MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
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Physiology Team 436

CNS PHYSIOLOGY

- Text
- Important
- Formulas
- Numbers
- Doctor notes
- Notes and explanation

Lecture No.25

"If It Doesn't Challenge You, It Won't Change You"

Brain Neurotransmitters

Objectives:

1-Describe the functions of glutamergic system

2- Describe the functions of NTs of the brain stem (the noradrenergic & serotonergic systems)

3-Describe the functions of NTs of the basal ganglial (cholinergic, dopaminergic, GABAergic systems)

4-Appreciate that many drugs and CNS disorders affect function of brain neurotransmitters

Definition & Classification of 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

- Amines are small molecule neurotransmitters
- Amino Acids are large molecule NTs
- Nitric oxide, Carbon monoxide and hydrogen sulfide are gaseous neurotransmitters

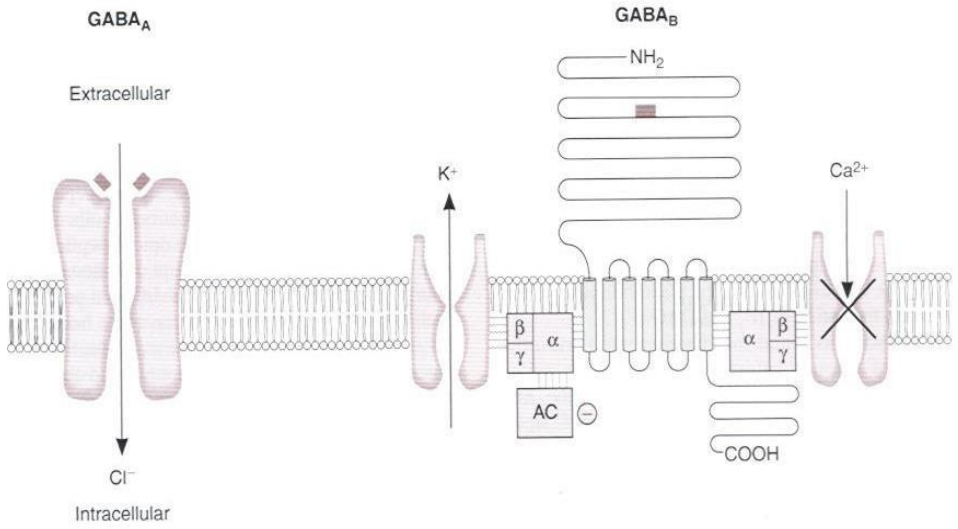
Classification of neurotransmitters

All the NT are proteins and the widely spread NTs in the brain are the amine.

AMINES		
Acetylcholine (ACh)	**Dopamine (DA)**	**Norepinephrine (NE)**
Serotonin (5-HT)	**Histamine**	**Epinephrine**
AMINO ACIDS		
Gamma-aminobutyric acid (GABA)		**Glutamate**
Glycine		**Aspartate**
NEUROACTIVE PEPTIDES		
Bradykinin	Substance P	Thyrotropin
Cholecystokinin	Somatostatin	Neuropeptide Y
Gastrin	Prolactin	Luteinizing hormone
Secretin	Galanin	Calcitonin
Oxytocin	Growth hormone- releasing hormone	Glucagon
Sleep peptides	Bombesin	Vasopressin
gonadotropin-releasing hormone	Dynorphin	Angiotensin 2
Beta- endorphin	Neurotensin	thyrotropin - releasing hormone
Enkephalin	Motilin	Vasoactive intestinal peptide
Soluble gases		
Nitric oxide (NO)	**Carbon monoxide**	

Team435 physiology

Classes of receptors



Metabotropic	Ionotropic
transmembrane receptor acts through a secondary messenger	Ligand gated ion channel

Extra

Criteria that Define a Substance as a NT

The substance must be present within the pre-synaptic neuron

Enzymes & precursors are present in pre-synaptic neuron

The substance must be released in response to depolarization

The release must be Ca^{2+} dependent

Specific receptors must be present on the postsynaptic cell

A neurotransmitter requires a target

Substances are referred to as "putative" neurotransmitters if they follow some but not all criteria

Synthesis & Recycling of Small- Molecule Neurotransmitters

In the neuronal cell body

Enzymes are produced

In the axon

Enzymes transported by slow axonal transport

Within presynaptic terminal cytoplasm

Enzymes & precursors are needed to synthesize NTs

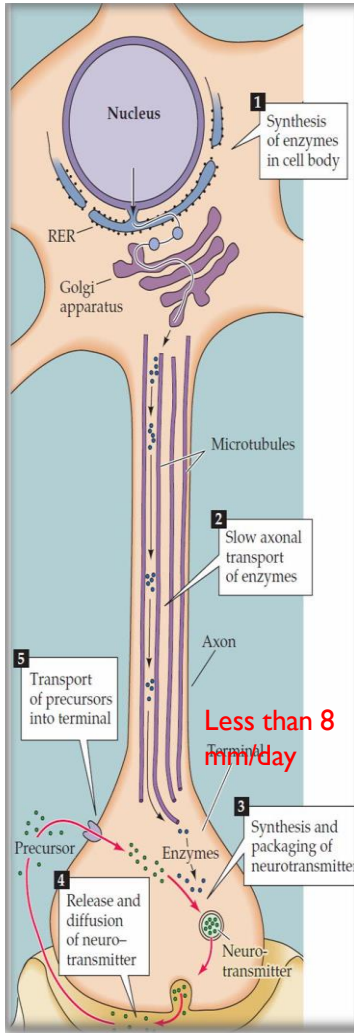
In the vesicles

NTs are loaded into the synaptic vesicle via transporters

At synaptic cleft

NTs are released and taken up into the nerve terminal

40 to 60 NTs
small clear-core vesicle



Synthesis & Recycling of Neuropeptides

At the cell body

Peptide NTs (pro-peptides) & enzymes are synthesized

In the golgi apparatus:

Enzymes and pro-peptides are packaged into vesicles

In the axon

Fast axonal transport of these vesicles to the synaptic terminals

At the terminal

Enzymes modify pro-peptides

vesicles

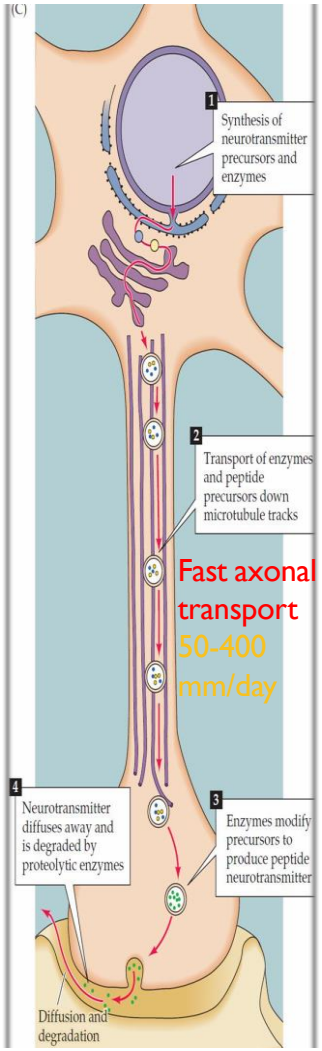
Large dense-core vesicles

On stimulus

Vesicle fusion and exocytosis

In the synaptic cleft

the peptides diffuse or degraded by enzymes



How are neurotransmitters released

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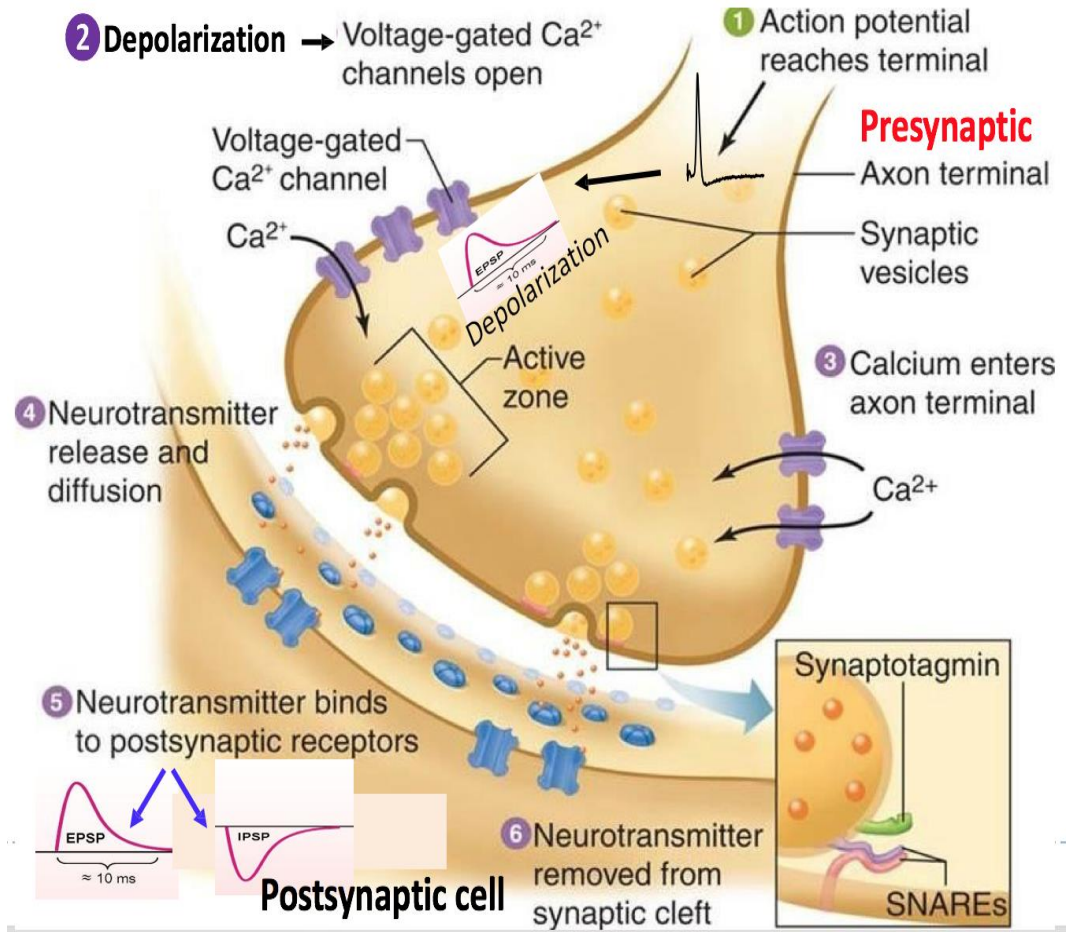


