Brain Neurotransmitters

Dr. Salah Elmalik

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
gonadotropnin-releasing hormone	growth hormone-releasing hormone	luteinizing hormone	vasoactive intestinal peptide

Soluble Gases	
Nitric Oxide (NO)	Carbon Monoxide

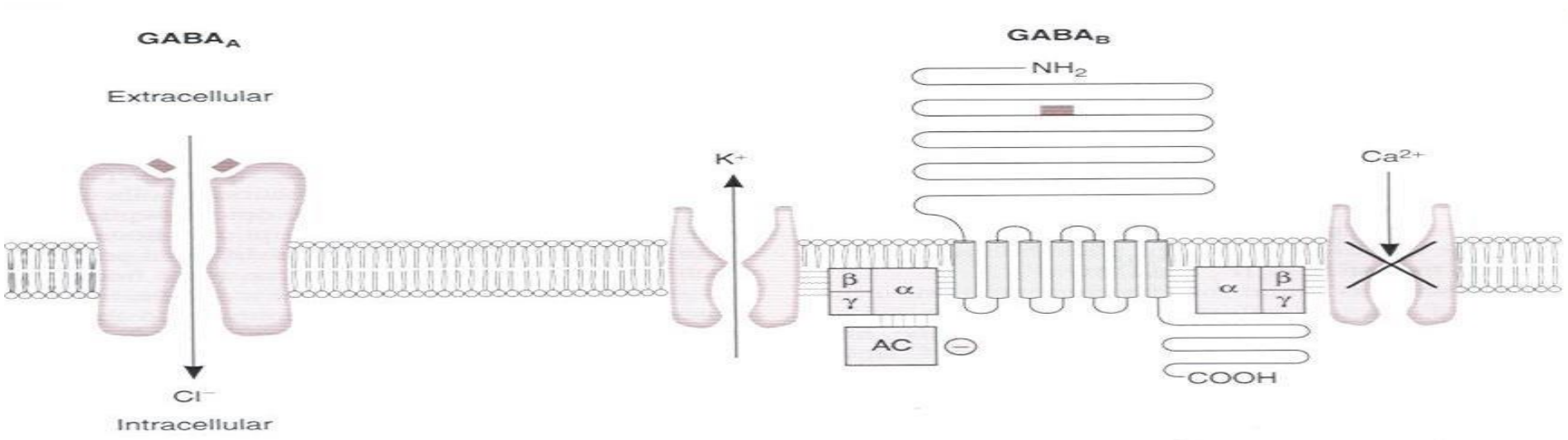
Some of the Brain Neurotransmitters

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

Classes of Receptors

- **Metabotropic** = trans membrane receptor acts through a secondary messenger

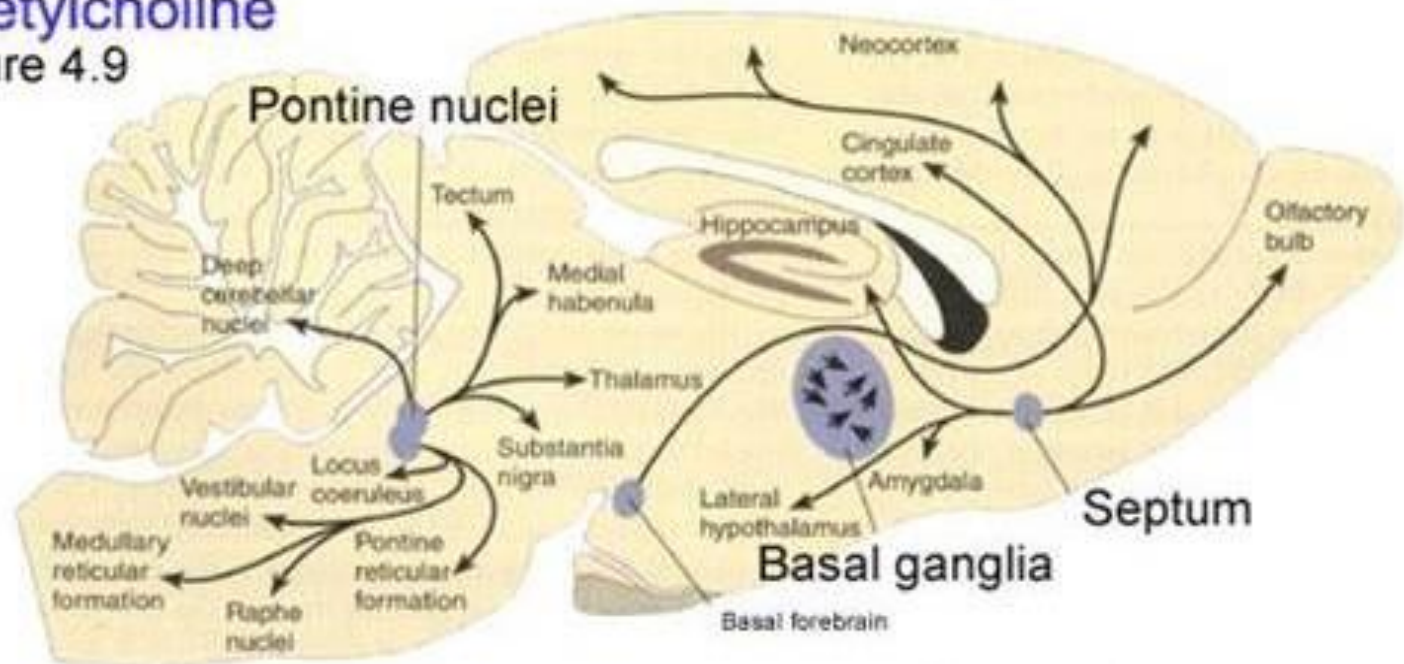
- **Ionotropic** = Ligand gated ion channel



Major Brain Pathways

Acetylcholine

Figure 4.9

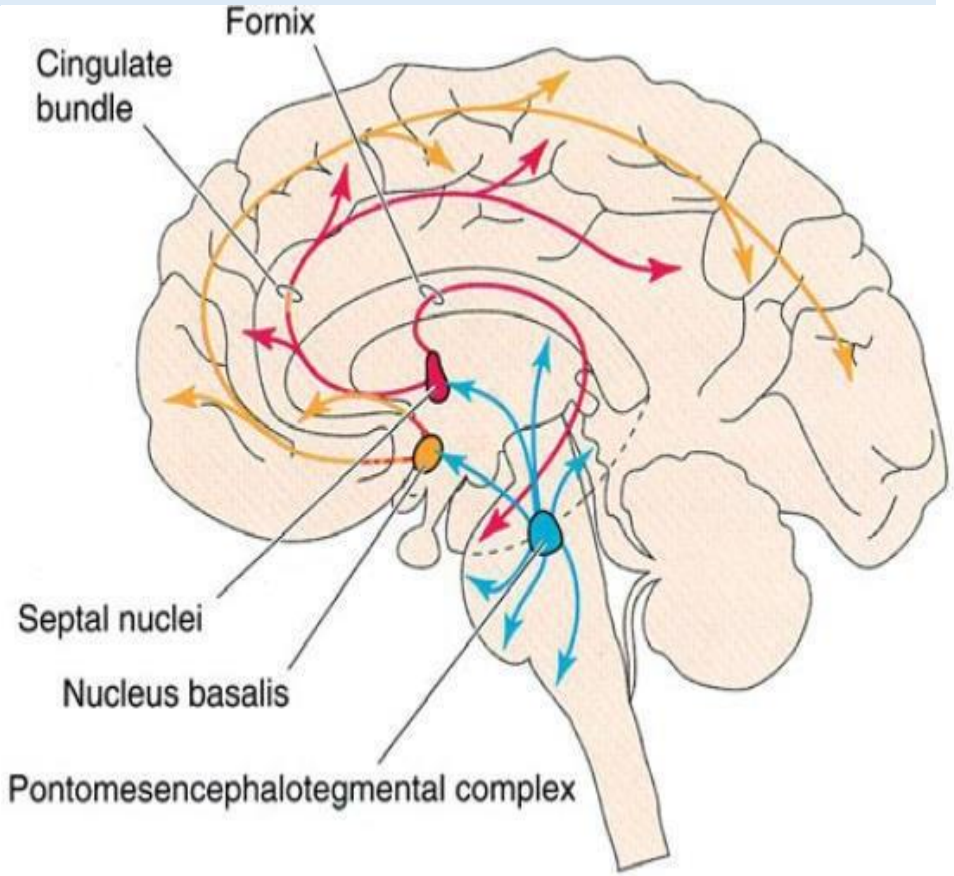


Cholinergic System

- 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 Myenert and septal nuclei)

