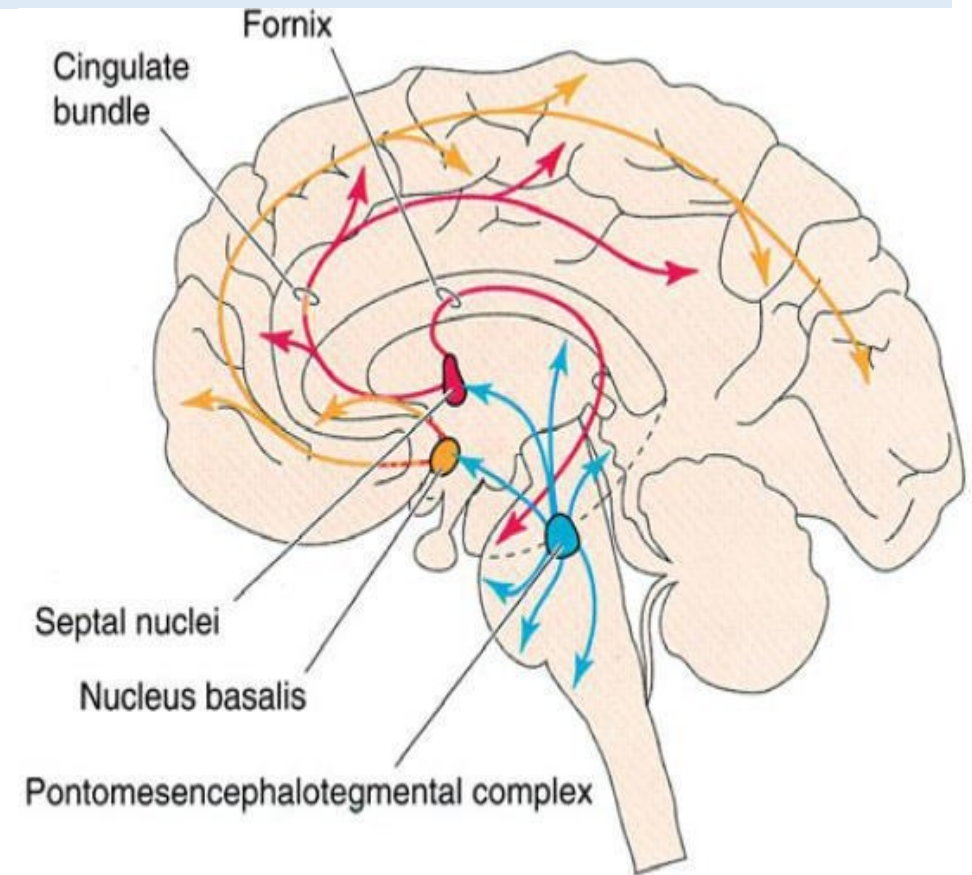
# Major Brain Pathways

Acetylcholine  
Figure 4.9



# Cholinergic System

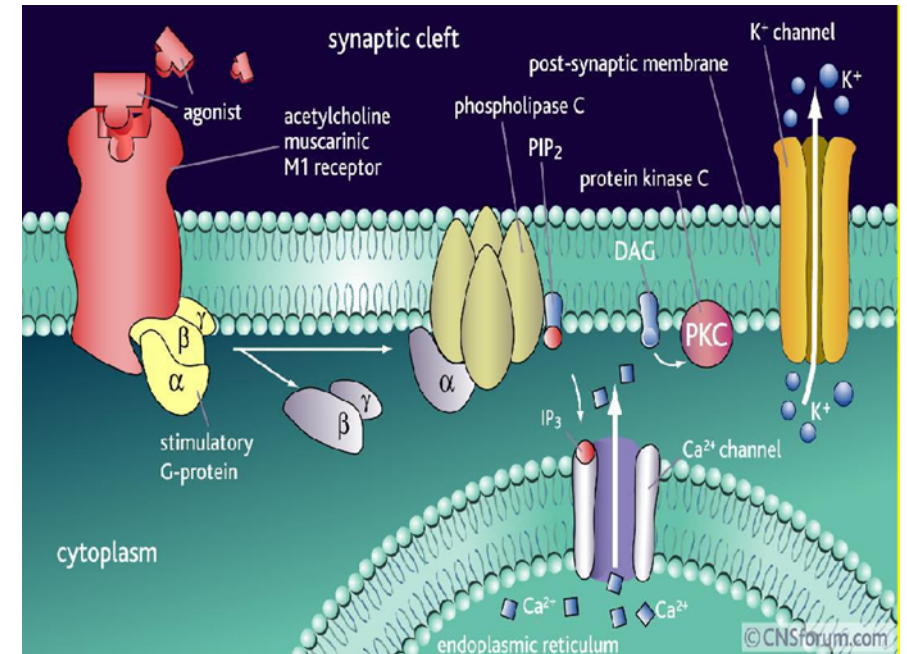
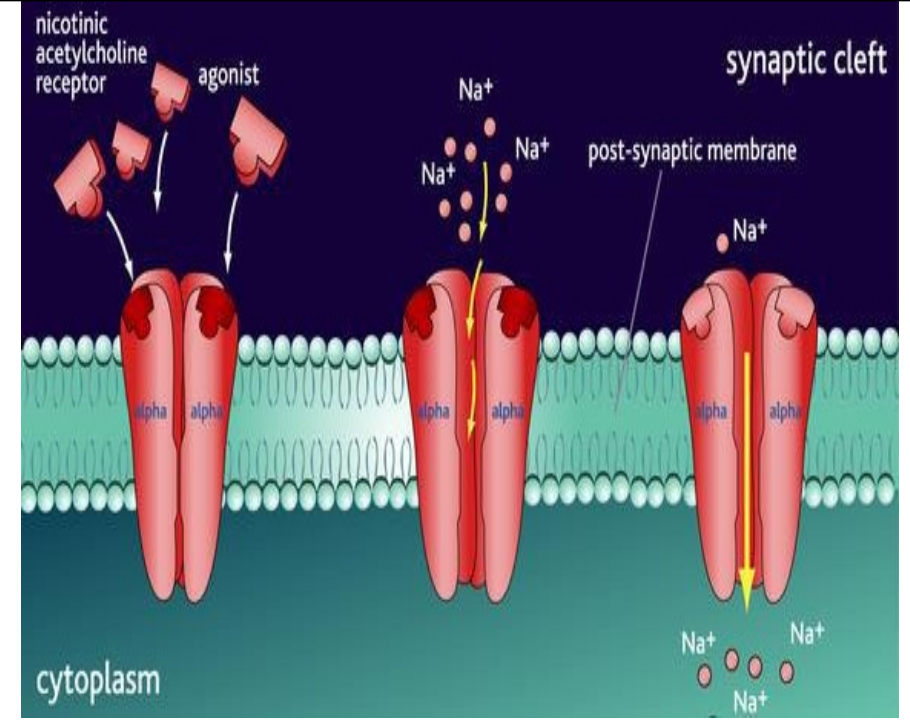
- Acetylcholine is the major neurotransmitter in the peripheral nervous system
- In the brain , cholinergic ( ACh producing ) neurons are present mainly in 2 areas :
- 1) Basal Forebrain ( namely Nucleus Basalis of Meynert and septal nuclei)
- (2) Mesopontine tegmental area which is also called ponto-mesencephalic cholinergic complex