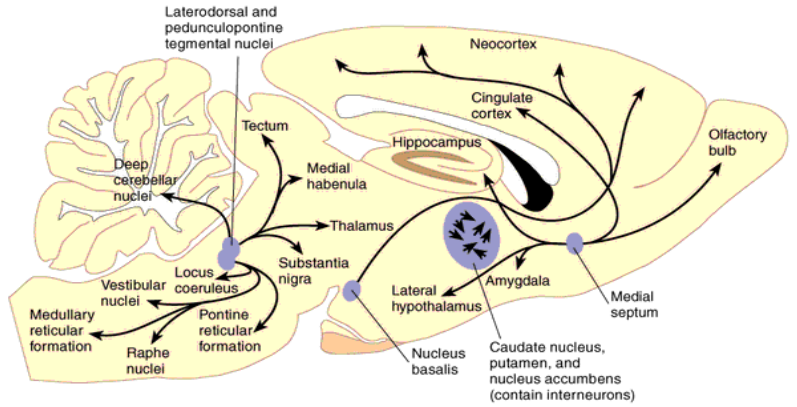
Some of NTs Systems in the Brain

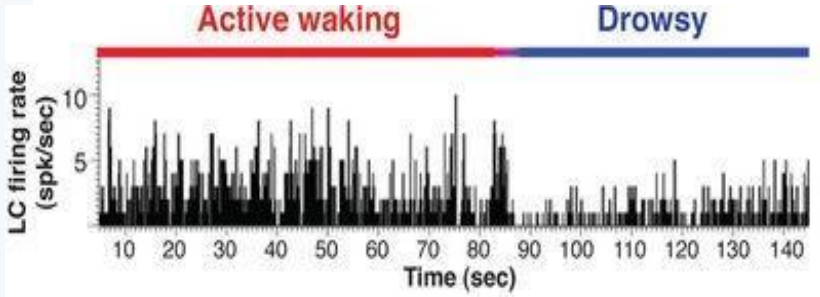
1) Noradrenergic system (Noradrenaline)
2) Cholinergic system (Acetylcholine)
3) Glutamergic system (Glutamate)
4) GABAergic system (GABA)
5) Serotoninergic system (Serotonin)
6) Dopaminergic system (Dopamine)

1) norepinephrine system

The Locus Coeruleus / Nucleus Coeruleus

- **Location:** Nucleus Coeruleus is in the pons.
- **Responds/activated:** by stress and panic (physiological)
- **Co-ordinates responses via:** projections to thalamus, cerebral cortex, cerebellum, hippocampus, amygdala, hypothalamus, autonomic brainstem centers, and the spinal cord (Very wide-spread projection system)
- **Activated during:** Sleep, Attention/Vigilance
- **Deactivated/decreased:** Their firing decreases markedly during slow-wave sleep. and virtually disappears during REM sleep.





- Locus coeruleus neurons fire as a function of vigilance and arousal
- Irregular firing during quiet wakefulness and sustained activation during stress
- Stress causes very high levels of LC activity

Norepinephrine (NE) Implicated in Stress-Related Disorders

- Depression
- Withdrawal from some drugs of abuse

Norepinephrine system

- **Noradrenaline** (NA): 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)**
- NA is believed to play a role in both **learning** and **memory.**

Functions

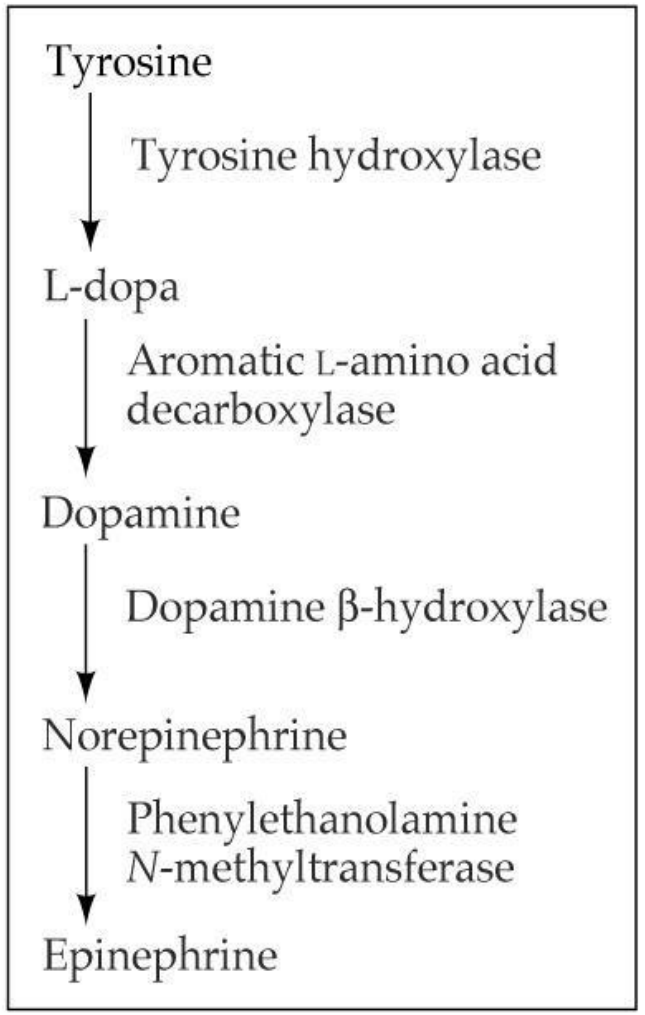
- Attentiveness & Vigilance
- Learning
- Aggressive behaviour
- Fight-or-Flight response
- It constitutes part of the Reticualr Activating System (RAS) → attention# vigilance

Disorders (in both male and female slides)

- Depression and panic disorders
- Withdrawal from some drugs of abuse

Deficiencies in NA

- Alzheimer's disease
- Parkinson's disease
- Korsakoff's syndrome (chronic alcoholism)



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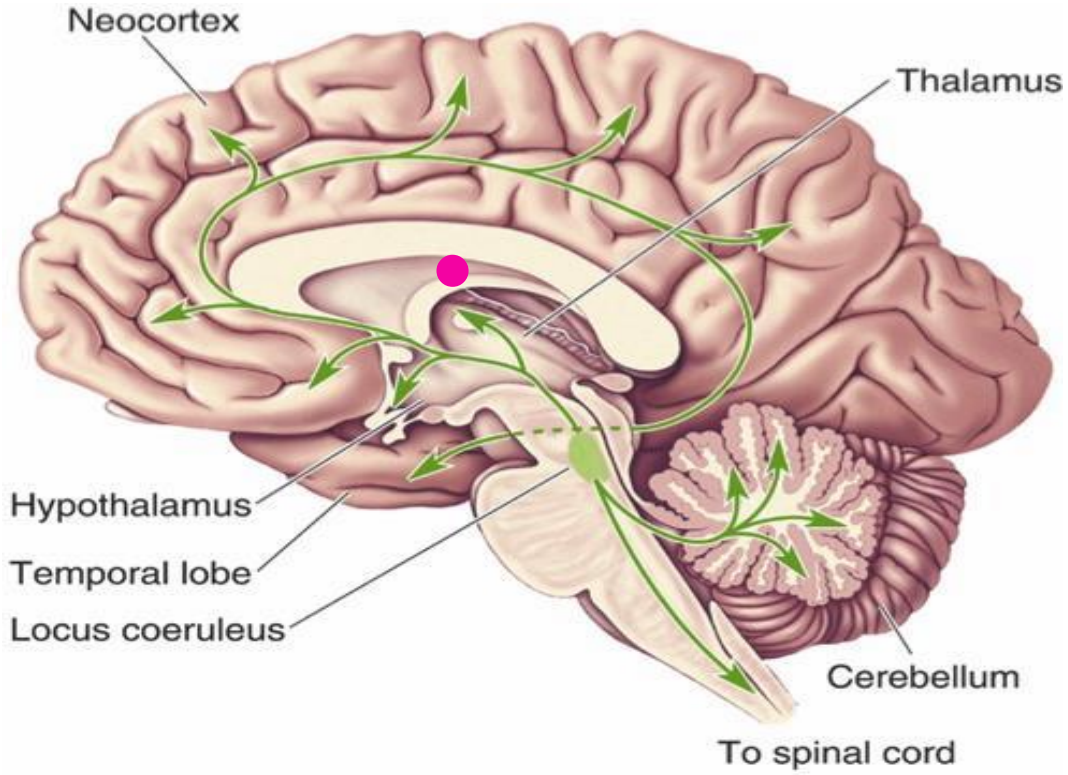
- It constitutes part of the Reticualr Activating System (RAS) → alertness