- (2) Ponto-Mesencephalic Cholinergic Complex

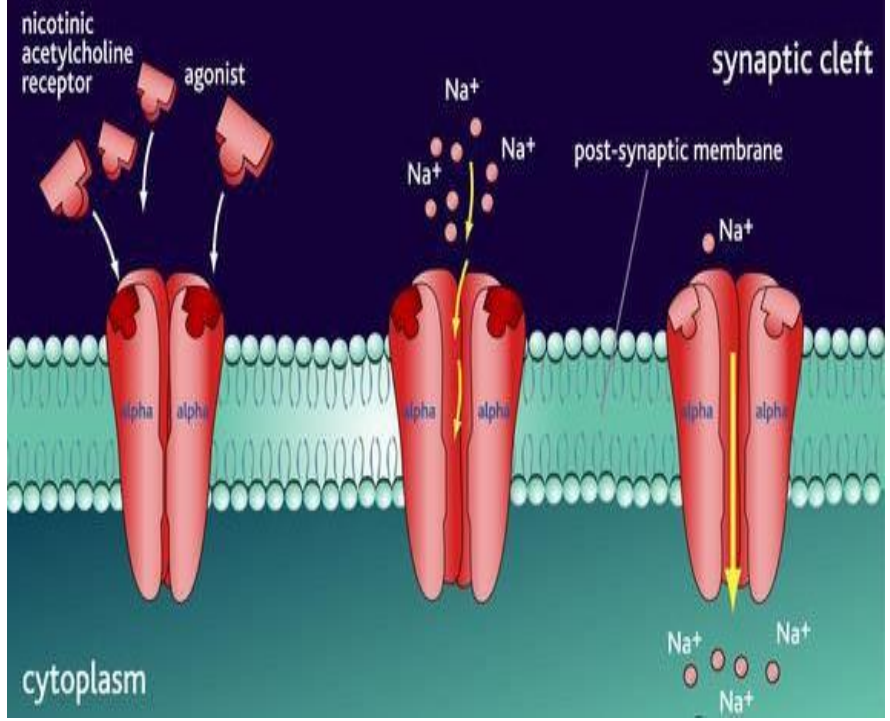


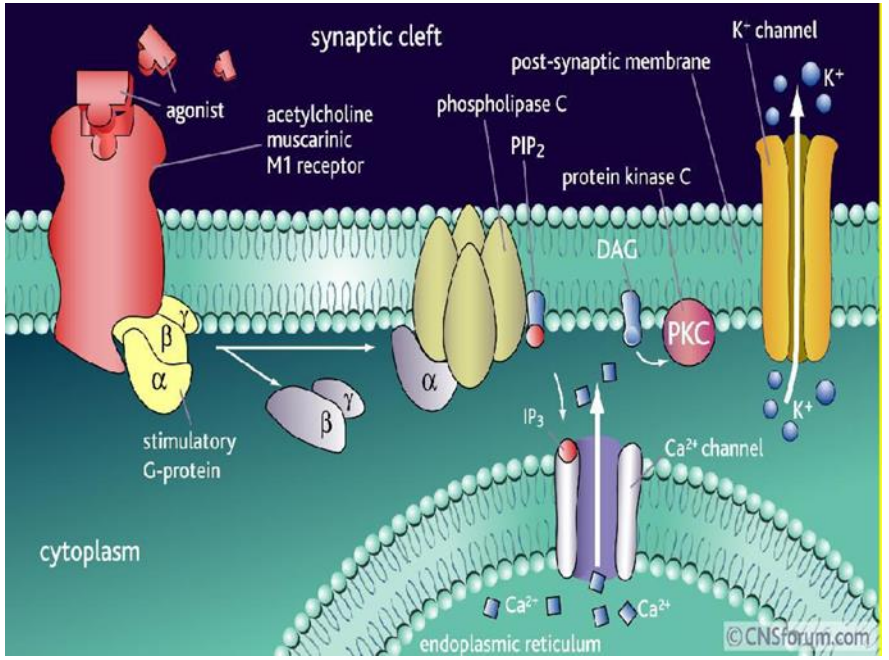
Acetylcholine Receptors

- Acts on 2 cholinergic receptors:

- ❶Nicotinic (ionotropic) (antagonist-Curare): excitatory

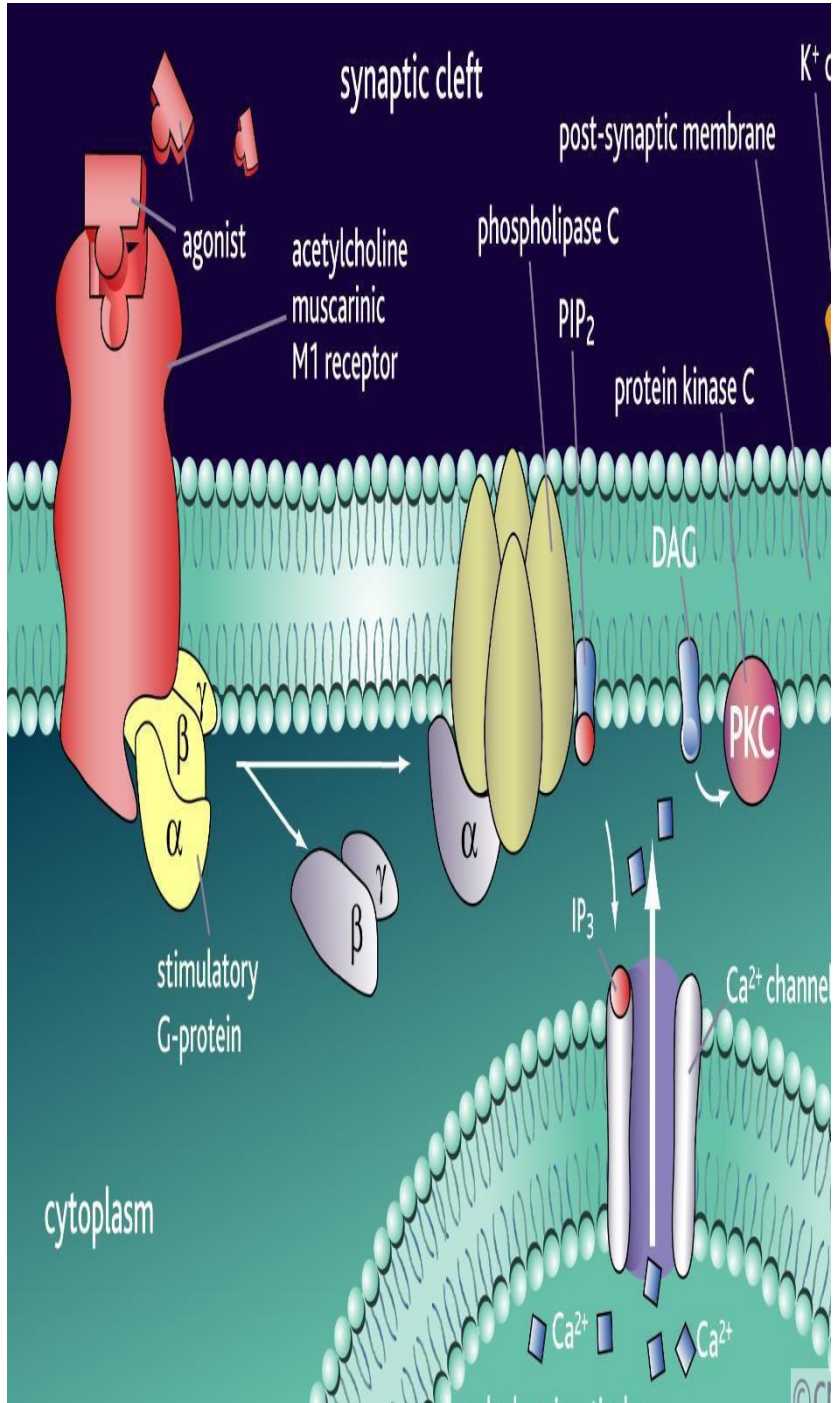
- ❷Muscarinic (metabotropic) (antagonist- Atropine): •Excitatory or inhibitory •
- Five subtypes (M1-M5): all are found in the brain but M1 is abundant.