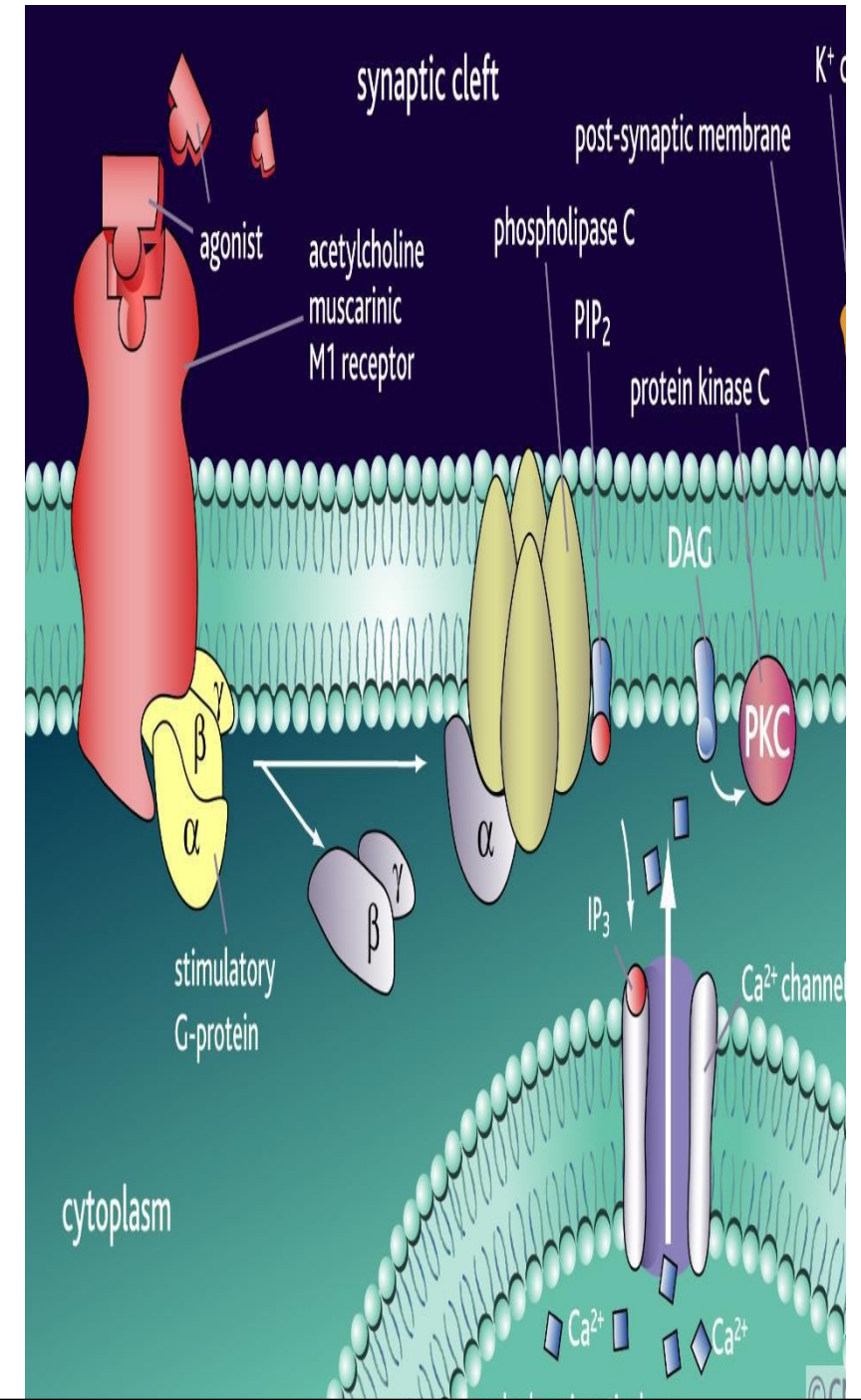
# Acetylcholine Receptors

- Acts on 2 cholinergic receptors:
  - **1** Nicotinic (ionotropic)
  - (The muscle-type can be selectively blocked by curare, the neuronal-type 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.



# Muscarinic Receptors

- 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

- ACh influences mental processes such as
  - Learning
  - Memory
  - Alertness
  - sleep.
- Alzheimer's Disease- the most common form of dementia that is associated with acetylcholine loss
- Damage to Ach producing cells in the basal forebrain
  - Bipolar disorder
  - Mood swings
  - Depression
  - *Inhibitors of acetylcholinesterase in the brain are the main drugs used to treat Alzheimer's disease.*

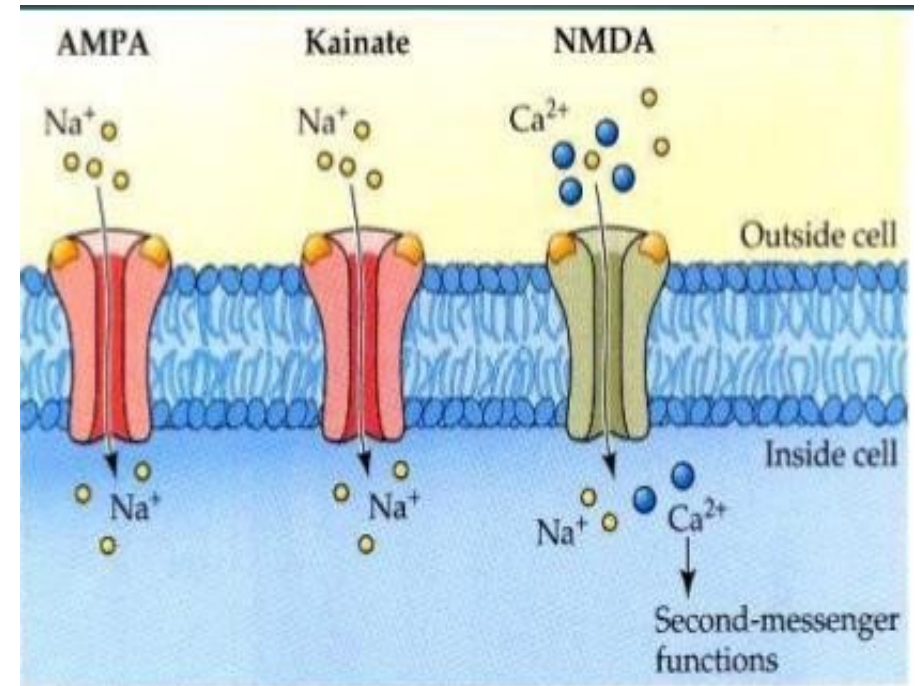
# Glutaminergic System

- Glutamate is the most commonly found NT 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; hypo function of NMDA receptors in this area and prefrontal cortex is associated with schizophrenia



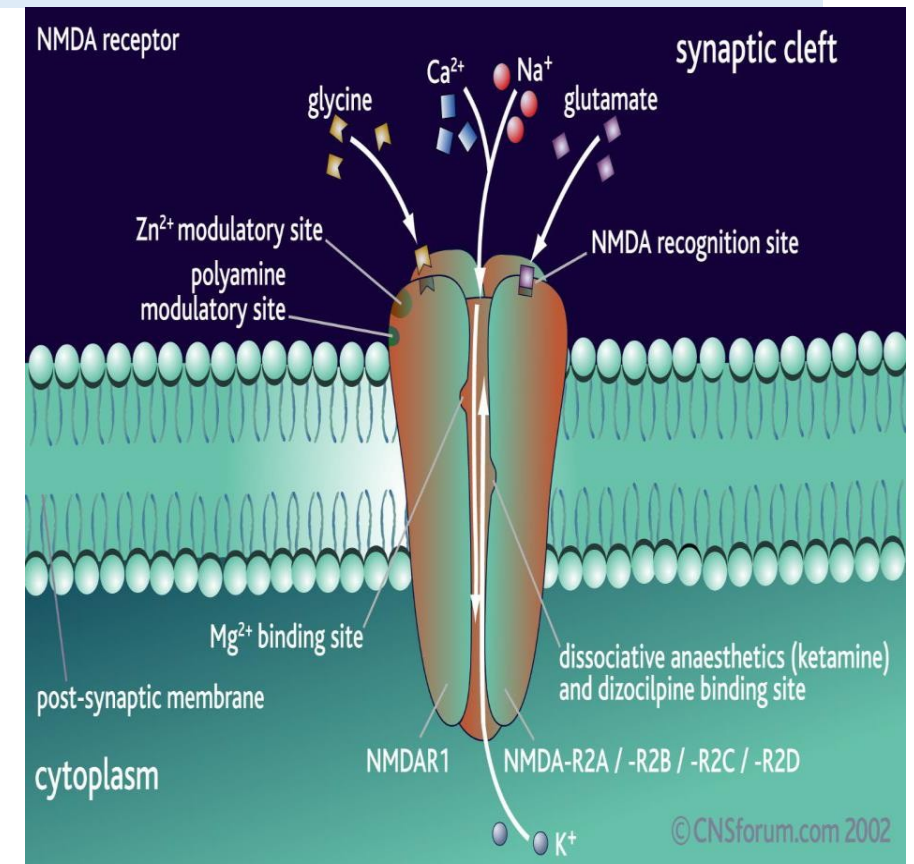
# Glutamate Receptors

- Are widely distributed in the brain; they are of two types:
  - 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.
  - Iontropic receptors** (ligand-gated ion channels).
    - Three types: •
      - AMPA receptors ( $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate)
      - Kainate receptors (kainite is an acid isolated from seaweed),
      - NMDA receptors (for N-methyl D-aspartate); play a role in long term potentiation so they are involved in learning and memory