- The LC is activated by similar stimuli to those that activate ANS
- ANS mobilizes the body
- LC mobilizes the brain for action

✓ Drugs that suppress LC have a powerful sedating effect because LC controls arousal level



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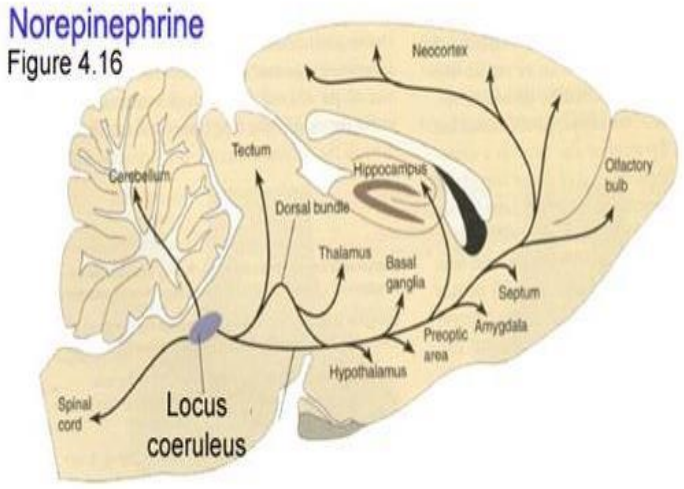
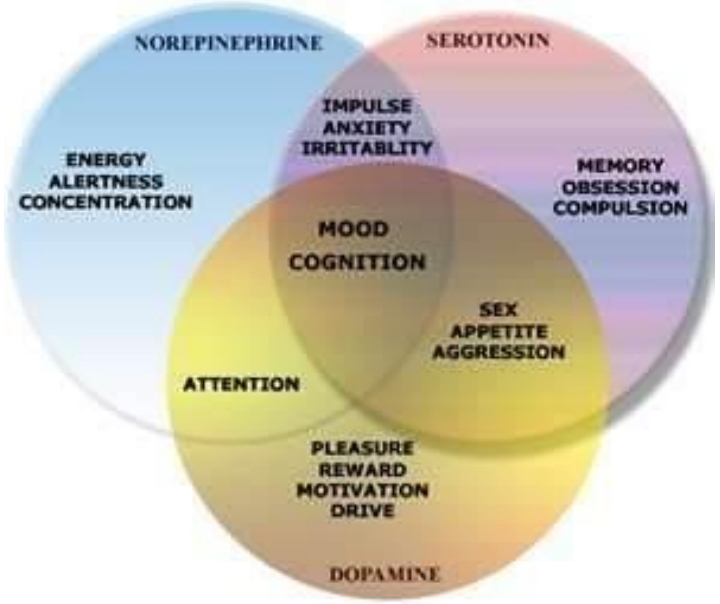
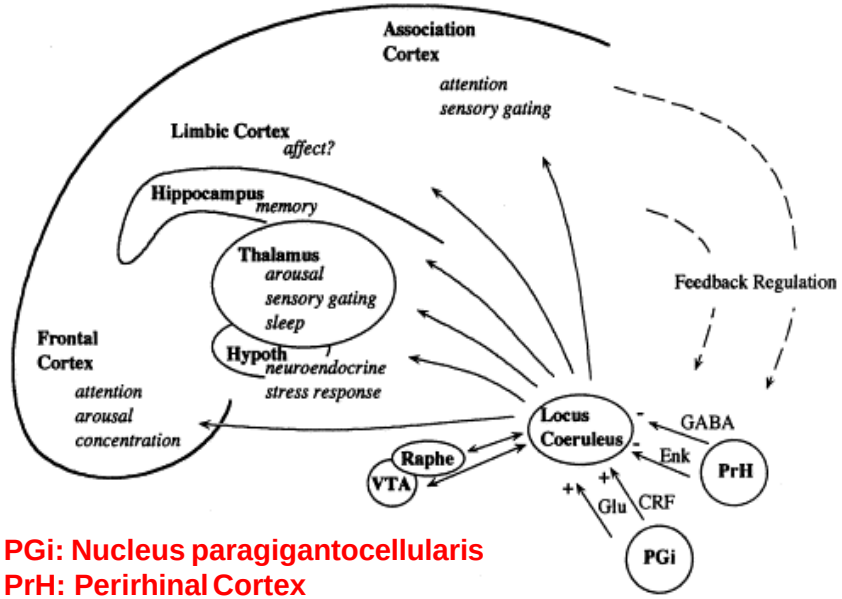


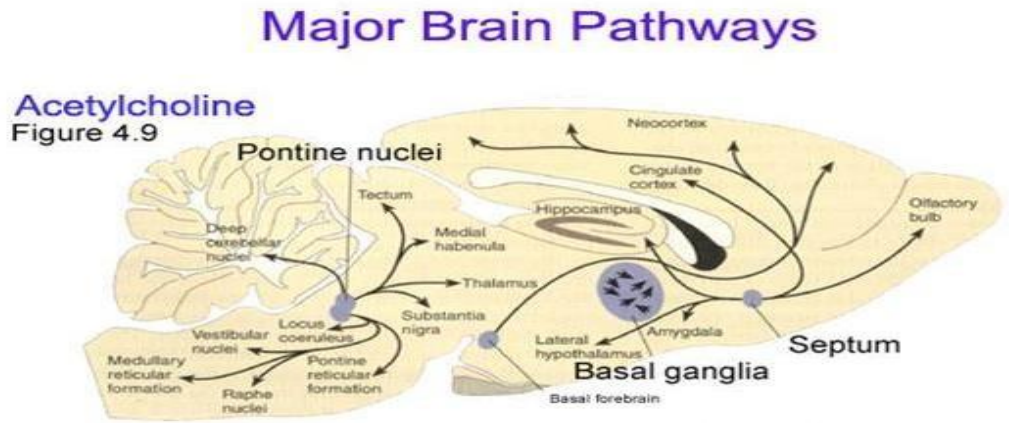




PGi: Nucleus paragigantocellularis
PrH: Perirhinal Cortex

2) Acetylcholine

- Major neurotransmitter in the peripheral nervous system. Produced by the neurons in the parietal lobes of the brain
- **Acetylcholine (Ach) is the 1st** neurotransmitter to be identified (about 90 years ago)
- It is released by lower motor neurons and neurons in many brain regions



- Associated with:

Thought, Memory, Muscular coordination,
Speed of information processing in the brain,
Production of myelin sheath

- Mental processes influenced by Ach(Functions):

Learning, Memory, Sleeping, Dreaming, Wakefulness, Anger & aggression, sexuality and thirst.

- **Ach-related disorders:**

➢ Alzheimer's Disease- the most common form of dementia that is associated with acetylcholine Damage to Ach producing cells in the basal forebrain (death of Ach neurons)
➢ Bipolar disorder
➢ Mood swings
➢ Depression
➢ Mental attension
➢ Myasthenia gravis

Acetylcholine

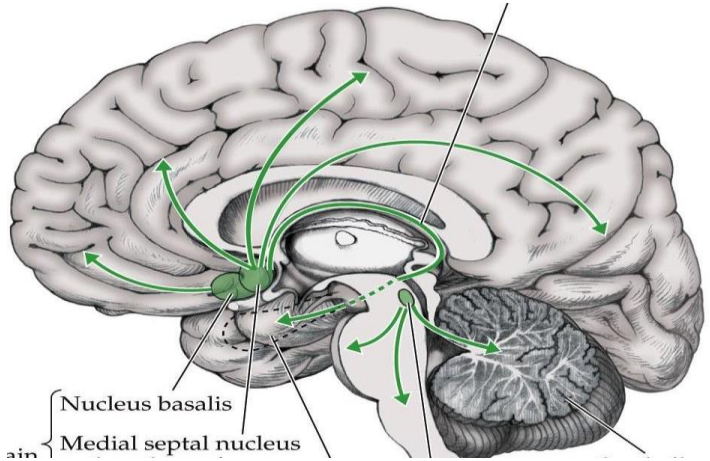
- Ach is released from cholinergic neurons of:

1-**The basal forebrain nuclei** (nucleus basalis & septal)

- The nucleus basalis (Meynert) provides innervation to the entire cortex, amygdala, hippocampus & thalamus.
- The medial septal nuclei

provide cholinergic innervation to the cerebral cortex, hippocampus, and amygdala

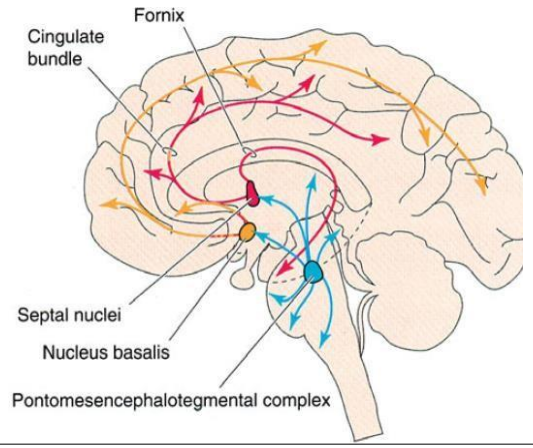
Inhibitors of acetylcholinesterase in the brain are the main drugs used to treat Alzheimer's disease.