Muscarinic Receptors

- M1 receptors most involved in cognitive functioning (evidence from Knockout mice and pharmacologic human studies with M1blocking 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
  - Sleeping
  - Dreaming.
- 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

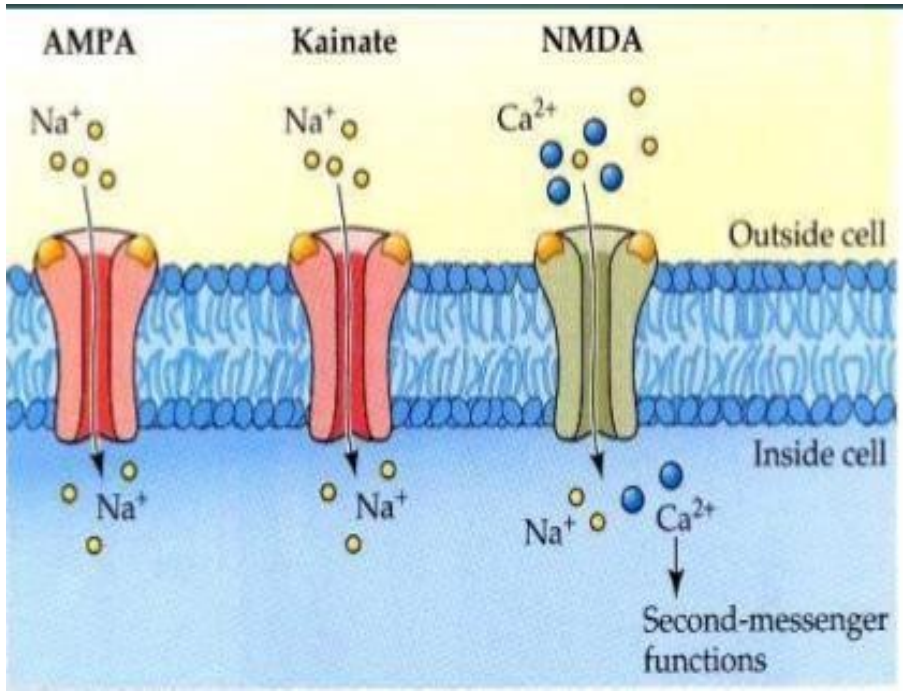
- Are widely distributed in the brain; they are of two types:

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.

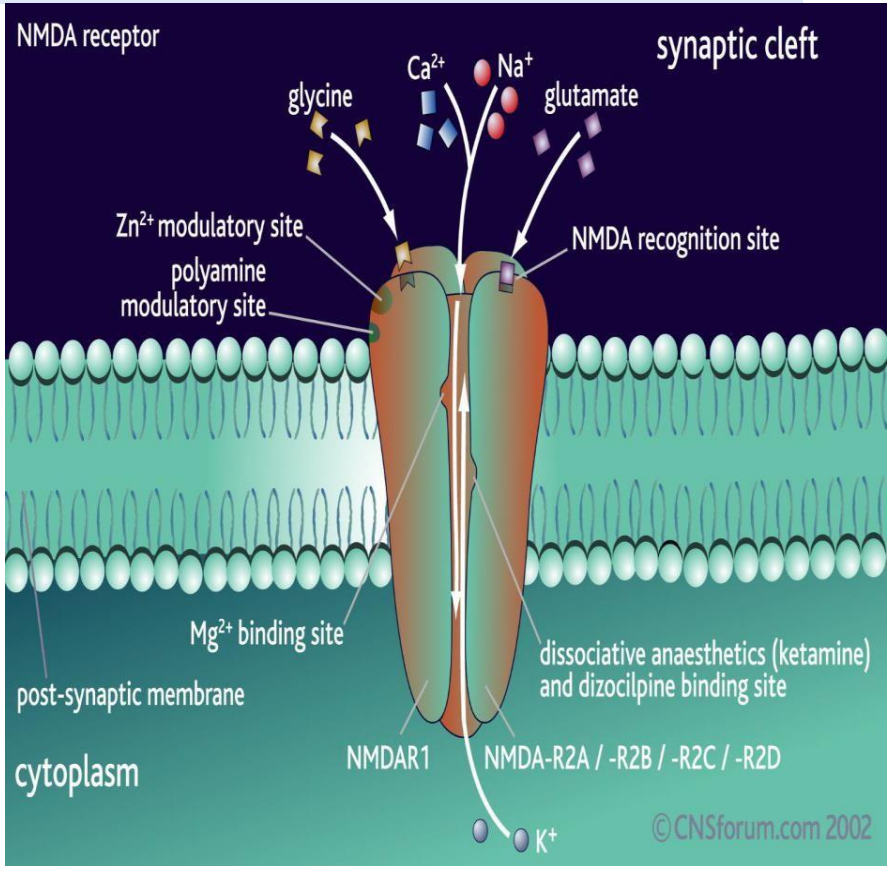
2. Ionotropic receptors (ligand-gated ion channels).

- Three types: •
- AMPA receptors (a-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 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 e.g. AMPA) NMDA Receptors
- ❑ Excitatory post synaptic potential induced by activation of NMDA receptor is slower than that elicited by activation of AMP and kainate receptors