# NMDA Receptors

- Permits passage of  $\text{Na}^+$  and large amounts of  $\text{Ca}^{2+}$ . They are unique:
  - ❑ Glycine is essential for their normal response to glutamate.
  - ❑ The channel is blocked by  $\text{Mg}^{2+}$  ion at normal membrane potentials
  - ❑ This blockade is removed by depolarization (caused by e.g. AMPA)
  - ❑ Excitatory post synaptic potential induced by activation of NMDA receptor is slower than that elicited by activation of AMP and kainate receptors





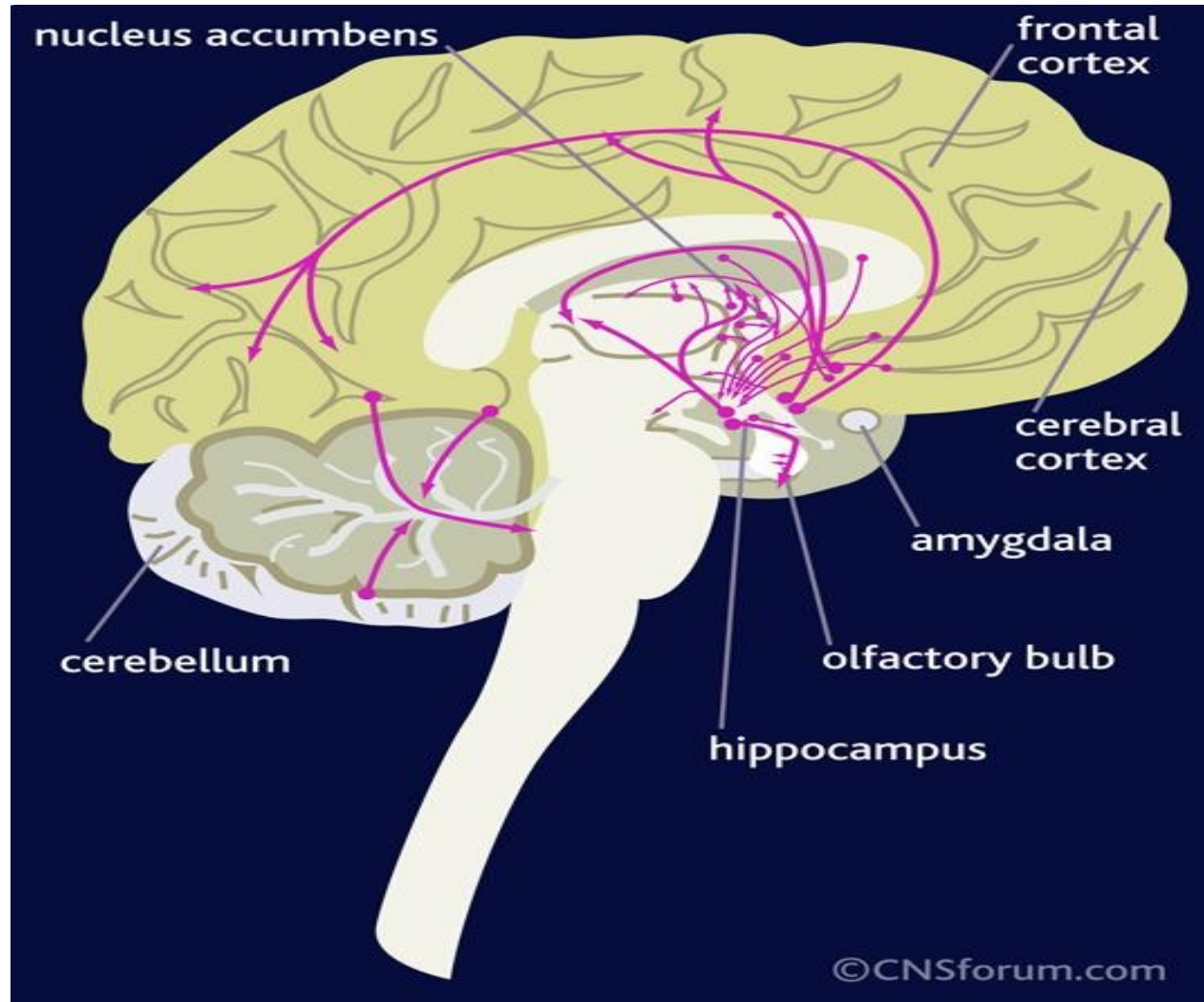
# Functions & Disorders Of Glutamate

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

## 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 diseases, it acts as an excitotoxin ,producing excessive influx of calcium into the neurons and causing neuronal death .