2- **ponto- mesencephalic cholinergic complex**

project to basal ganglia, thalamus, cerebellum hypothalamus, reticular formation

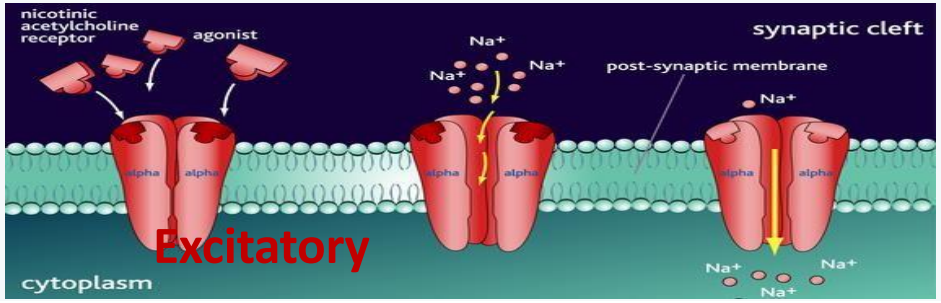
Degeneration in Alzheimer's disease



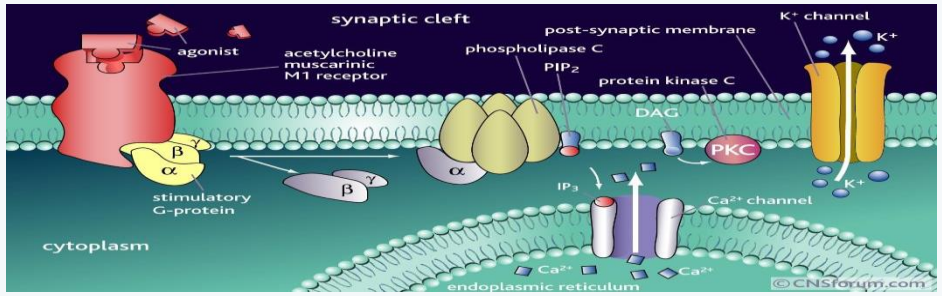
Acetylcholine

Acts on 2 cholinergic receptors:

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



- **Muscarinic** (metabotropic) (antagonist-Atropine):
  - Excitatory or inhibitory
  - Five subtypes (M1-M5): all present in the brain



- **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

3) Glutamate

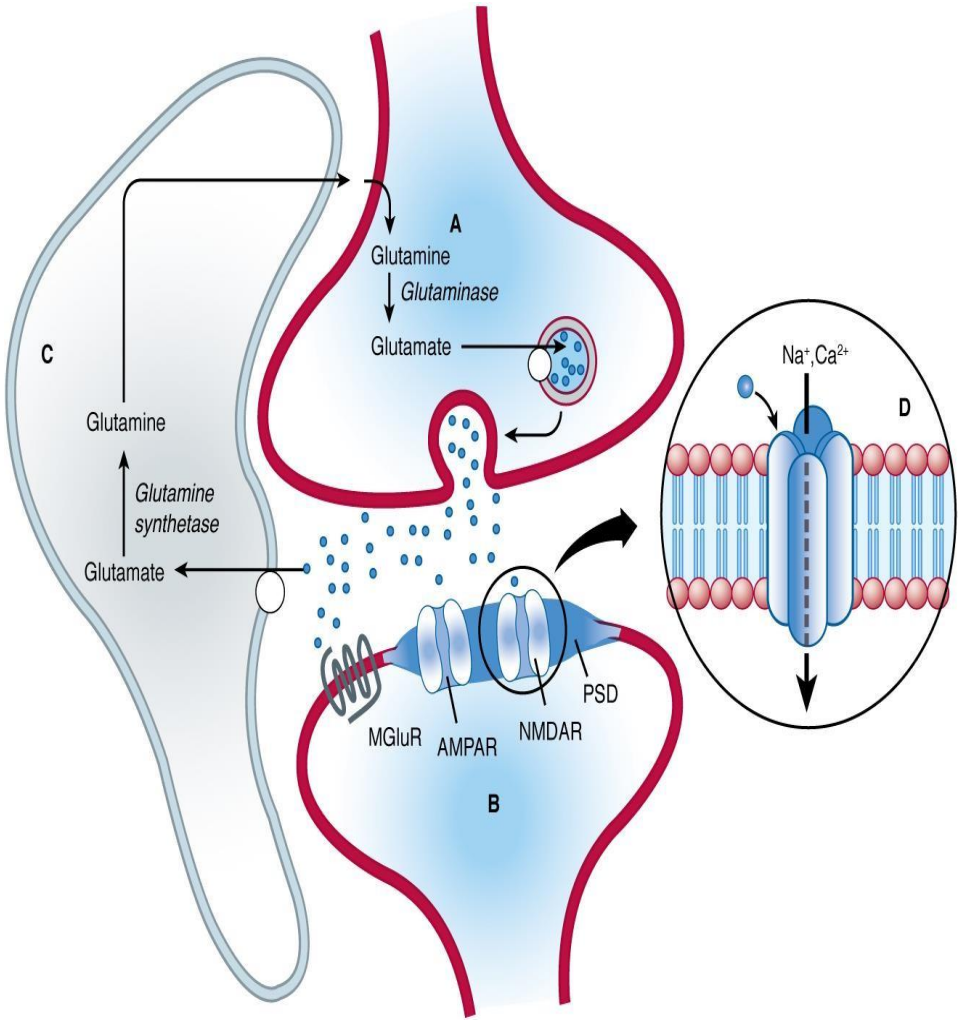
* It is the most commonly found neurotransmitter in the brain. (**king** of NTs, ~50% neurons).
* It is always excitatory.
* Glutamate is formed (alpha ketoregulation) Kreb's cycle → carried into astrocytes → converted to glutamine → passed on to glutaminergic neurones

Reduced level in:

- Stroke
- Autism
- Intellectual disability
- Alzheimer's disease

Important role in

- Learning
- Memory



Glutamate

- Glutamate (can cause excitotoxicity) is converted in astrocytes into glutamine (not toxic) and passed onto glutaminergic neurons

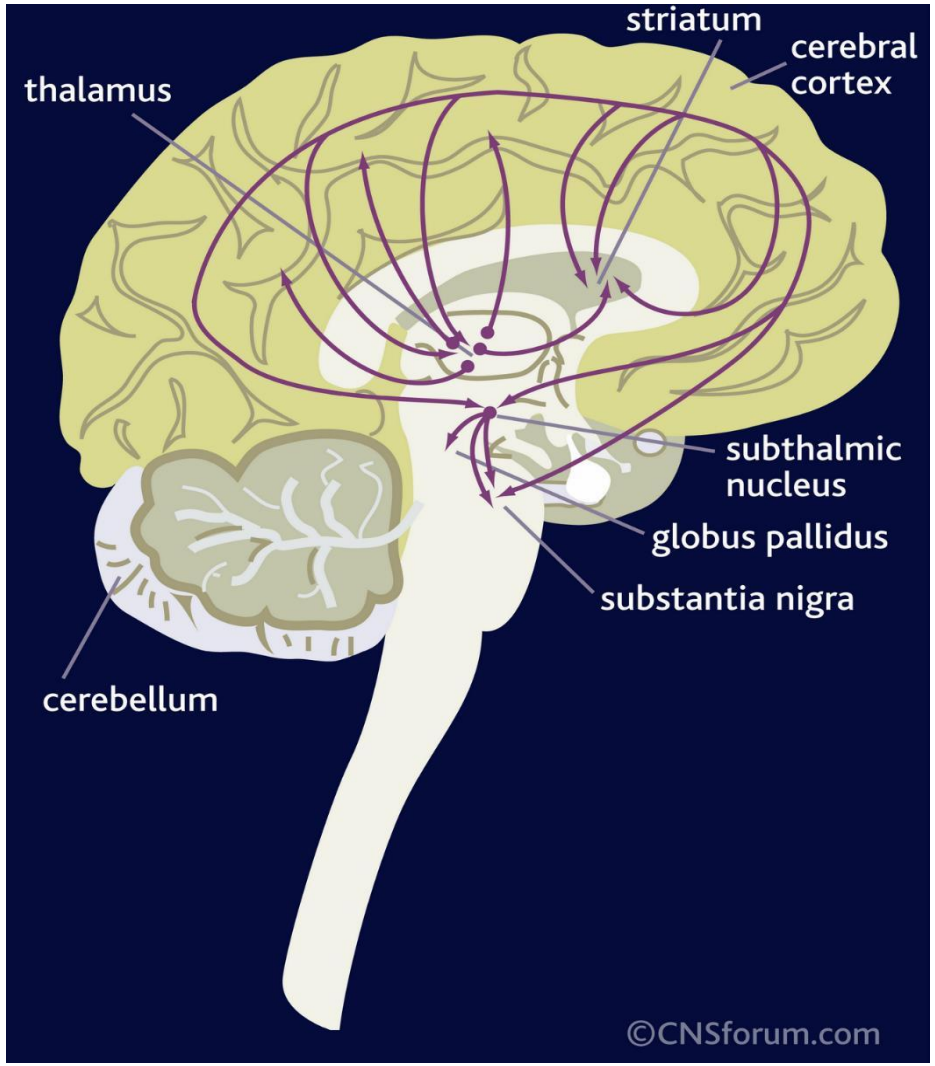
- Wide spread, but high levels in hippocampus; hypofunction of NMDA receptors in this area and prefrontal cortex is associated with schizophrenia

