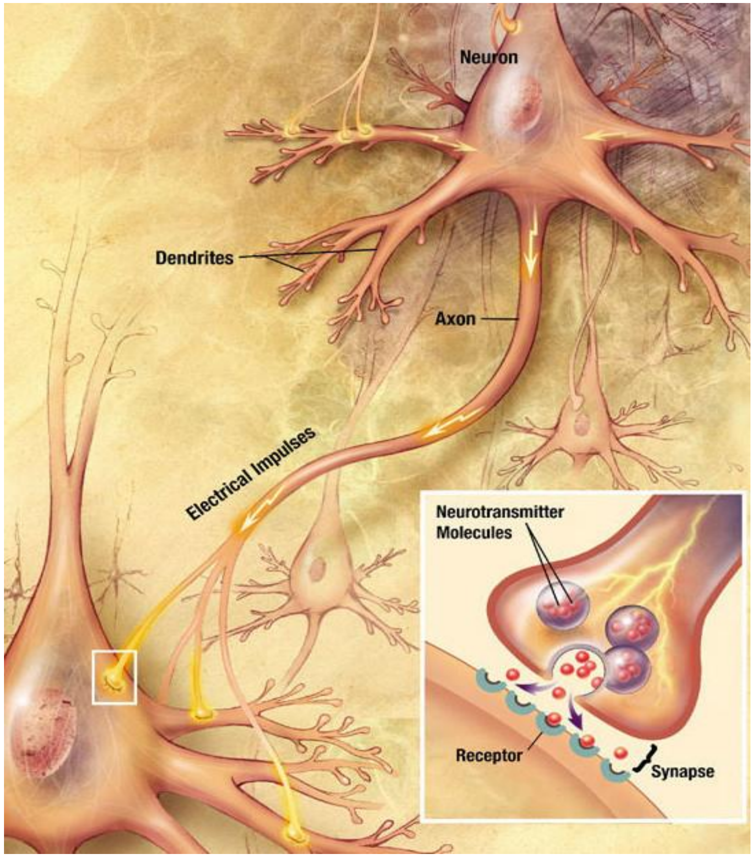
Neuropsychiatry Block

جامعة الملك سعود
King Saud University

Brain Neurotransmitters

By Laiche Djouhri, PhD
Dept. of Physiology
Email:
ldjouhri@ksu.edu.sa
Ext:71044



Text Books

❶ Chapter 7

Neurotransmitters & Neuromodulators

(Ganong)

❷ Chapter 56

Behavioral and Motivational Mechanisms of the Brain—The Limbic System and the Hypothalamus

(Guyton & Hall)

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 stem (the noradrenergic & serotonergic systems)
- Describe the functions of NTs of the basal ganglial (cholinergic, dopaminergic, GABAergic systems)
- Appreciate that many drugs and CNS disorders affect function of brain neurotransmitters

Classification of Neurotransmitters (NTs)

A. Small-molecule NTs

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

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

B. Large-molecule NTs

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

C. Gaseous NTs

Soluble Gases	
Nitric Oxide (NO)	Carbon Monoxide

hydrogen sulfide.