# GABAergic System

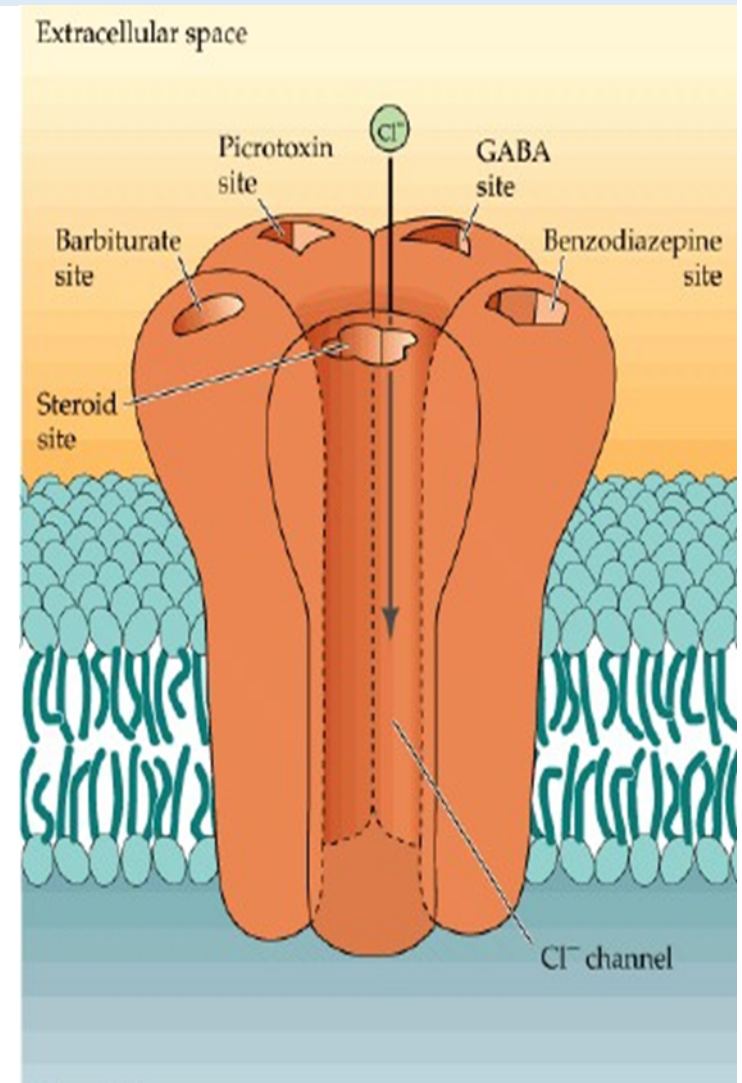


# GABAergic System

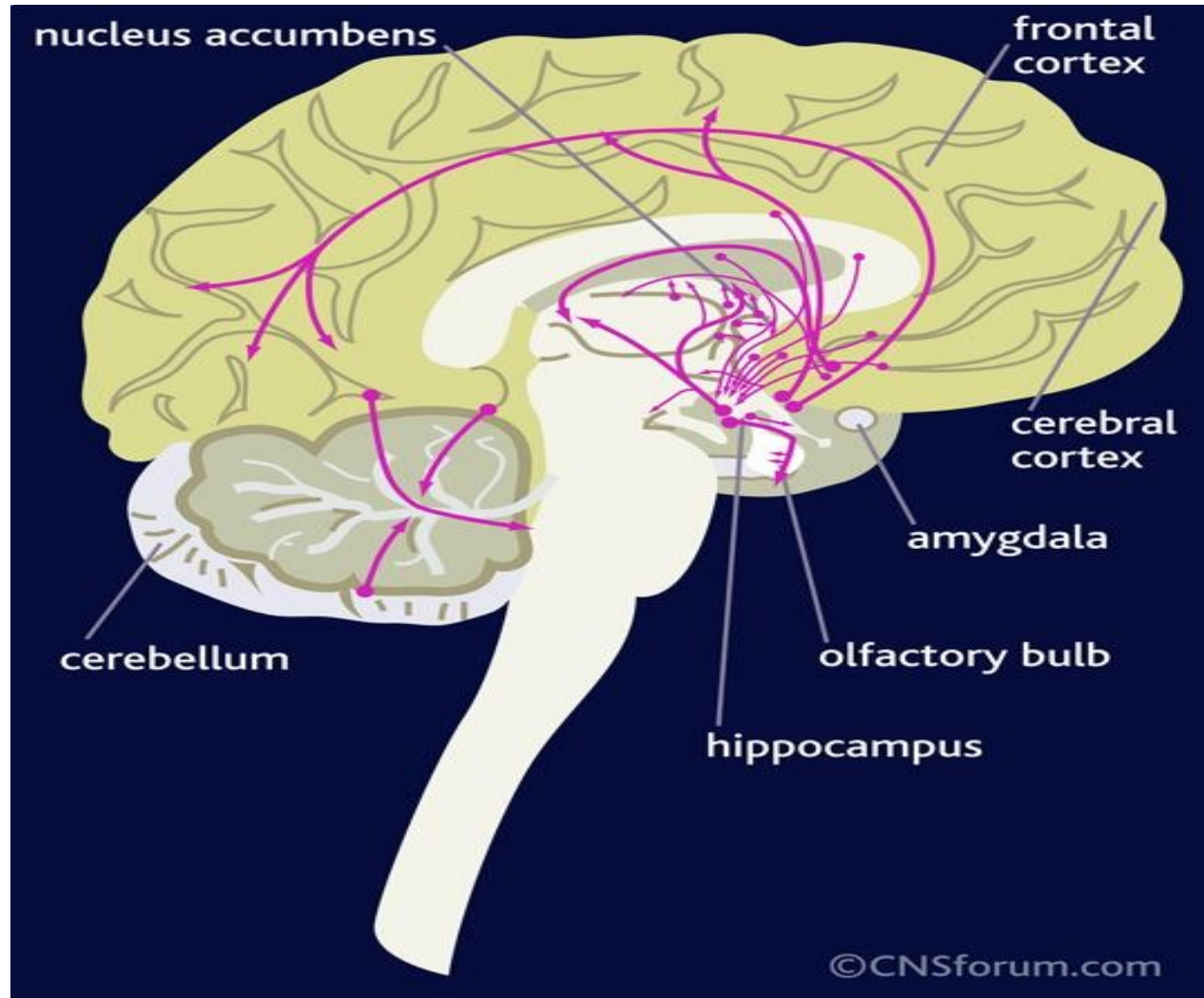
- GABA is the main inhibitory neurotransmitter in the central nervous system (CNS).
- GABAergic inhibition is seen at all levels of the CNS
- (Hypothalamus, hippocampus, cerebral cortex and cerebellar cortex).
- GABA interneurons are abundant in the brain, with 50% of the inhibitory synapses in the brain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

# Gamma Aminobutyric acid (GABA)

- Formed by decarboxylation of glutamate.
- Three types of GABA receptors
  - e.g. GABA<sub>A</sub>, B & C.
- GABA<sub>A</sub> & B receptors are widely distributed in CNS.
- GABA<sub>C</sub> are found in retina only
- GABA<sub>B</sub> are metabotropic (G-protein) in function.
- GABA<sub>A</sub> and C receptors (ionotropic) have multiple binding sites (for benzodiazepine and barbiturates).
- The channel is a Cl<sup>-</sup> channel (not Na)



# GABAergic System



# Functions & Disorders of GABAergic System

## Functions:

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

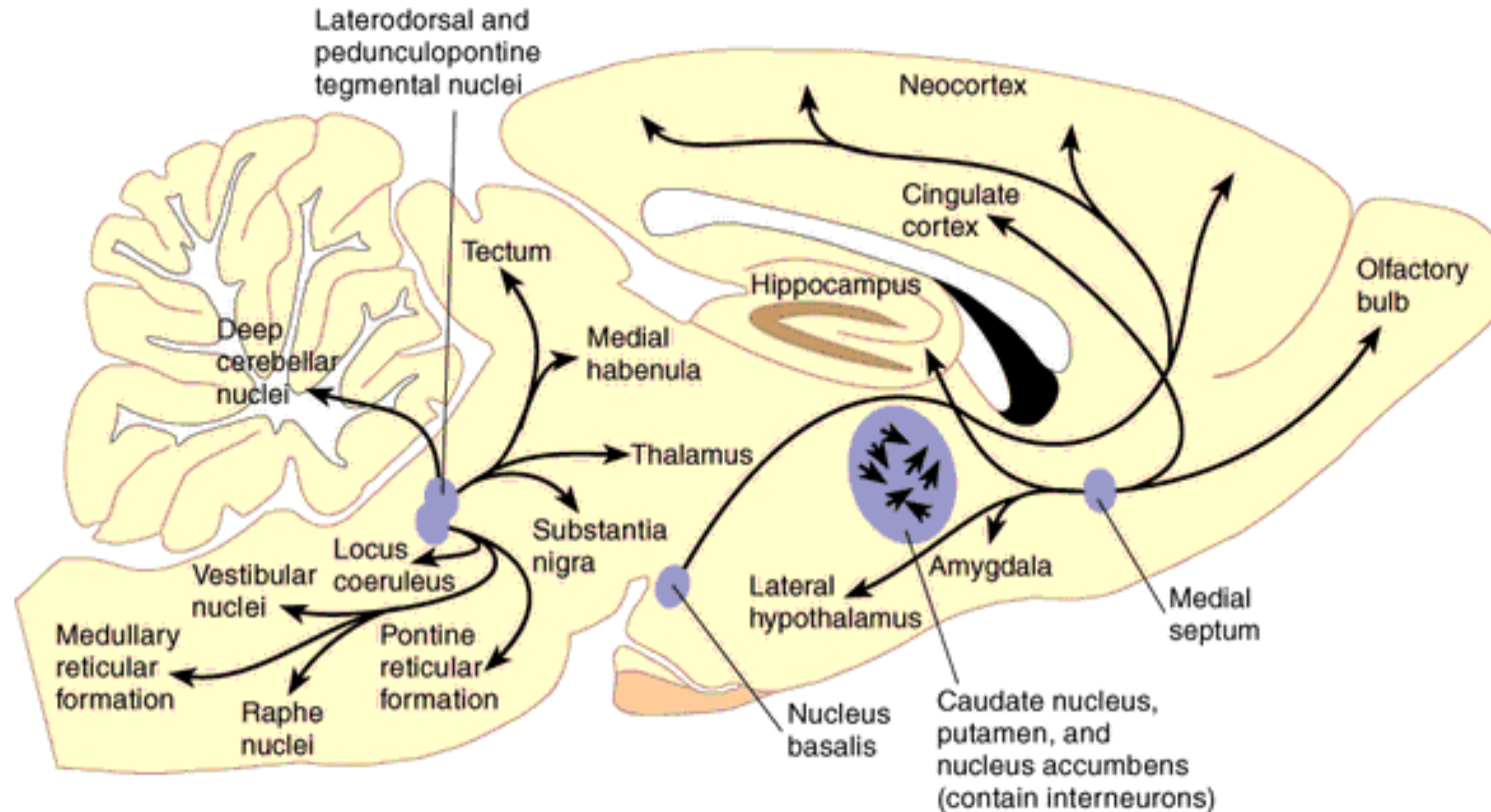
## Disorders:

-under activity of GABA leads to seizures.