Functions

- Learning/memory (hippocampus)
- Motor coordination (cerebellum)

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



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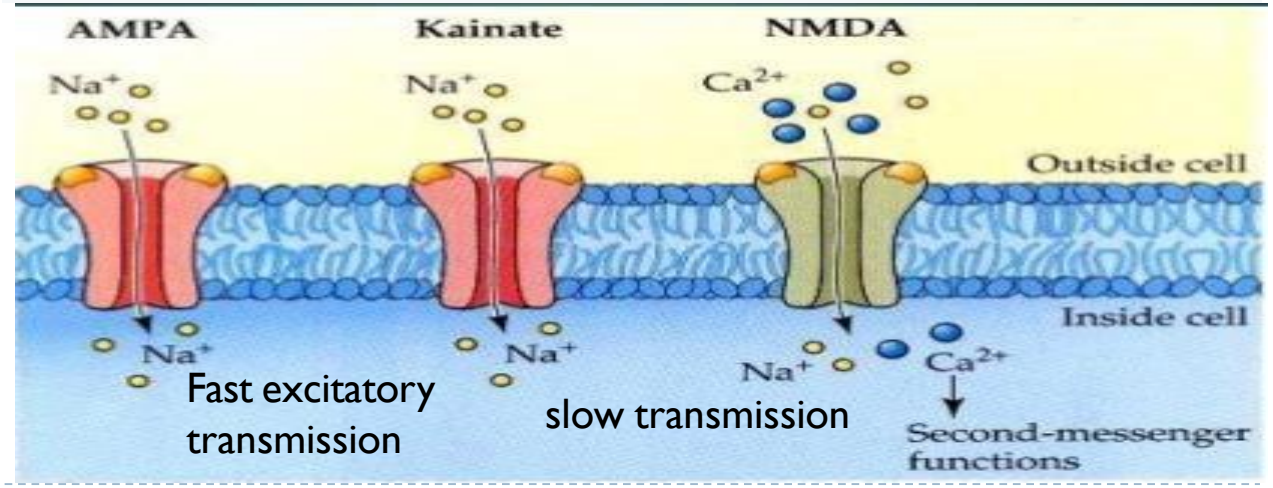
Are widely distributed in the brain; they are of two types:

1- **Metabotropic receptors** (G protein-coupled receptors): mGluR1-mGluR11

- Found in hippocampus, cerebellum and the cerebral cortex
- Activate biochemical cascades, leading to modification of other proteins such as ion channels.

2- Ionotropic receptors (ligand-gated ion channels).
Three types:

AMPA receptors (α-amino-3-hydroxy-5-methylisoxazole-4-propionate)
Kainate receptors (kainate is an acid isolated from seaweed),
NMDA receptors (for N-methyl- D-aspartate); play a role in synaptic plasticity related to learning and memory



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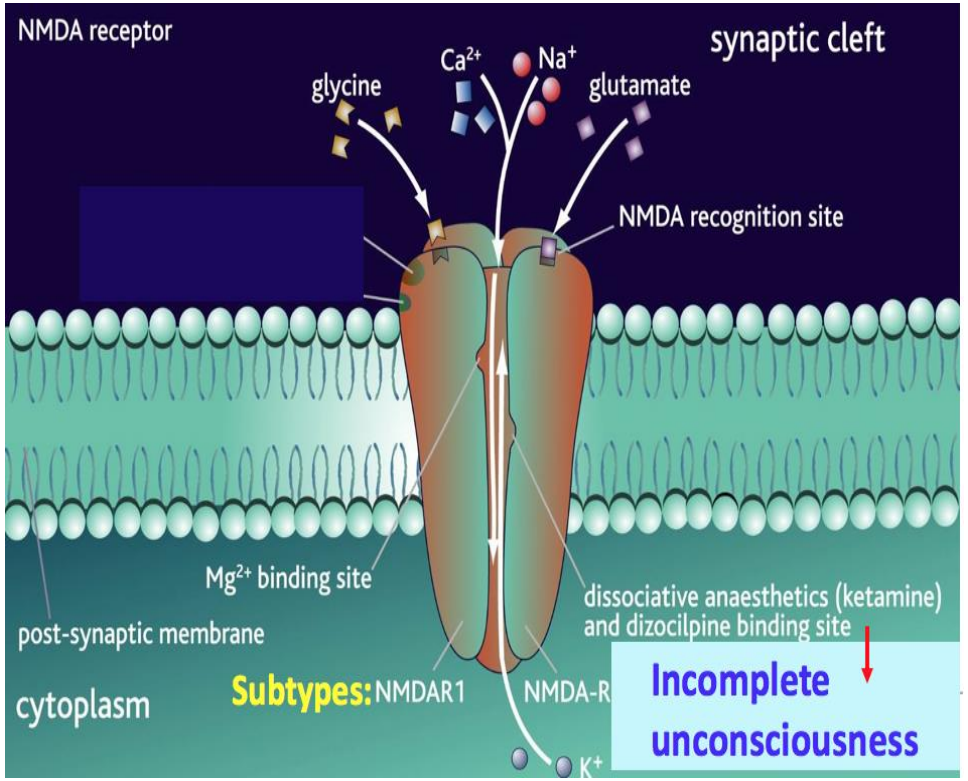
NMDA Receptors

- Permits passage of Na^+ and large amounts of Ca^{2+}. They are unique:
- **Glycine** is essential for their normal response to glutamate.
- The channel is blocked by **Mg^{2+}** ion at normal membrane potentials
- This blockade is removed by **depolarization** (caused by e.g. AMPA)
- Binding site for dissociative anaesthetics (**blockade** e.g. ketamine)
- The channel opens only when both **glycine** and **glutamate** bind to the receptor



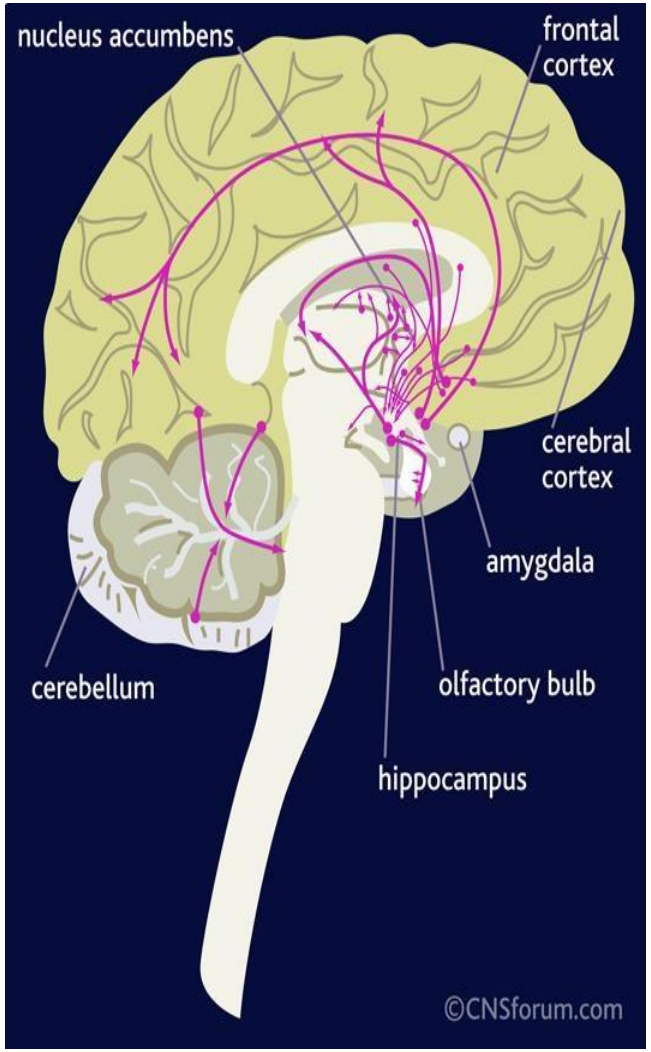
4) Gamma Aminobutyric Acid (GABA)

* Inhibitory neurotransmitter of CNS and is also found in retina. (GABA is the main inhibitory neurotransmitter in the central nervous system)
* Formed by decarboxylation of glutamate.