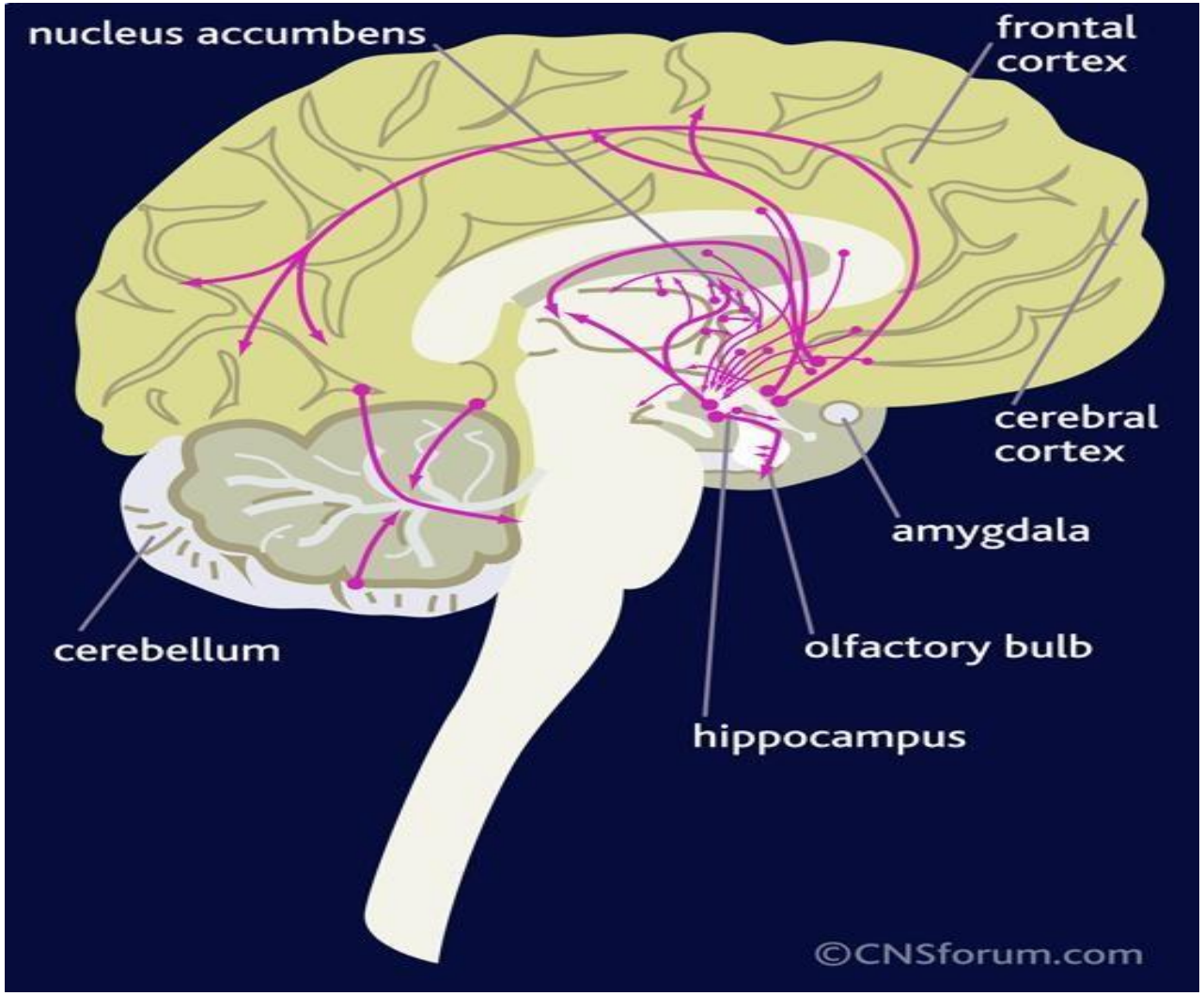
Functions & Disorders Of Glutamate

- 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) , and Alzheimer's diseases, it acts as an excitotoxin ,producing excessive influx of calcium into the neurons and causing neuronal death .

GABAergic System

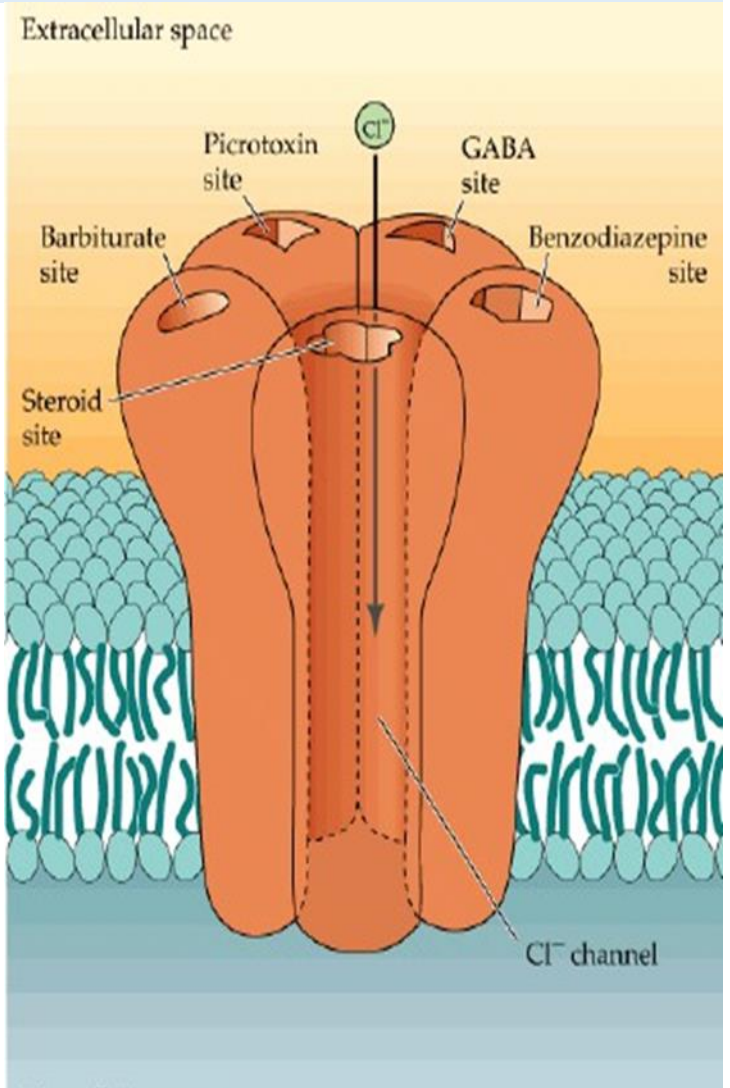


GABAergic System

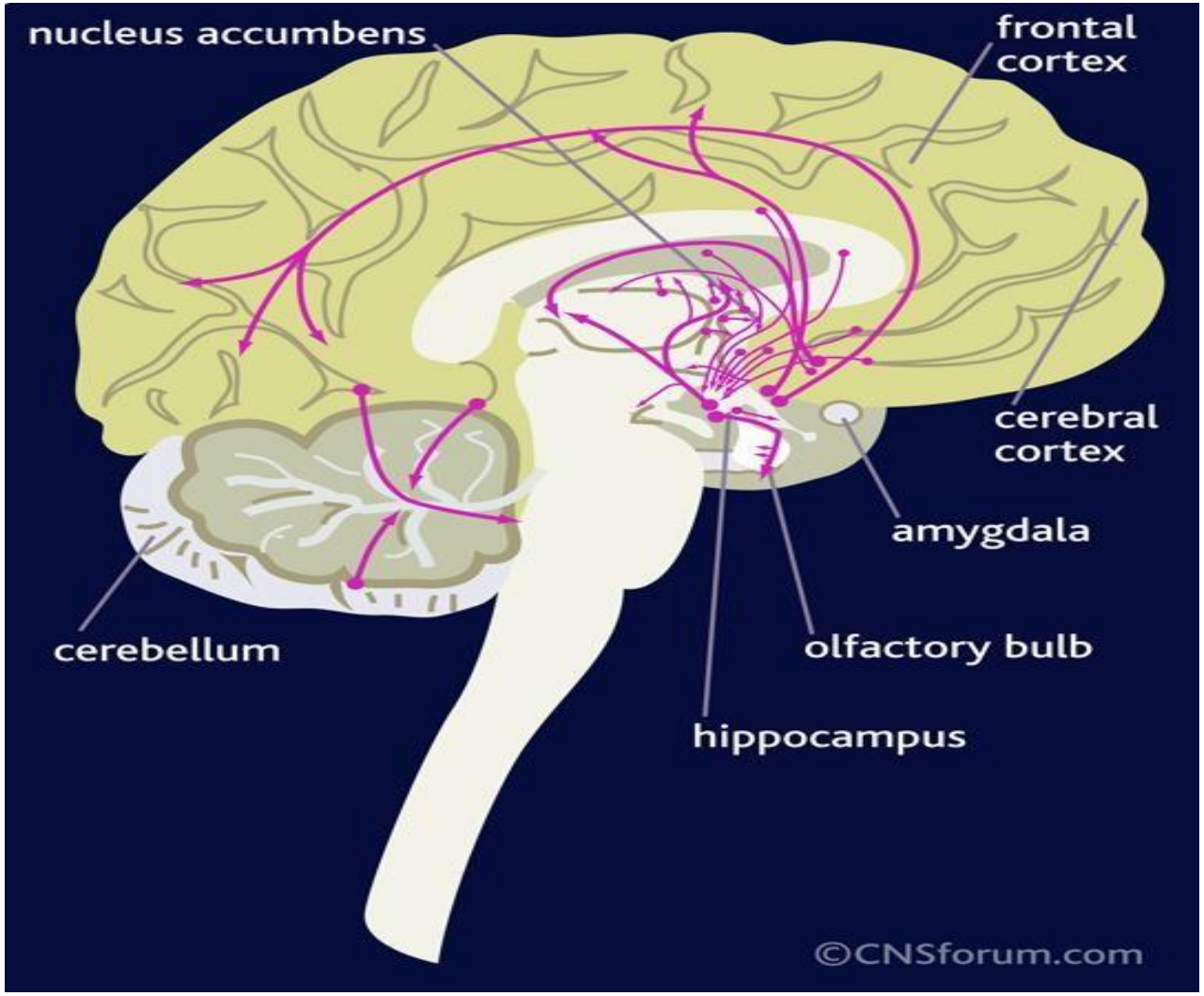
- GABA is the main inhibitory neurotransmitter in the central nervous system (CNS).
- GABAergic inhibition is seen at all levels of the CNC
- (Hypothalamus, hippocampus,cerebral cortex and cerebellar cortex.
- GABA interneurons are abundant in the brain, with 50% of the inhibitory synapses in the brain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