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

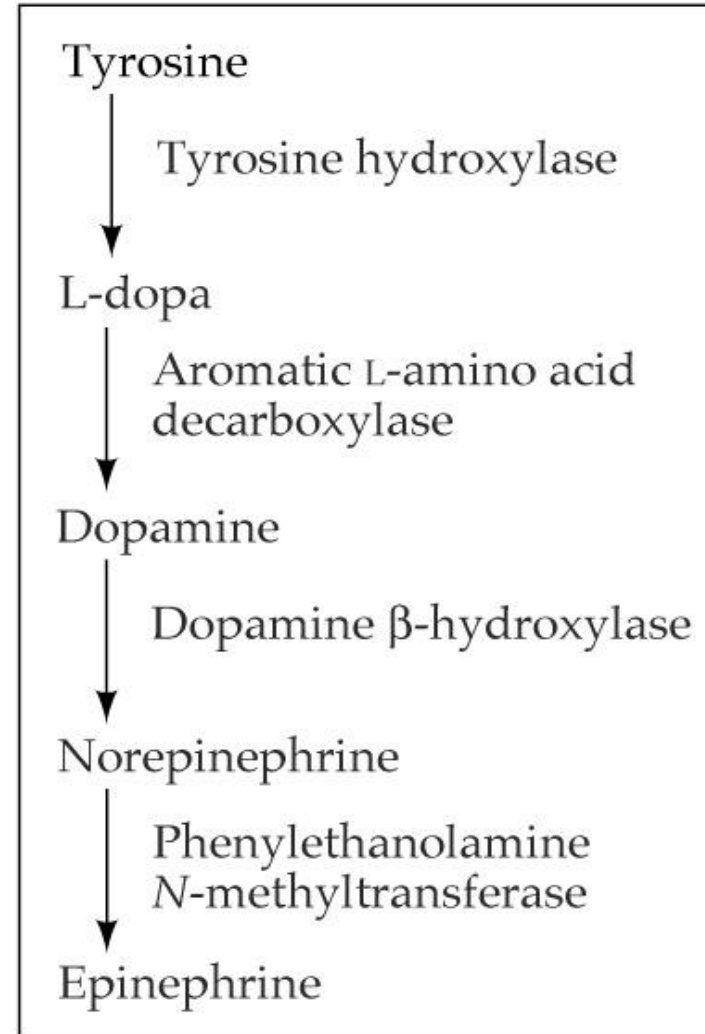


# Norepinephrine System



# Noradrenergic System

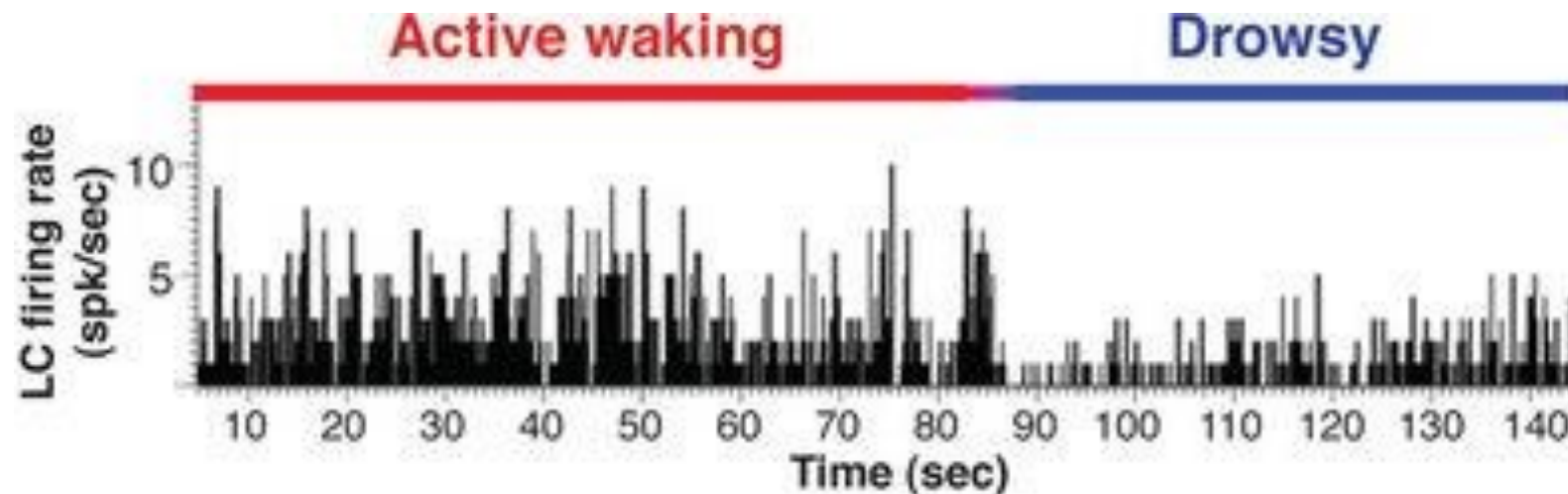
- Norepinephrine(NE): is a catecholamine that is synthesized from Dopamine
- It is released from sympathetic nerves, the adrenal medulla and brain stem neurons
- It acts on both  $\alpha$ -and  $\beta$ -adrenergic receptors (G-protein-coupled receptors)
- NE is believed to play a role in both learning and memory



# Noradrenergic System

- The Noradrenergic System has a very wide- spread projection system
- 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

- Locus ceruleus 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.