There are 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. (increase K^+ conductance and decrease Ca^{+2} influx).
- GABA A and C receptors (**ionotropic**) have **multiple binding sides** (for benzodiazepine and barbiturates)**. The channel is a Cl^- channel** (not Na^+)

* GABAergic inhibition is seen at all levels of the CNS
* (Hypothalamus, hippocampus, cerebral cortexand cerebellar cortex.
* GABA interneurones are abundant in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated.



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Functions & Disorders of GABAergic System

Functions

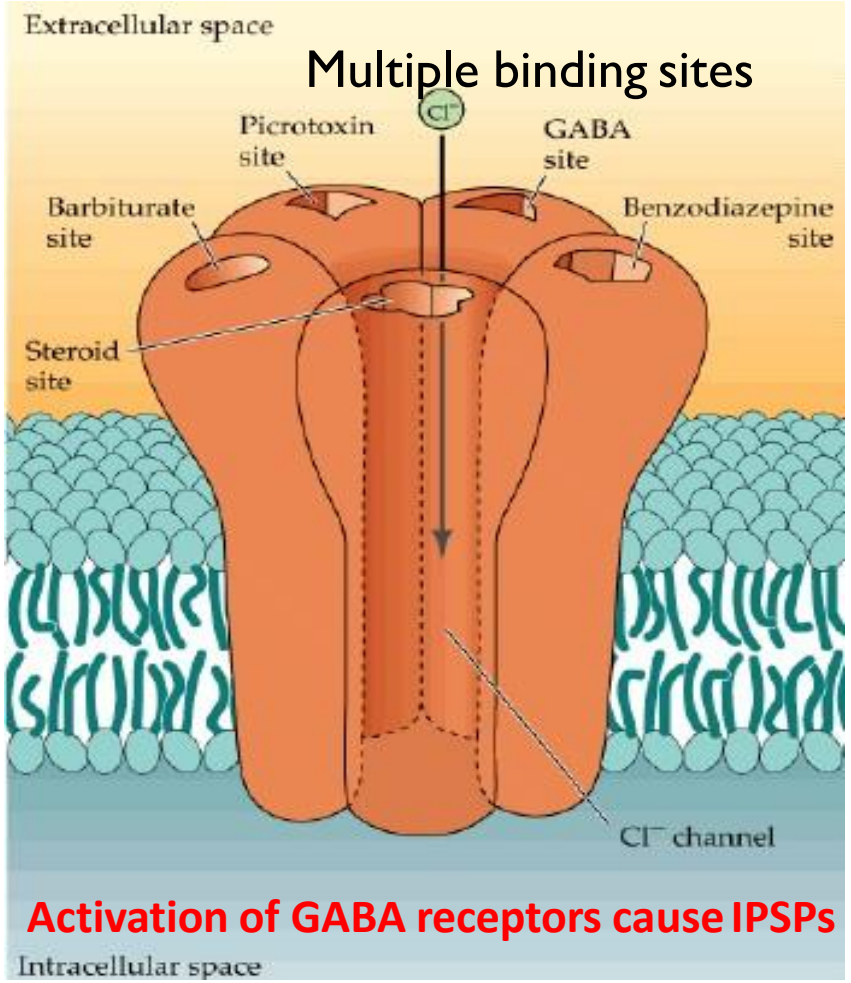
- Presynaptic inhibition
- GABAA receptors in the CNS are chronically stimulation to regulate neuronal excitability

Disorders

- Seizures (under activity of GABA)

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

The fabulous GABA receptor



5) Serotonin

The serotonin pathways in the brain:

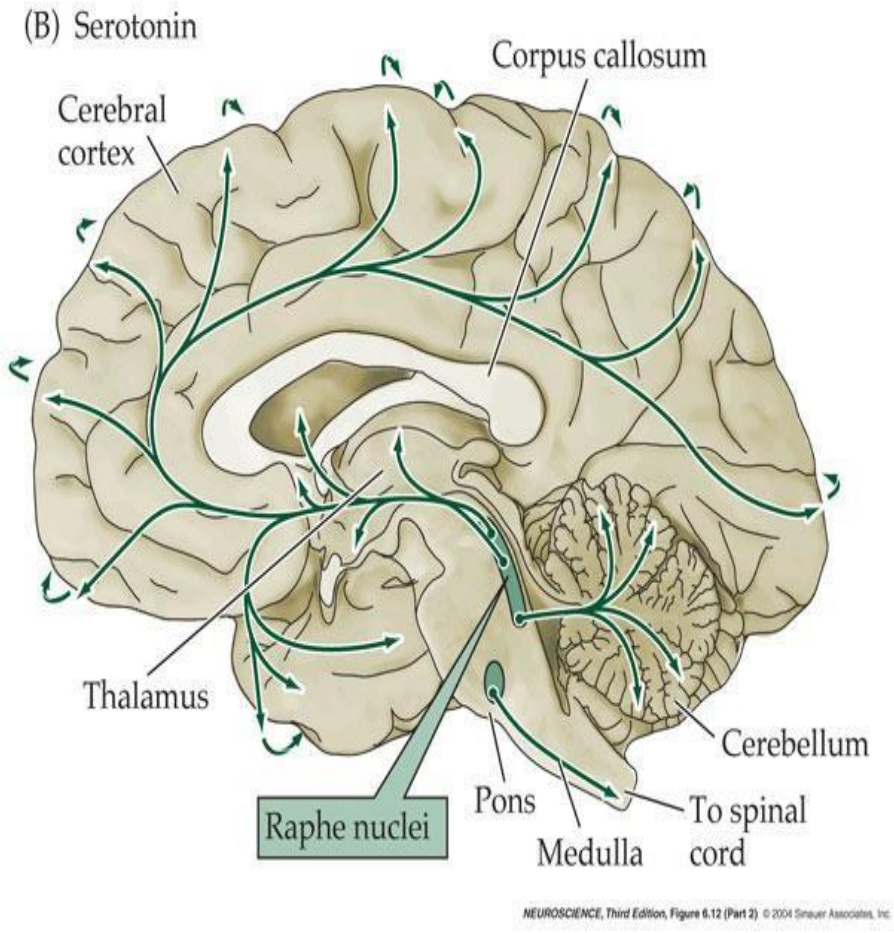
The principal centers for serotonergic neurons are:
the rostral and caudal raphe nuclei

Projections:

- 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) Disorders

- Depression
- Anxiety



The Serotonin System

- 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 14 serotonin receptors (excitatory or inhibitory) in different parts of CNS (most are metabotropic, except 5-HT_3)
- Mice in which the gene for 5-HT2 C receptors has been
  - knocked out are obese

The Serotonin System

Extra

Neurons in caudal raphe nuclei project to:

- Cerebellum
- Medulla
- Spinal cord

Neurons in rostral raphe nuclei project to:

- Thalamus
- Basal ganglia
- Limbic system
- Cerebral cortex

Functions:

- Improved Mood
- Decrease appetite
- Sleep

Disorders:

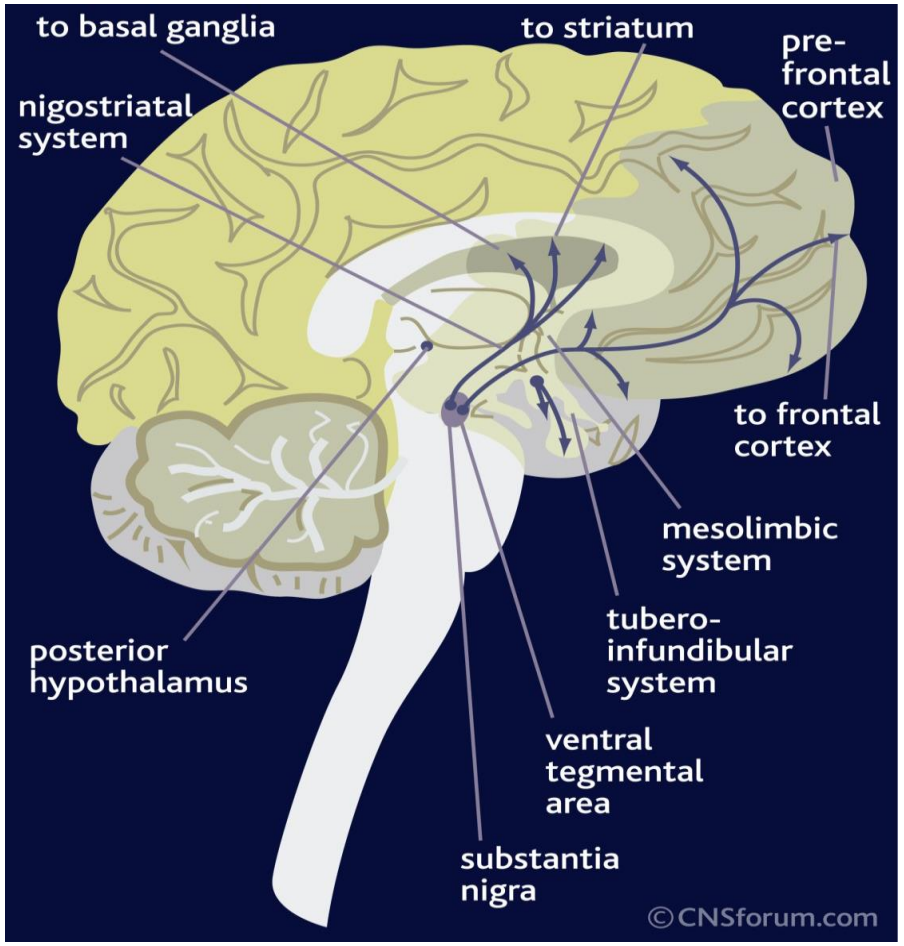
- Depression
- Anxiety and suicide
- Aggressiveness

Serotonin innervates the entire CNS

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

6) Dopaminergic Pathways

Dopamine is transmitted via three major pathways	
The first extends from the substantia nigra to the caudate nucleus-putamen (neostriatum)	concerned with sensory stimuli and movement.
The second pathway projects to the mesolimbic forebrain	Related to cognitive, reward and emotional behavior
The third pathway, known as the tubero- infundibular system	Related to neuronal control of the hypothalmic-pituatory endocrine system.