Gamma Aminobutyric acid (GABA)

- Formed by decarboxylation of glutamate.
- Three types of GABA receptors
  - e.g. $GABA_{A\ B\ \&\ C}$.
- $GABA_{A\ \&\ B}$ 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)



GABAergic System



Functions & Disorders of GABAergic System

Functions:

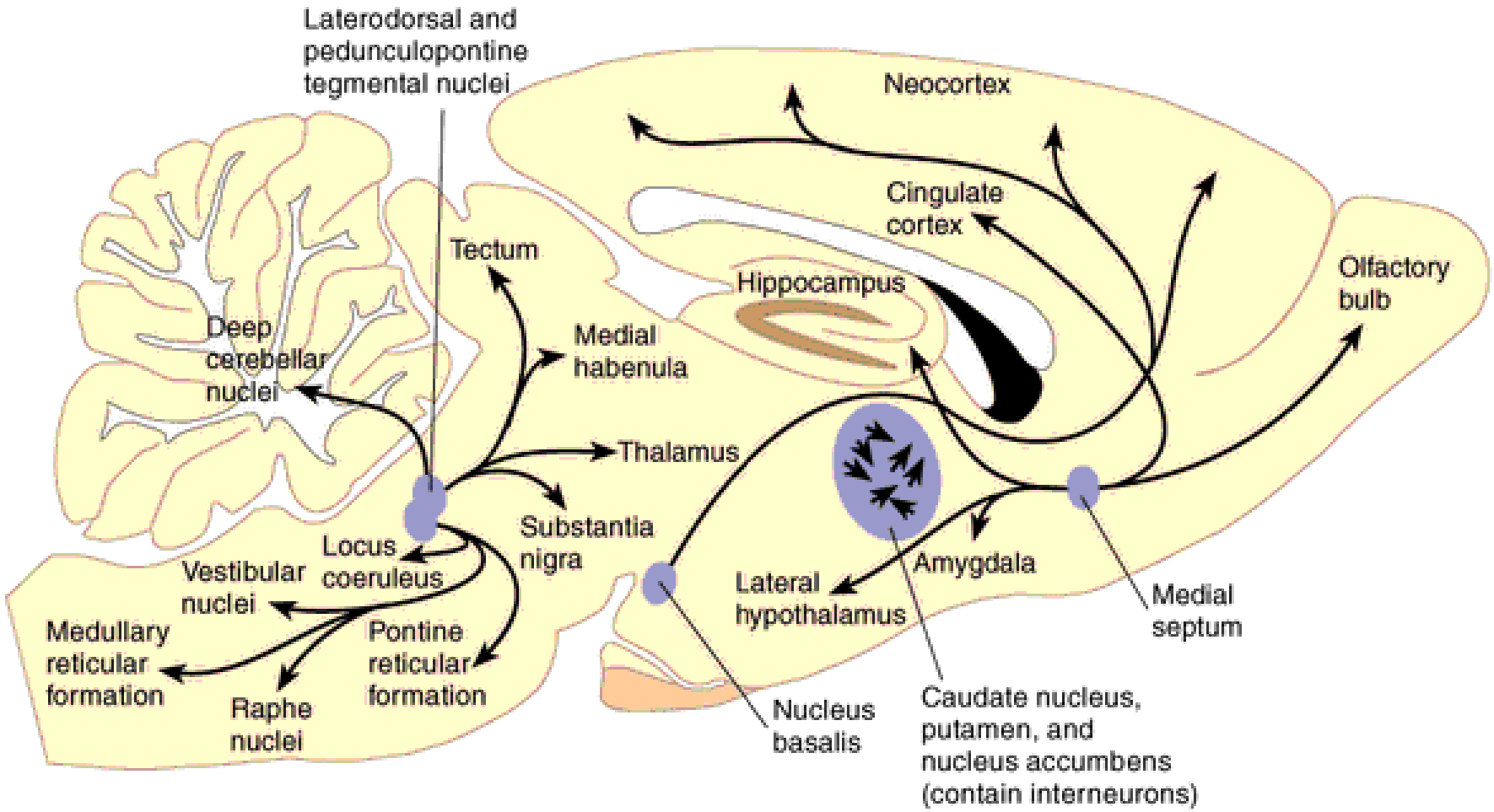
- Presynaptic inhibition
- GABAA receptors in CNS are chronically stimulated to regulate neuronal excitability.

Disorders:

-under activity of GABA leads to seizures.

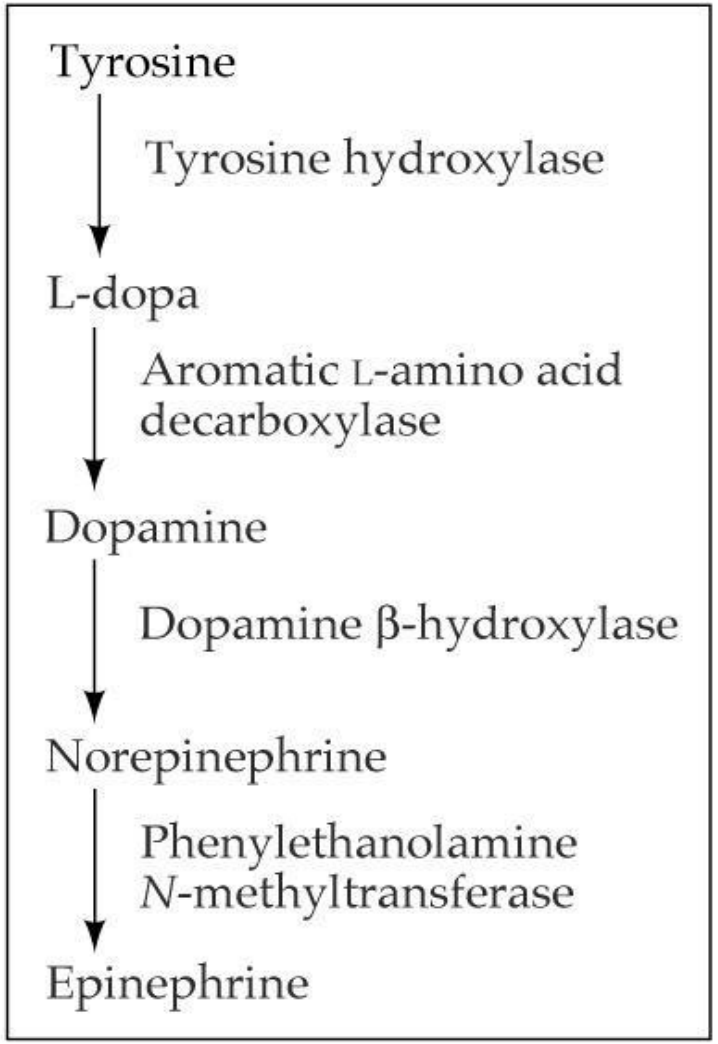
Depressant drugs (alcohol, barbiturates) work by increasing GABA activity

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 α-and β-adrenergic receptors (G-protein-coupled receptors)
- NE is believed to play a role in both learning and memory