# Functions of NE

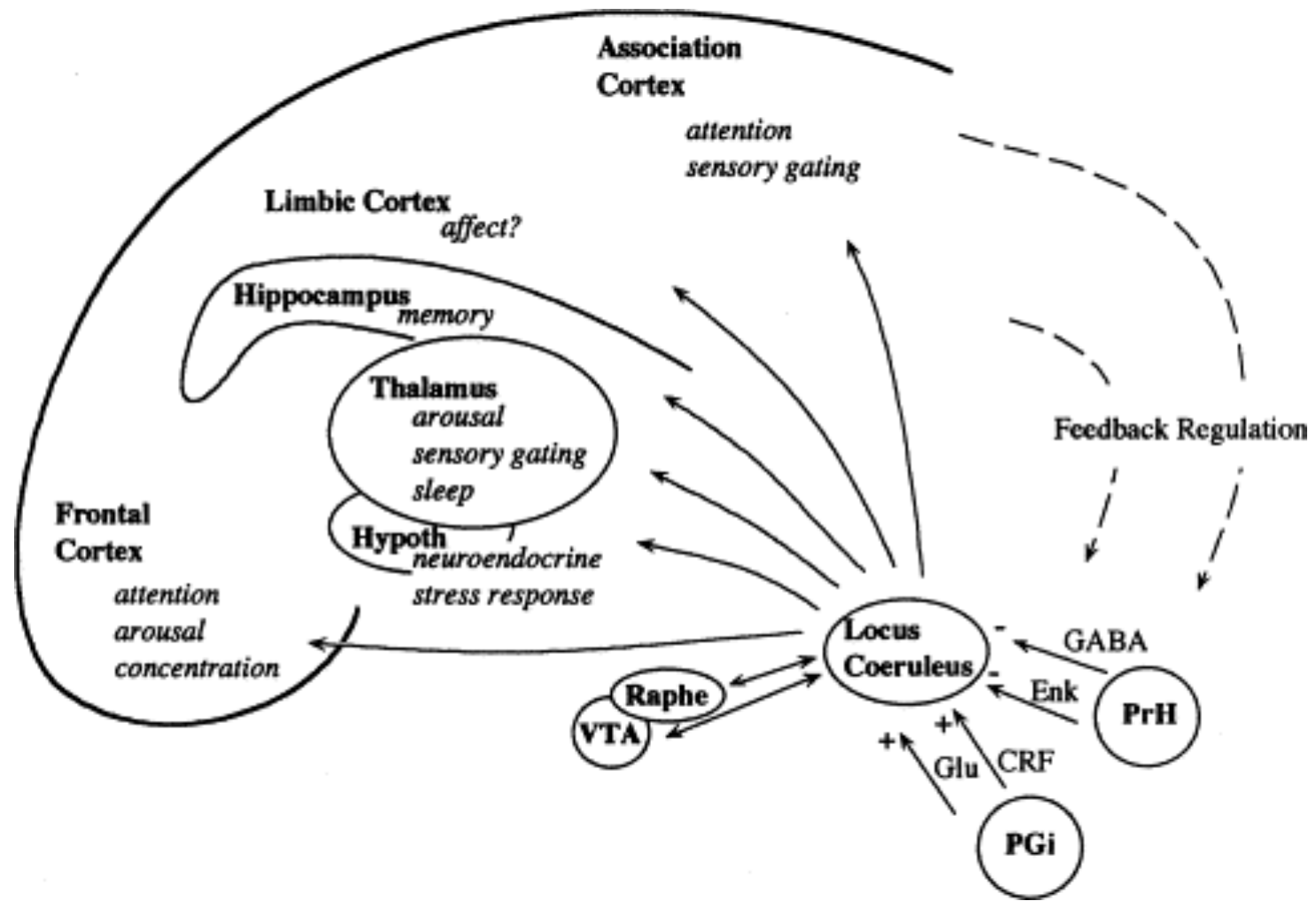
- It constitutes part of the RAS ( Reticular Activating System Attention/Vigilance
- Fight or flight response,
- Learning
- Enhances formation and retrieval of memory
- Aggressive behaviour .

# Disorders of NE

## Norepinehrine (NE) Implicated in Stress-Related Disorders:

- Depression
- Withdrawal from some drugs of abuse
- Anxiety and other stress-related disorders such as panic disorder.





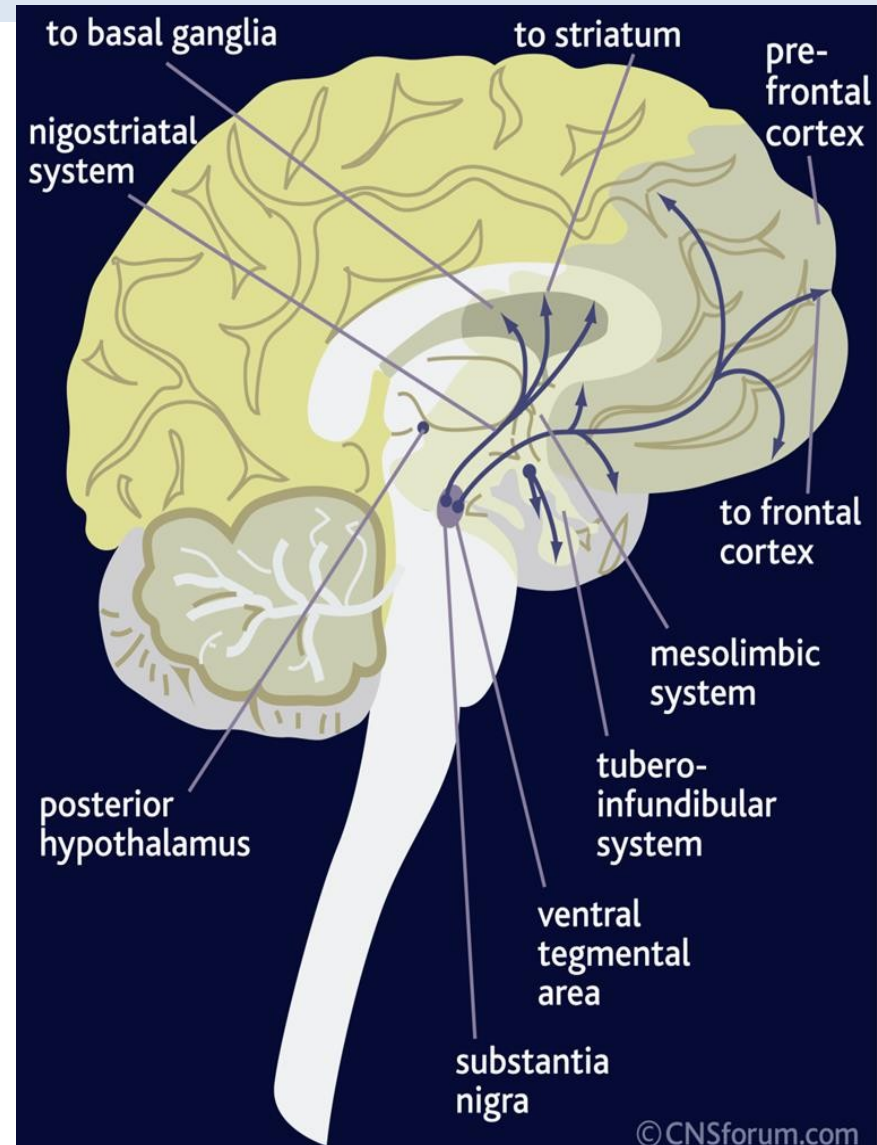
**PGi: Nucleus paraventricularis**  
**PrH: Perirhinal Cortex**

# Dopamine

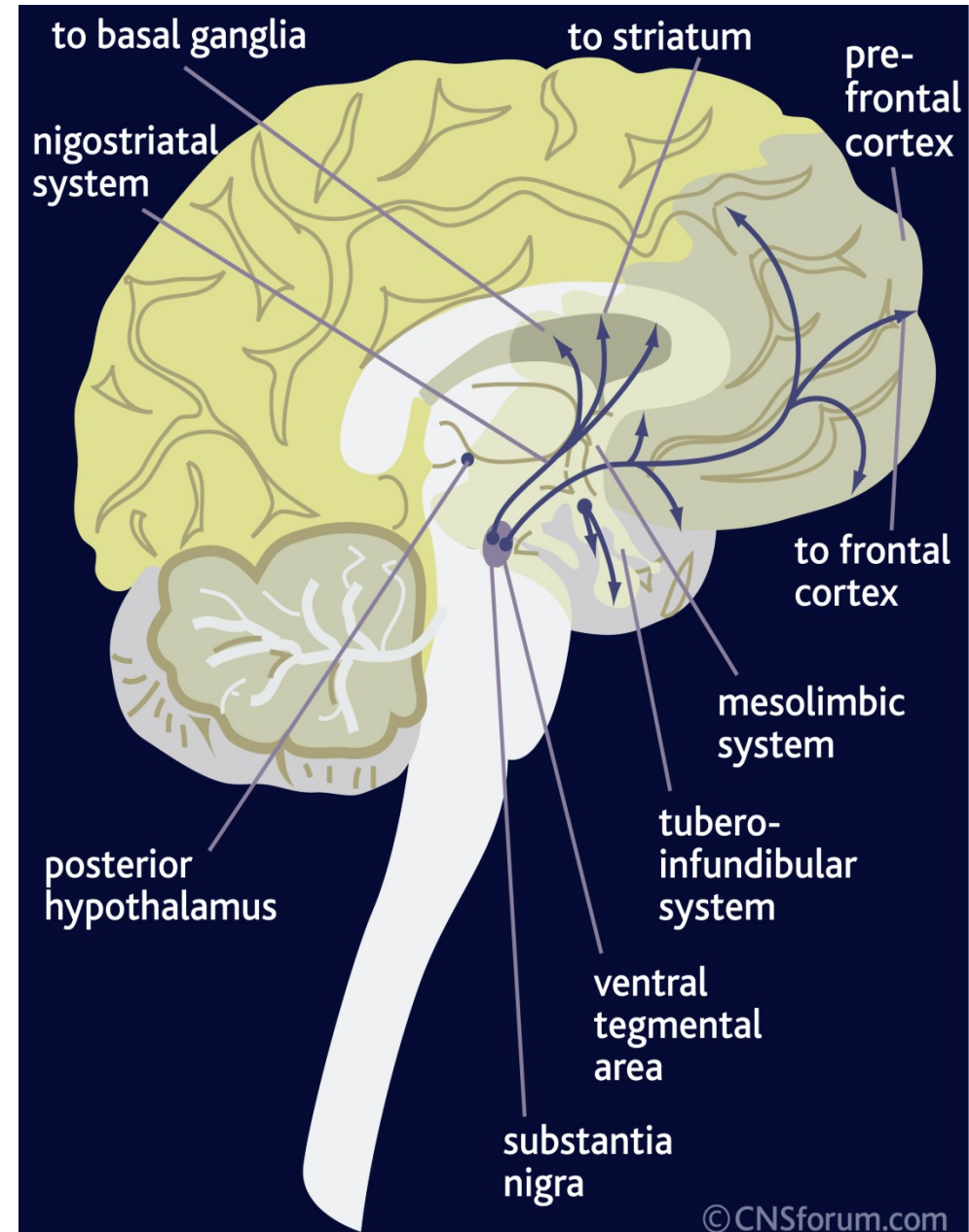
- Dopamine is a catecholamine that is synthesized from tyrosine
- Five dopaminergic receptors (D1-D5) .
- Overstimulation of D2 receptors is thought to be related to schizophrenia