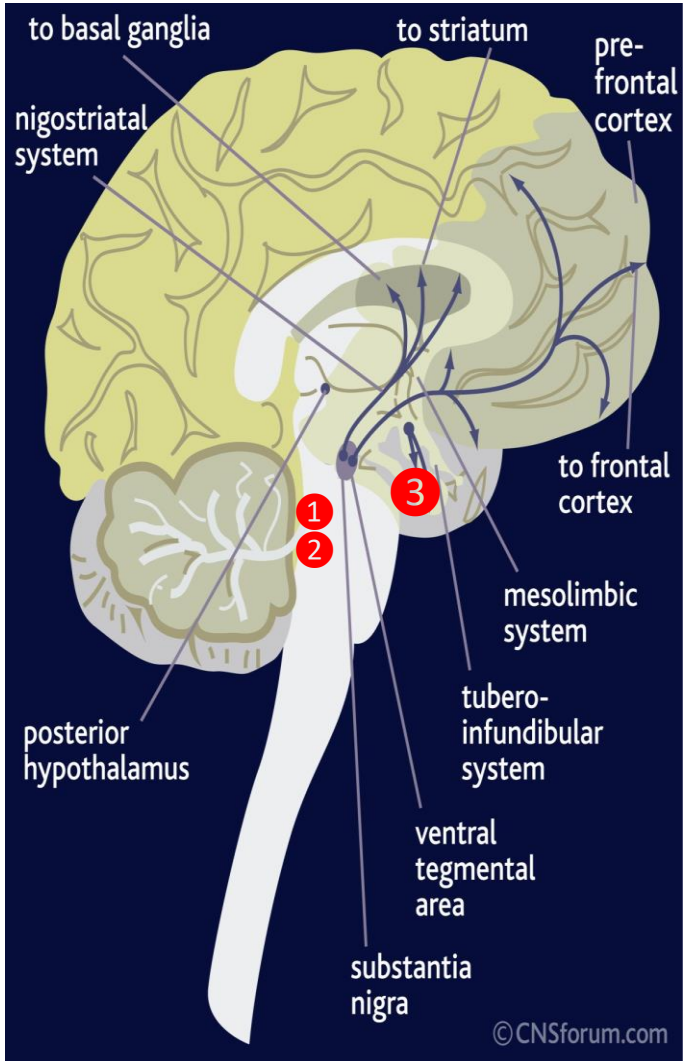
The Dopaminergic System

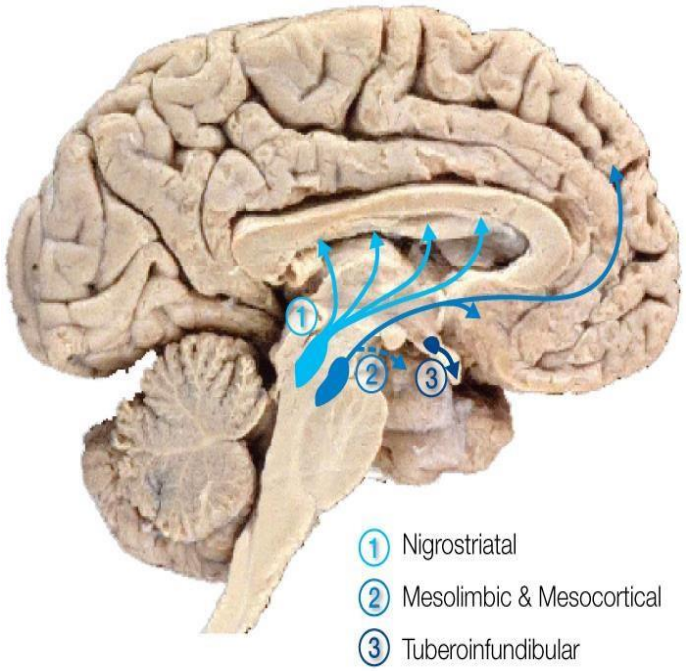
▪**Dopamine** is a catecholamine that is synthesized from **tyrosine**

▪It is present in 3 principal circuits in the brain:

1-Nigrostriatal
2-Mesolimbic & Mesocortical
3-Tuberoinfundibular

- Five dopaminergic receptors (D1-D5) .
- Overstimulation of D2 receptors is thought to be related to schizophrenia





1 **Nigrostriatal**

2 **Mesolimbic & Mesocortical**

3 **Tuberoinfundibular**

ONLY IN MALES' SLIDES

The Dopaminergic System

1- The Nigrostriatal circuit:

extends from the substantia nigra to the striatum (caudate nucleus-putamen)

- This circuit is concerned with motor control.
- Death of neurons in this pathway is linked to Parkinson's disease

2-The Mesolimbic & Mesocortical system

extends from the ventral tegmental area (**VTA**) to:

- Nucleus accumbens
- Amygdala & Hippocampus
- Prefrontal cortex

- Concerned with **memory, motivation, emotion, reward, desire & addiction**
- **Dysfunction** is connected to hallucinations and schizophrenia

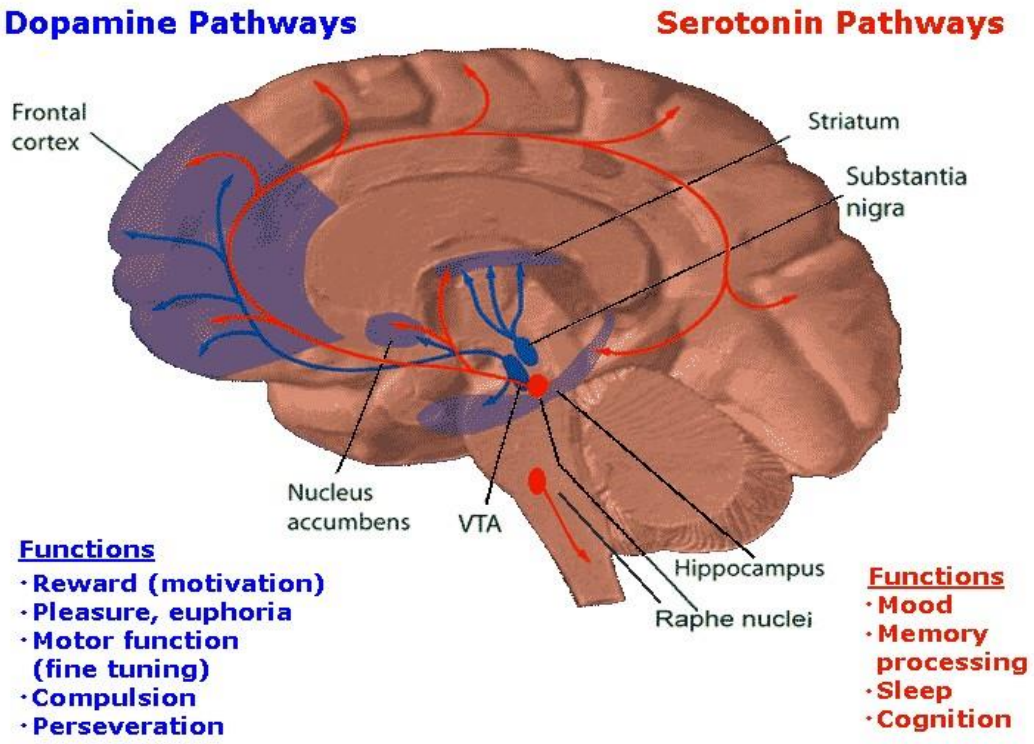
3-Tuberoinfundibular system

extends from infundibular region (median eminence of hypothalamus) to:

- Pituitary gand

- It is concerned with:
  - Regulation of hormones
  - Maternal behavior (nurturing)
  - Pregnancy

The dopaminergic system



Functions

- Motor & hormonal control
- Memory & motivation
- Emotion & reward
- Desire & addiction