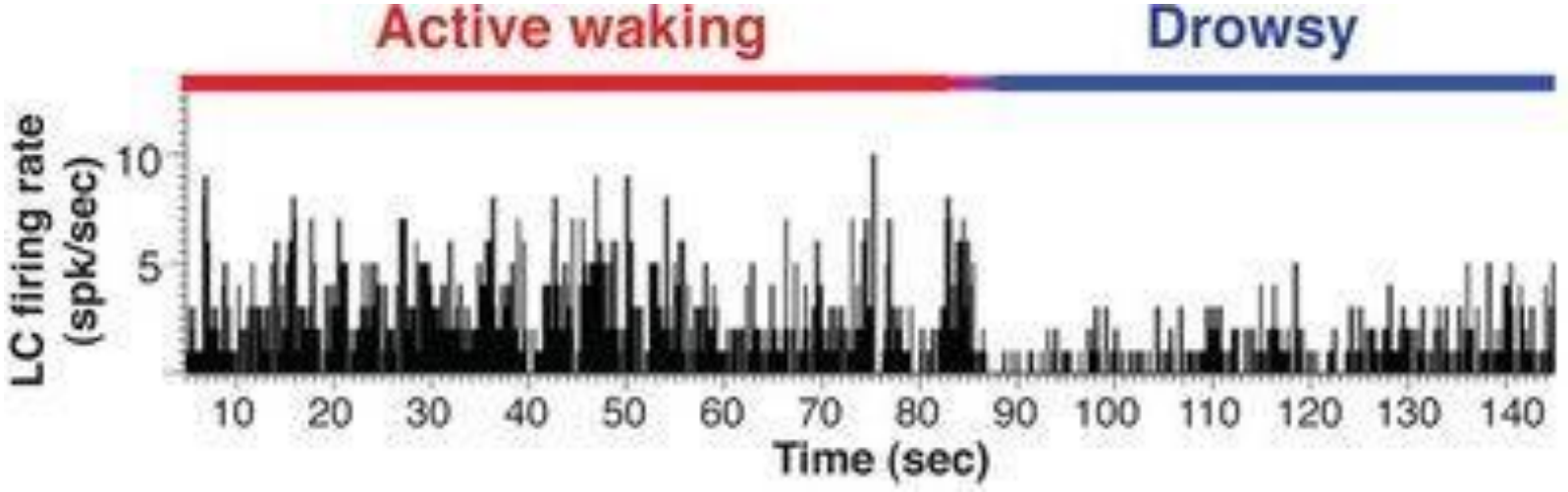
Noradrenergic System

- 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.



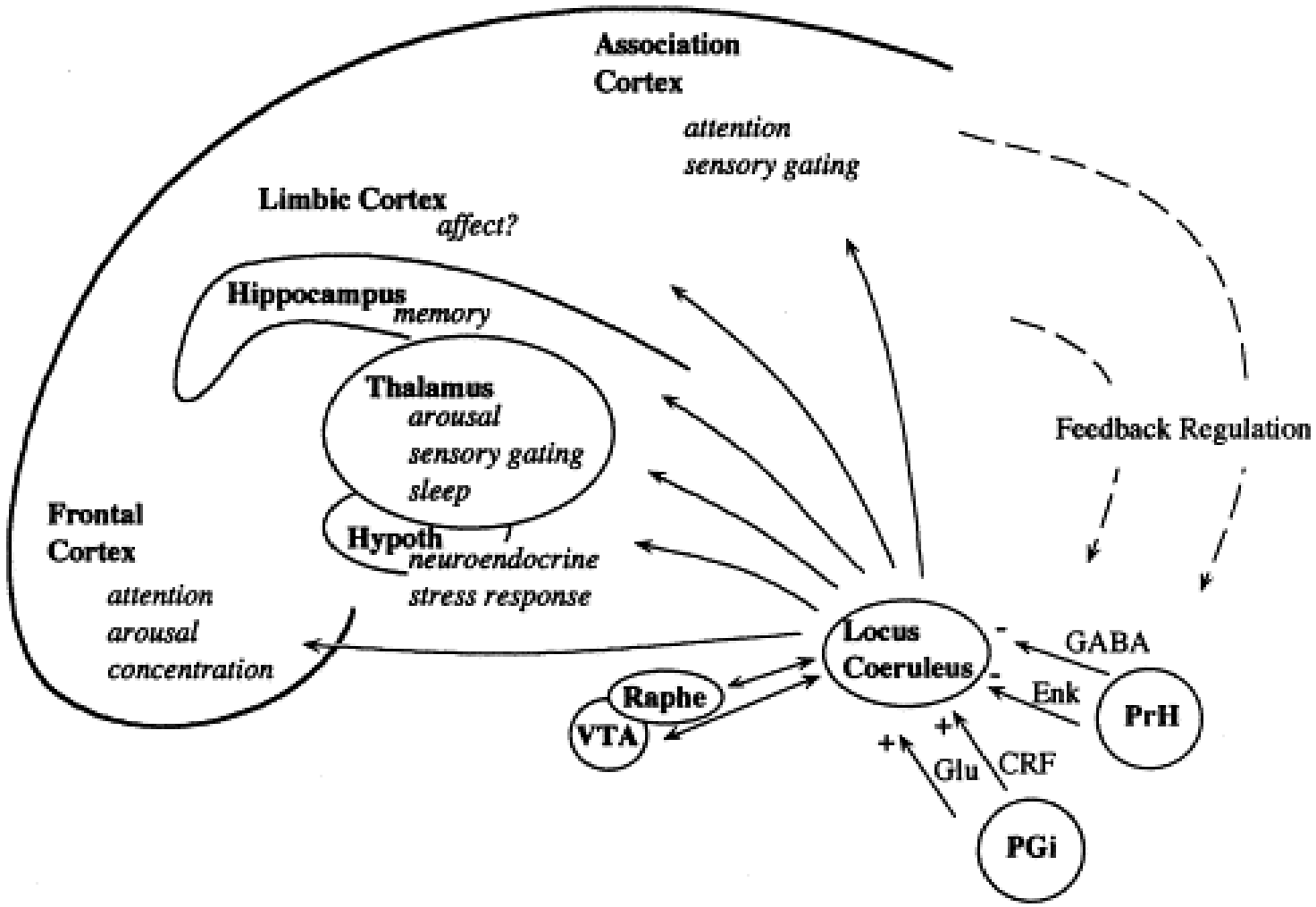
Functions of NE

- It constitutes part of the RAS (Reticular Activating System Attention/Vigilance
- Fight or flight response,
- learning
- aggressive behaviour .