# Dopaminergic Pathway

- Dopamine is transmitted via three major pathways:
- 1- The first (nigro striatal system) extends from the substantia nigra to the caudate nucleus-putamen (neostriatum) and is involved in motor control.



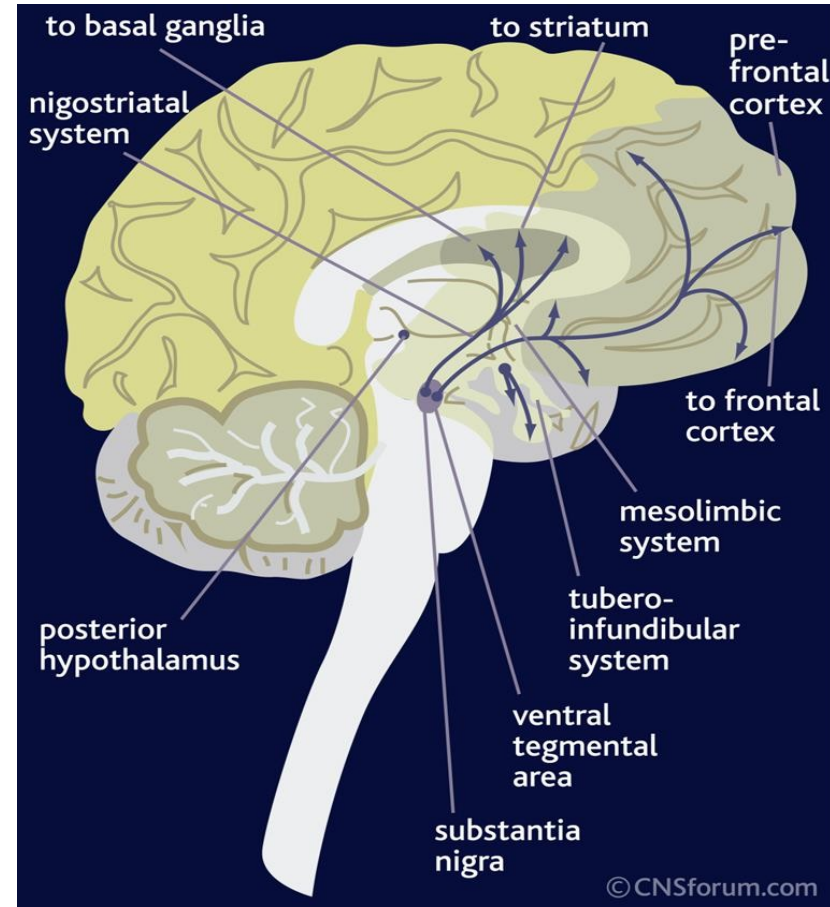
- 2- The second pathway project to the mesolimbic forebrain
- It involved in reward and emotional behavior and addiction
- *Dysfunction is connected to hallucinations and schizophrenia*



## *The Dopaminergic System cont ...*

3- The third pathway, known as the tubero- infundibular system It is concerned with:

- Regulation of secretion of prolactin from the anterior pituitary gland
- Maternal behavior (nurturing)