Disorders

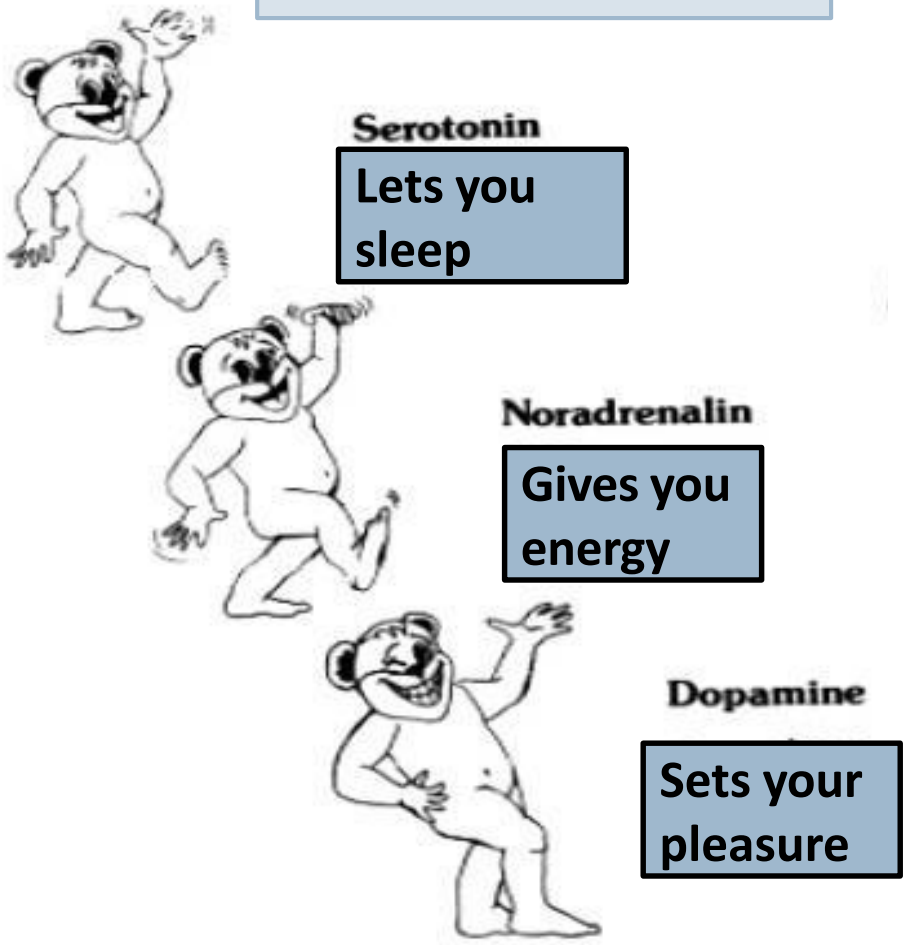
Parkinson's disease (decreased levels of dopamine)
Schizophrenia (over-activity at DA synapses)
Hallucinations

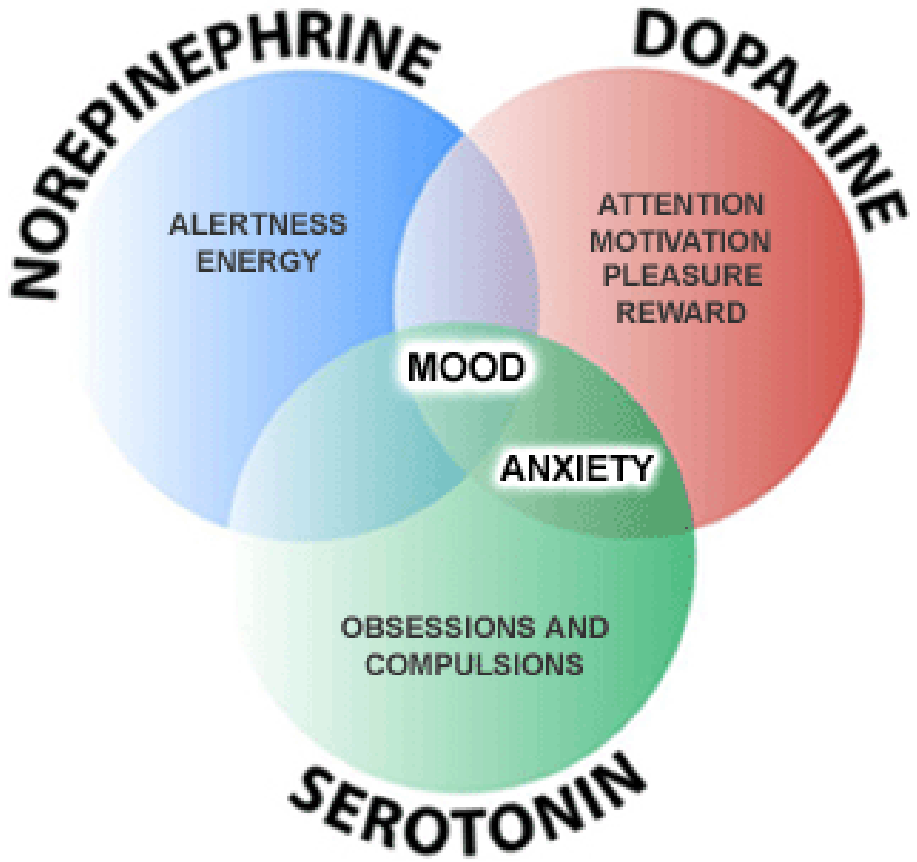
✓ **Cocaine elevate activity at dopaminergic synapses**

EUPHORIA

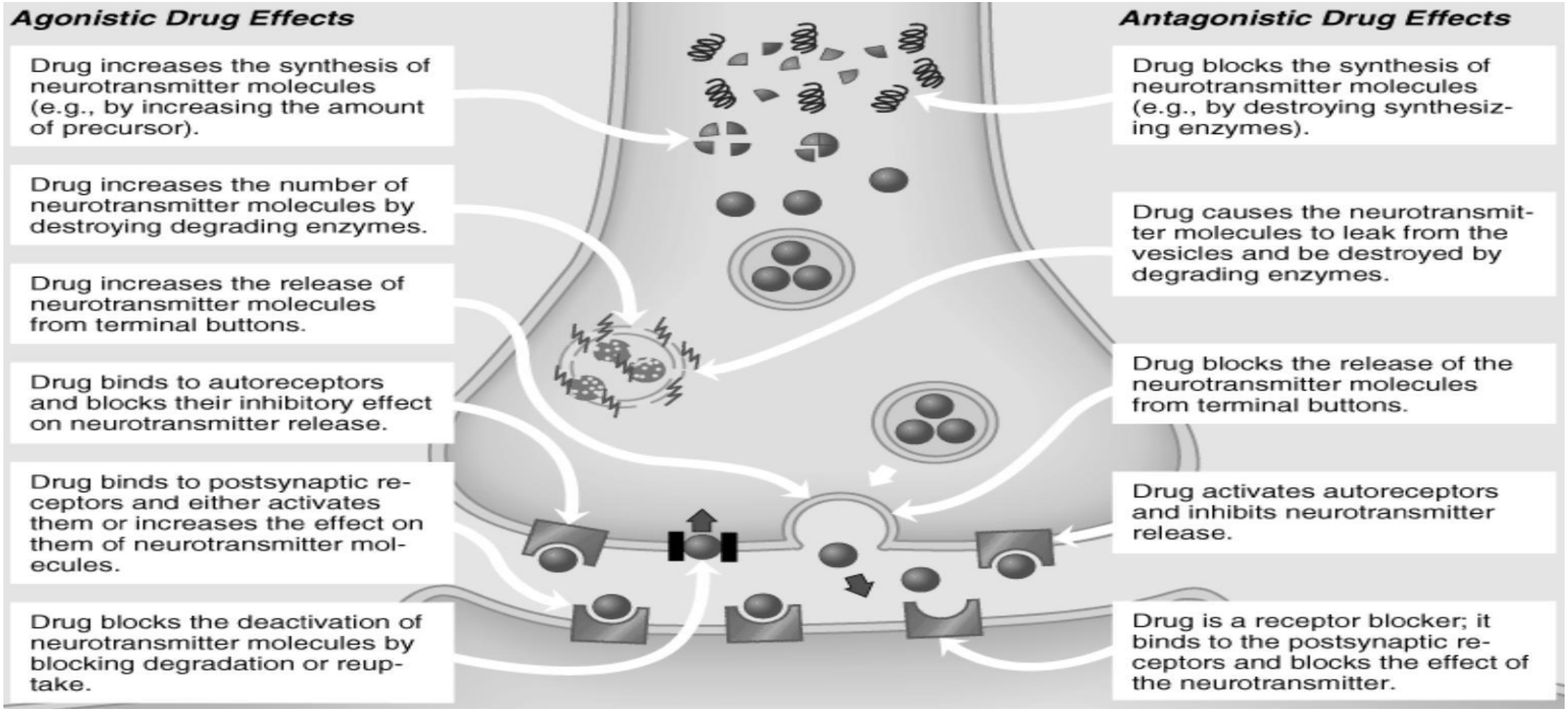
The three happy neurotransmitters

Extra





Some mechanisms of drug action



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.Muscarini c	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 phenylalanin e	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. nigrostriaal, mesocorticolim bic and	D_1 to D_5 receptor	Same as above	Sensory motor Cognetive/emotion al behavior Endocrine Hypothalamic Decreased dopamine in

Cont.

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-hydroxyindoleace tic 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 transmissio n 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.

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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.

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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اقتراحات وشكاوي

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