Disorders of NE

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

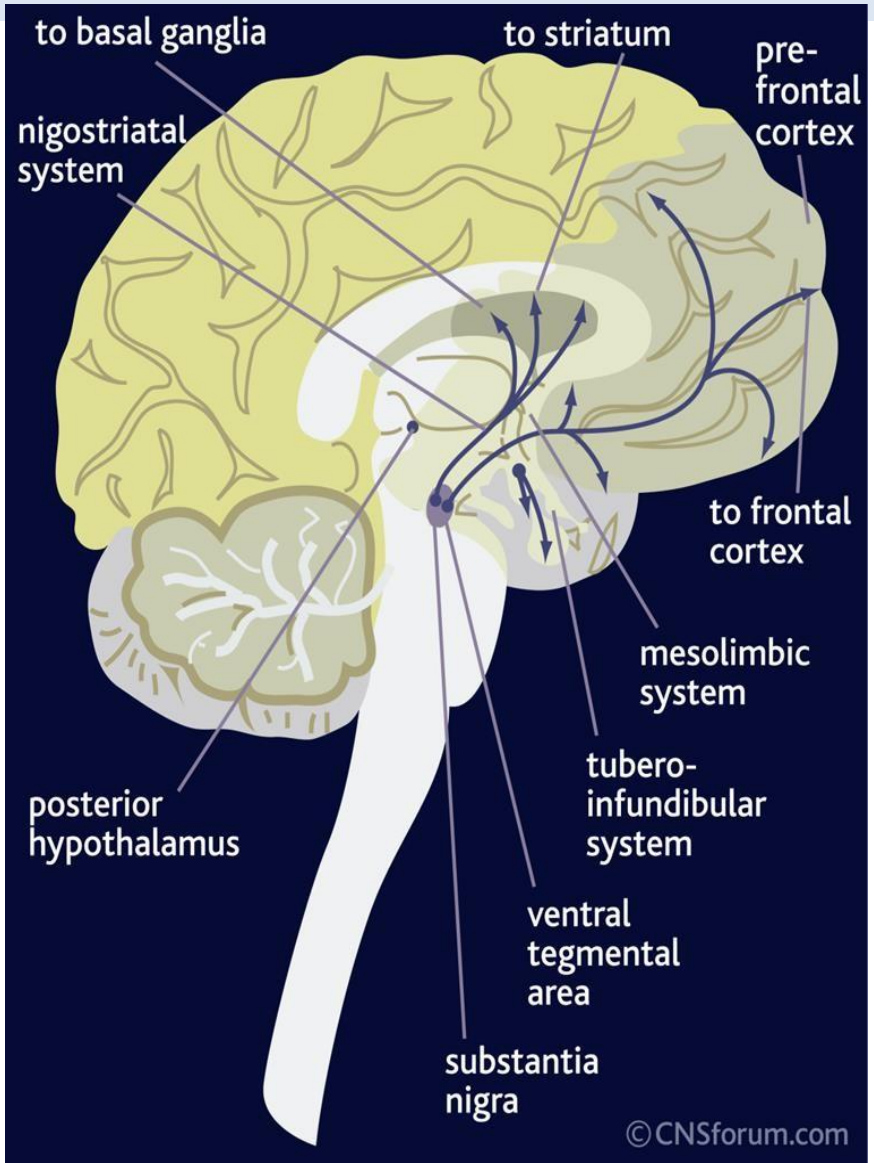
Dopamine

- 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

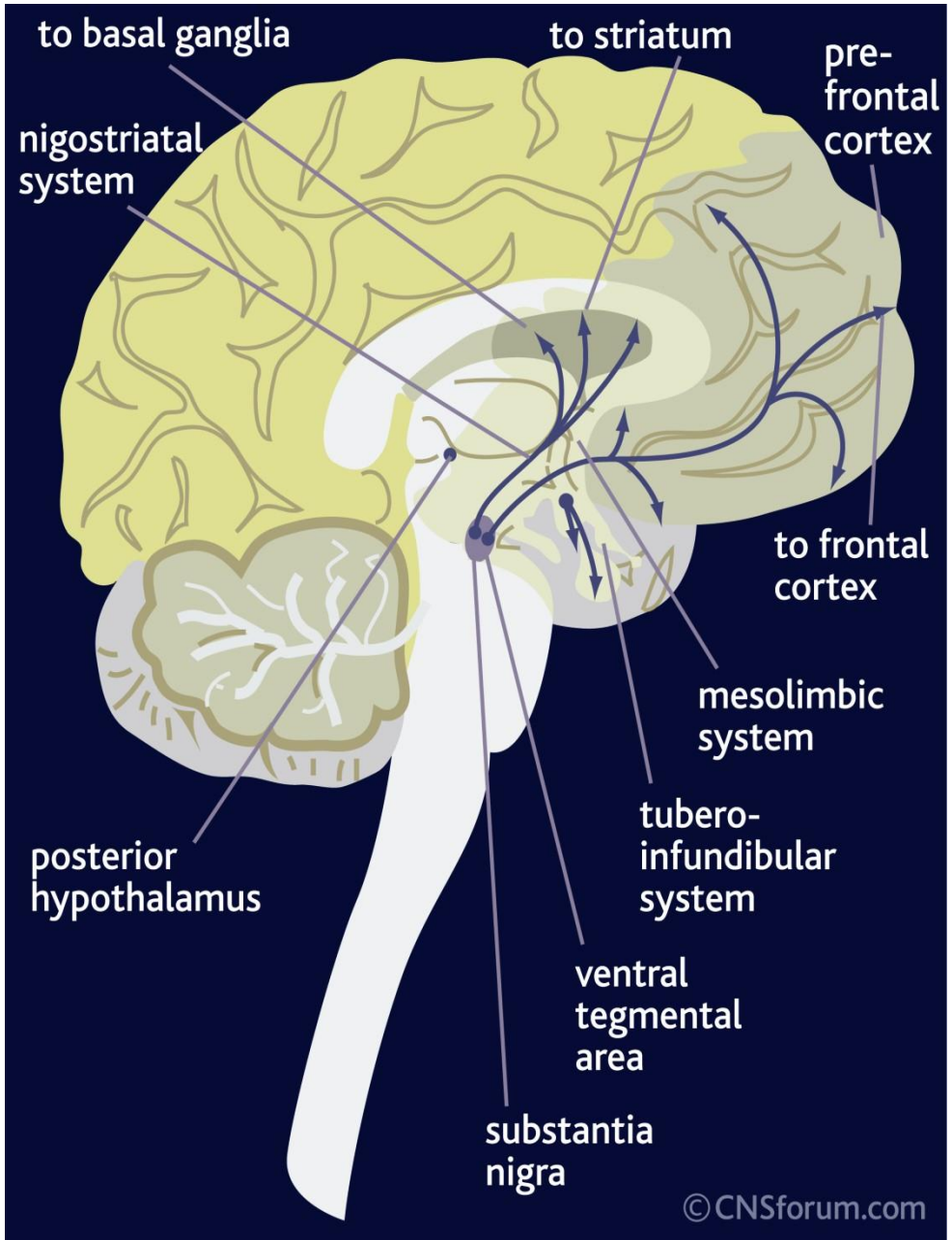
Dopaminergic Pathway

- 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.



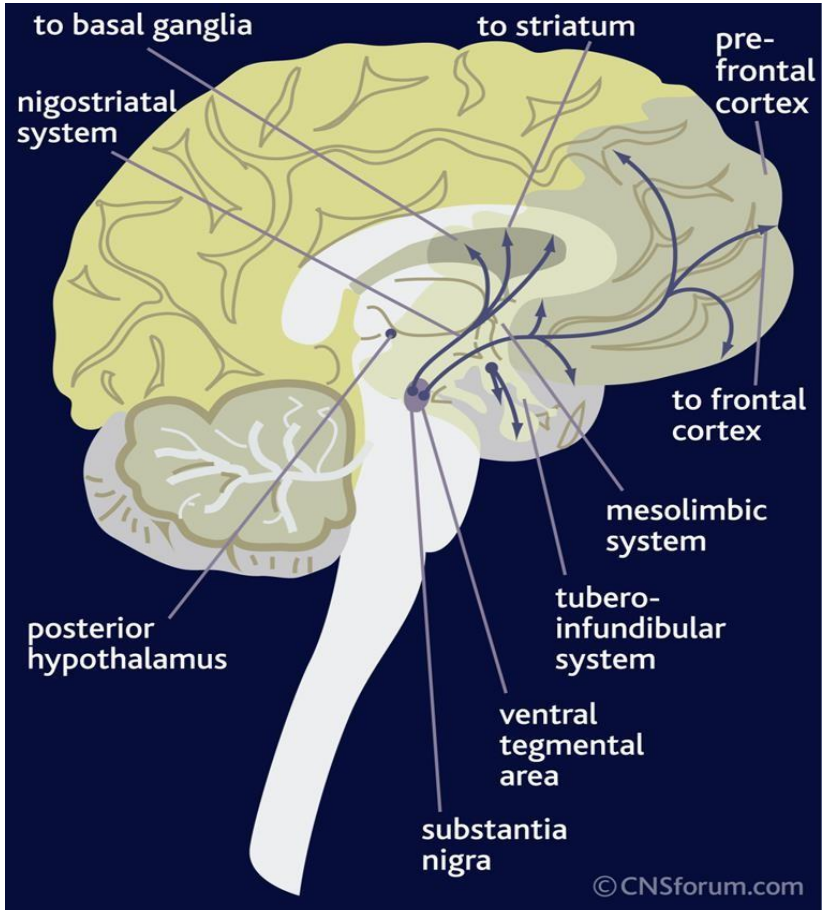
- 2- The second pathway project to the mesolimbic forebrain
- It involved in reward and emotional behavior and addiction
- *Dysfunction is connected to hallucinations and schizophrenia*