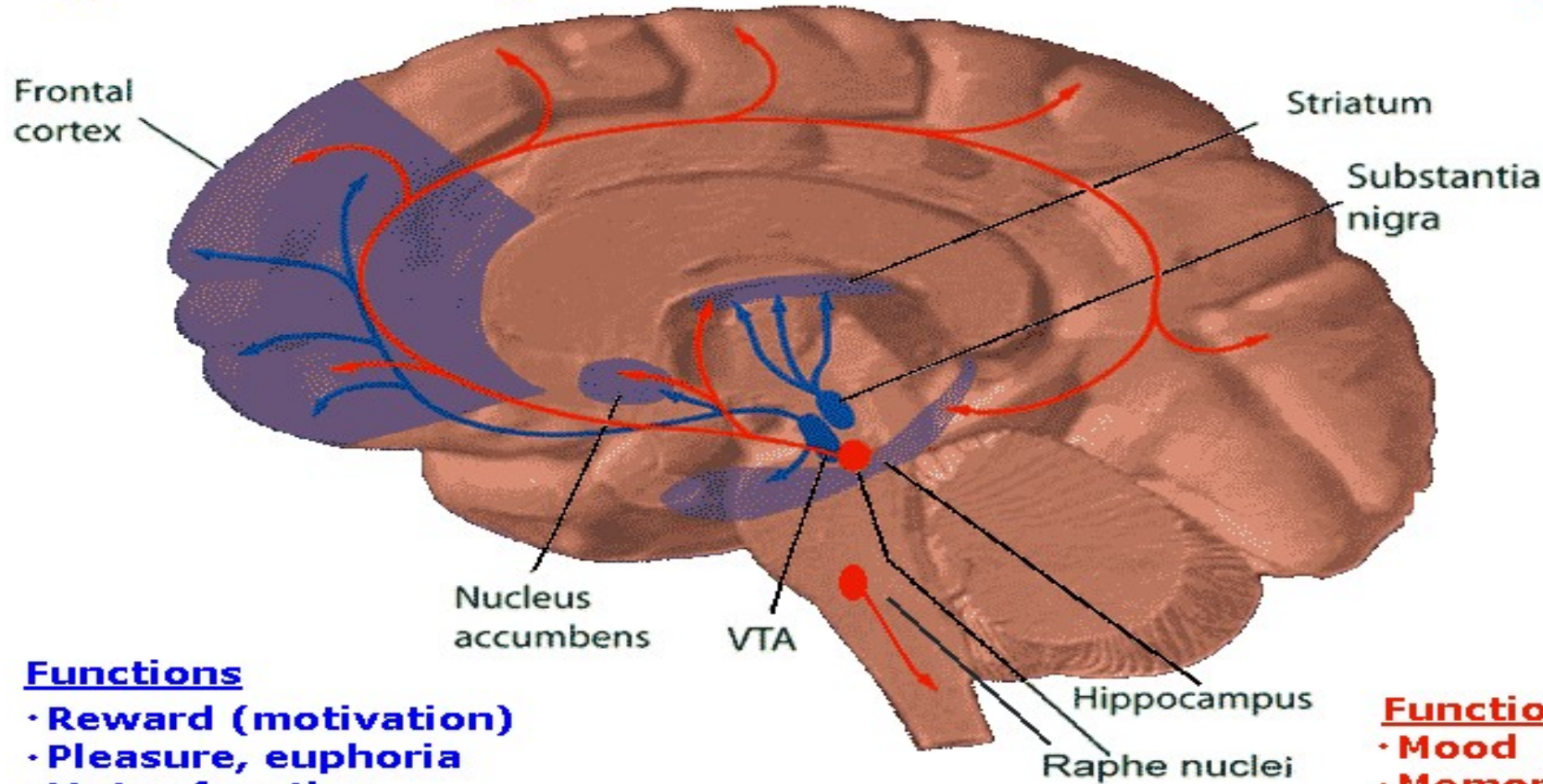




# Dopaminergic Pathways/Functions

## Dopamine Pathways

## Serotonin Pathways



### Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

### Functions

- Mood
- Memory processing
- Sleep
- Cognition



# Dopaminergic Neurons Disorders

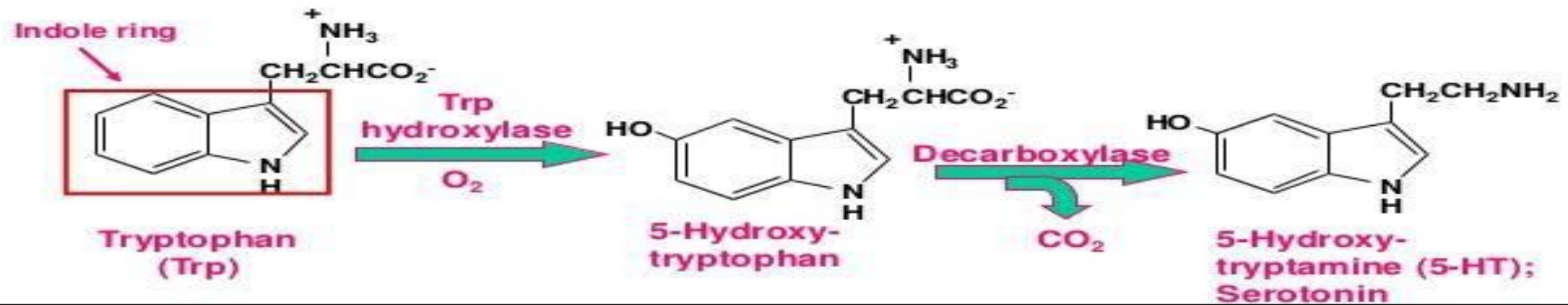
- Schizophrenia.
- Parkinson's Disease.

*Cocaine elevate activity at dopaminergic synapses*



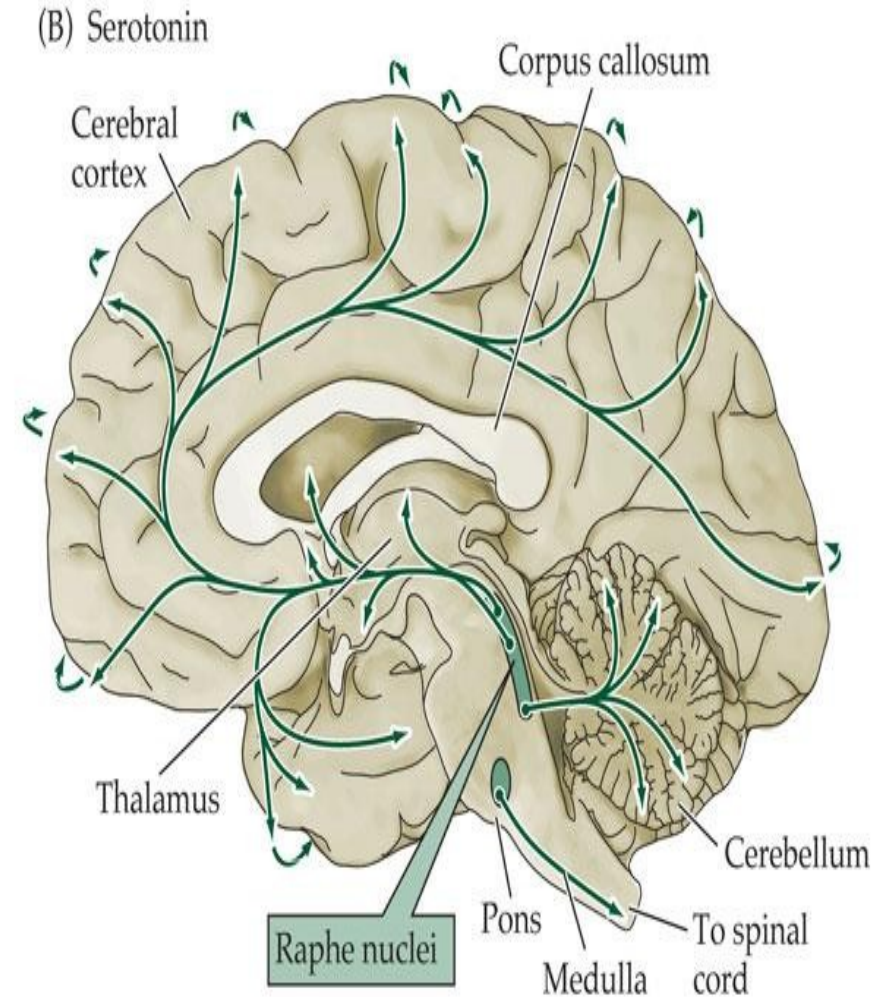
# Serotonin

- 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



# Serotonin

- The serotonin pathways in the brain:
- The principal centers for serotonergic neurons are the rostral and caudal raphe nuclei
- >>>> axons ascend to the cerebral cortex, limbic & basal ganglia
- Serotonergic nuclei in the Brain stem >>>> descending axons (terminate in the medulla & spinal cord)



# Serotonin (5-HT) Functions & Disorders

## Functions:

- Improved mood
- Decrease appetite .
- Sleep

## Disorders:

- Depression
- Anxiety
- *Drugs (e.g. Prozac) that prolong serotonin's actions relieve symptoms of depression & obsessive disorders*

Neurotransmitter	c effect	from	synthesis	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 $\alpha$ & beta $\beta$ 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.
ii. Norepinephrine	Excitatory	Tyrosine, found in pons. Reticular formation, locus coeruleus, thalamus, mid-brain	Begins inside axoplasm of adrenergic nerve ending is completed inside the secretory vesicles	$\alpha_1$ $\alpha_2$ $\beta_1$ $\beta_2$		
iii. Dopamine	Excitatory	Tyrosine	CNS, concentrated in basal ganglia and dopamine pathways e.g. nigrostriatal, mesocorticolimbic and tuberohypophyseal pathway	D <sub>1</sub> to D <sub>5</sub> receptor	Same as above	Sensory motor Cognitive/emotional behavior Endocrine Hypothalamic  Decreased dopamine in parkinson's disease. Increased dopamine 36 concentration

er	effect		synthesis	receptor		
3. serotonin (5HT)	Excitatory	Tryptophan	CNS, Gut (chromaffin cells) Platelets & retina	5-HT <sub>1</sub> to 5-HT <sub>7</sub> 5-HT <sub>2A</sub> 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. Glutamate	Excitatory 75% of excitatory transmission in the brain	By reductive amination of Krebs's cycle intermediate $\alpha$ - 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 <sup>+</sup> dependent uptake system in neurons and neuroglia.	Long term potentiation involved in memory and learning by causing Ca <sup>++</sup> influx.
5. Gama amino butyric acid(GABA)	Major inhibitory mediator	Decarboxylation of glutamate by glutamate decarboxylase (GAD) by GABAergic neuron.	CNS	GABA - A increases the Cl <sup>-</sup> 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 <sup>-</sup> entry into the cell & cause soothing effects. GABA - B cause increase conductance of K <sup>+</sup> into the cell.



**THANK YOU**