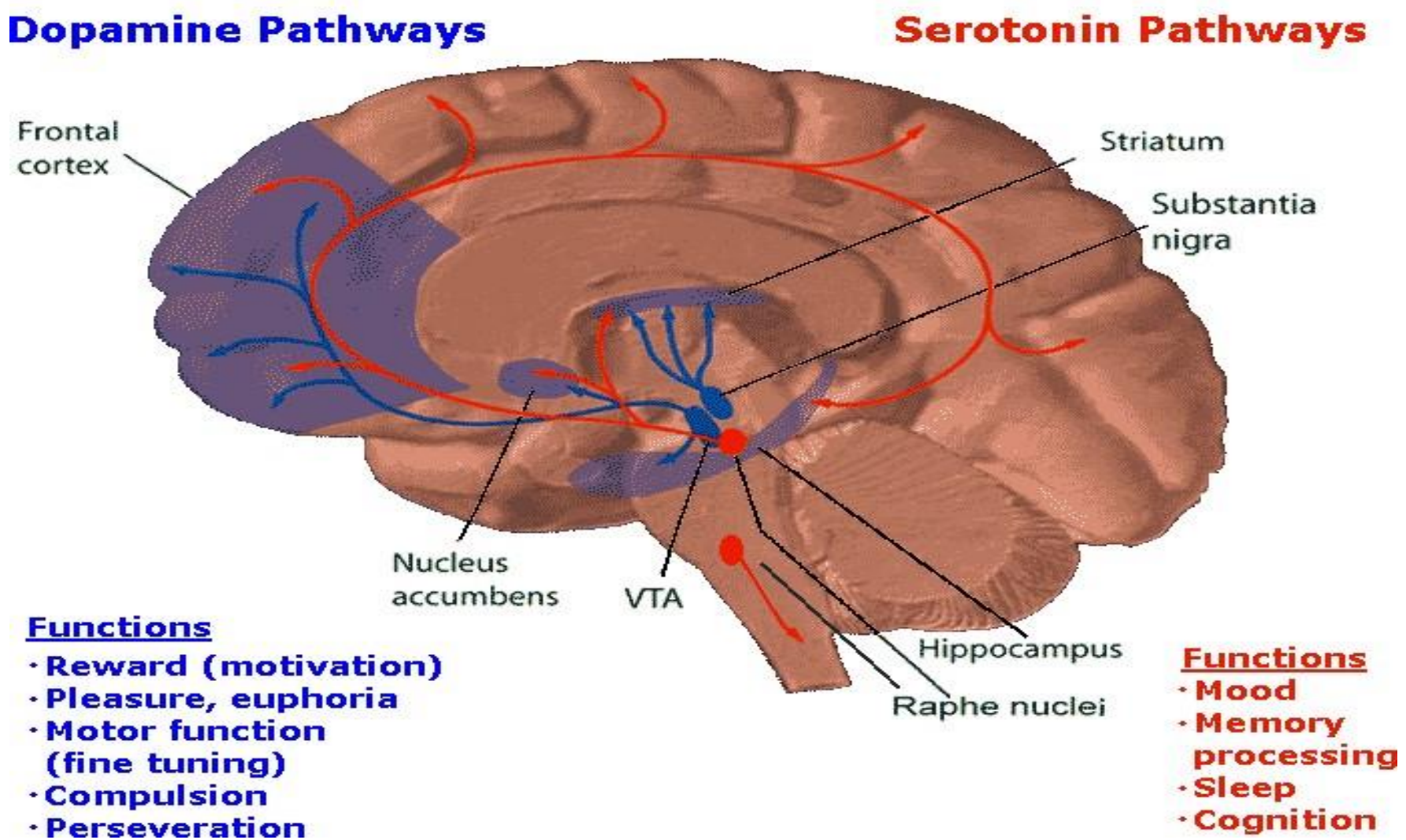
The Dopaminergic System cont …

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



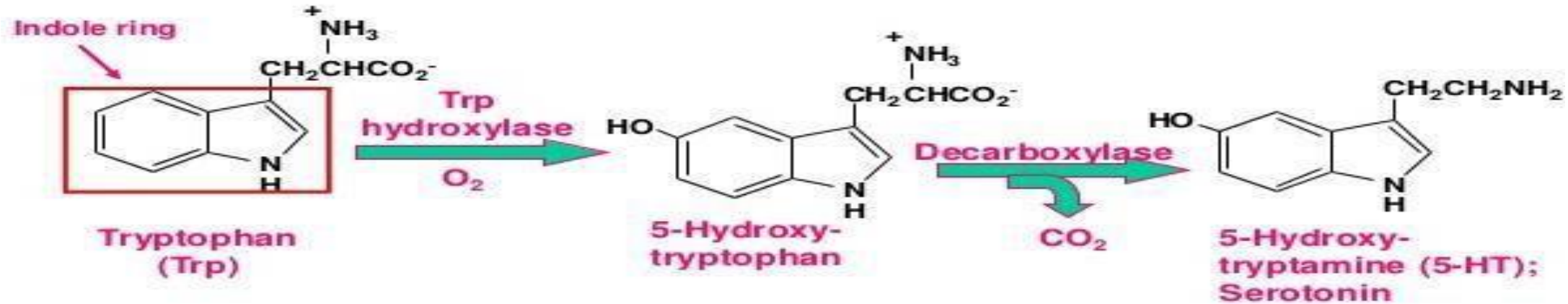
Dopaminergic Neurons Disorders

- Schezophrenia.
- Parkinson's Disease.

Cocaine elevate activity at dopaminergic synapses

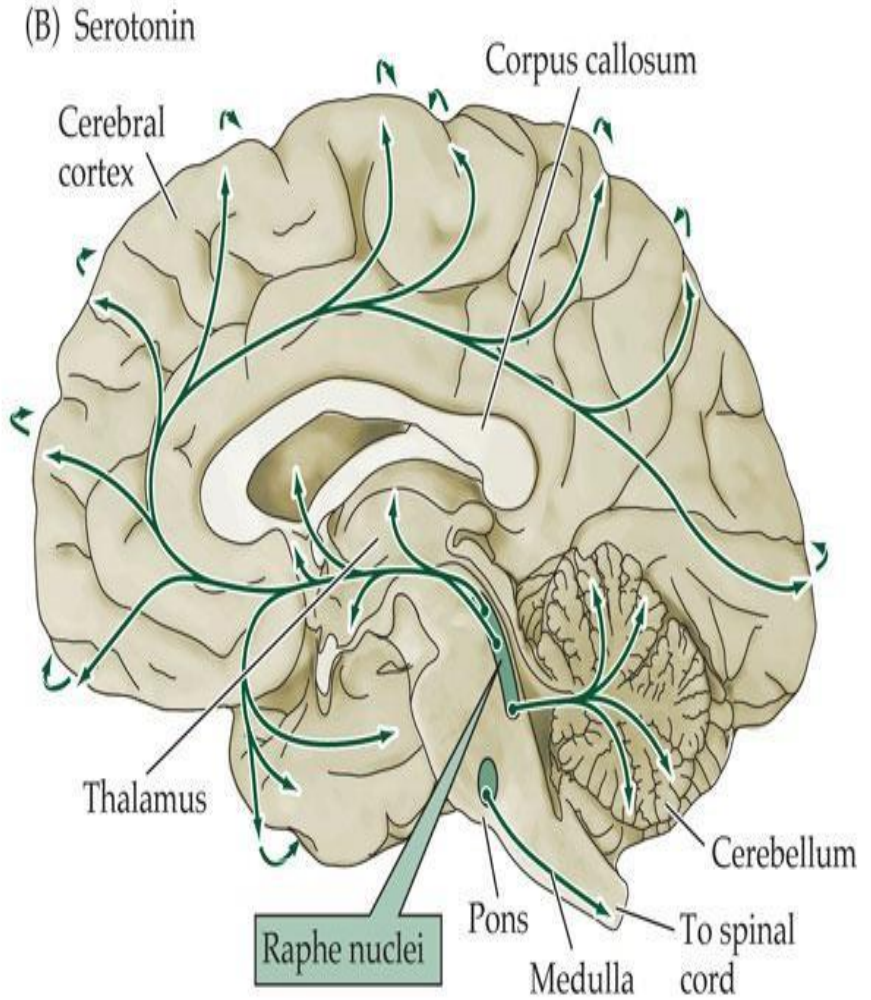
Serotonin

- 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



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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 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

er	effect		synthesis	receptor		
3. serotonin (5HT)	Excitatory	Tryptophan	CNS, Gut (chromaffin cells) Platelets & retina	5-HT_1 to 5-HT_7 5-HT_2 A 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 Kreb's cycle intermediate a – 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.
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^- 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.

THANK YOU