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

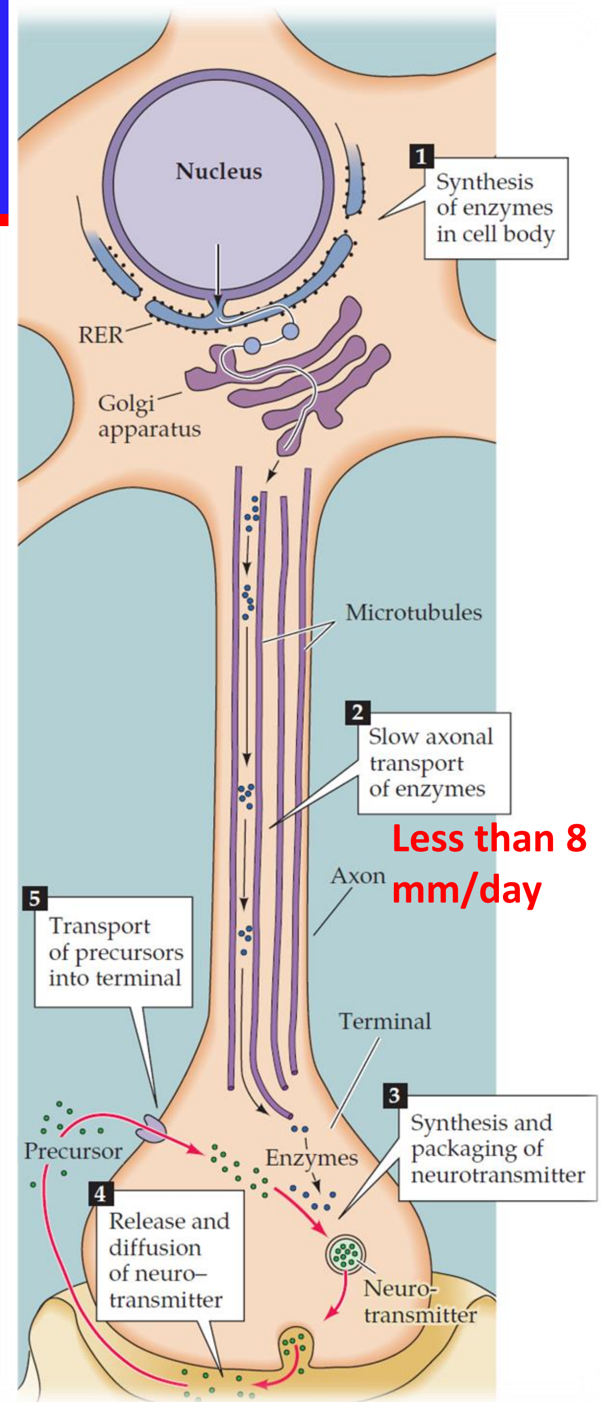
In the vesicles

NT is loaded into synaptic vesicles via transporters

At synaptic cleft

NT is released and taken up into the nerve terminal

40 to 60 nm — Small clear-core vesicles



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

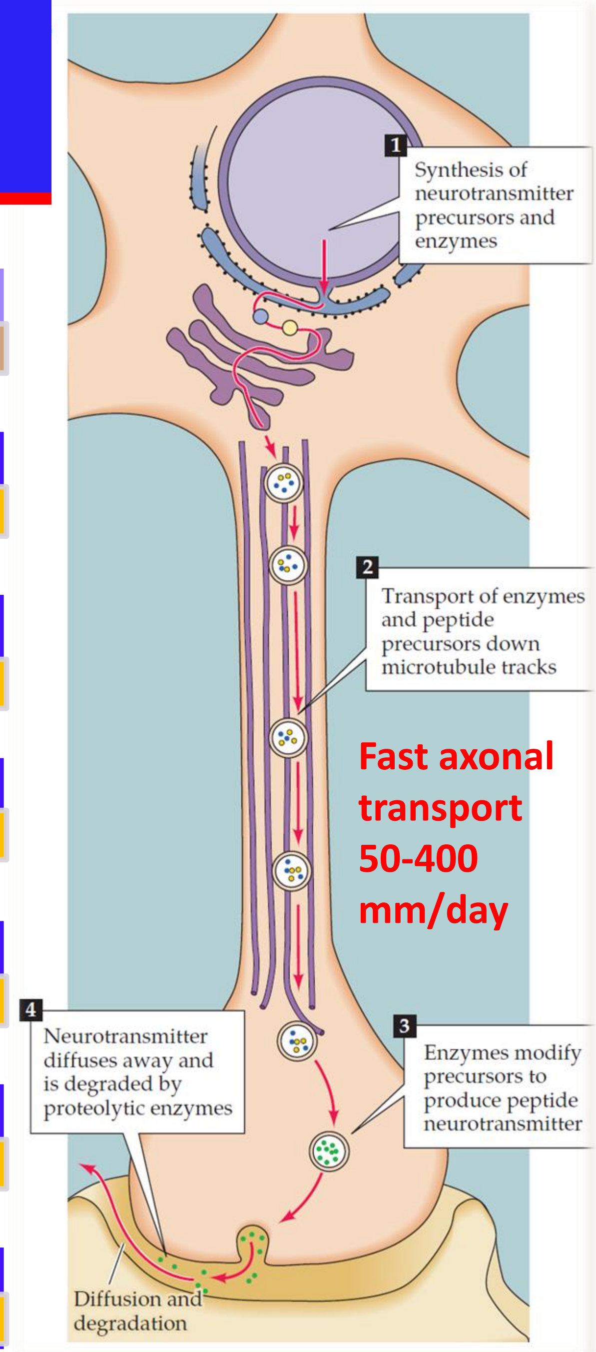
Large dense-core vesicles

On stimulus

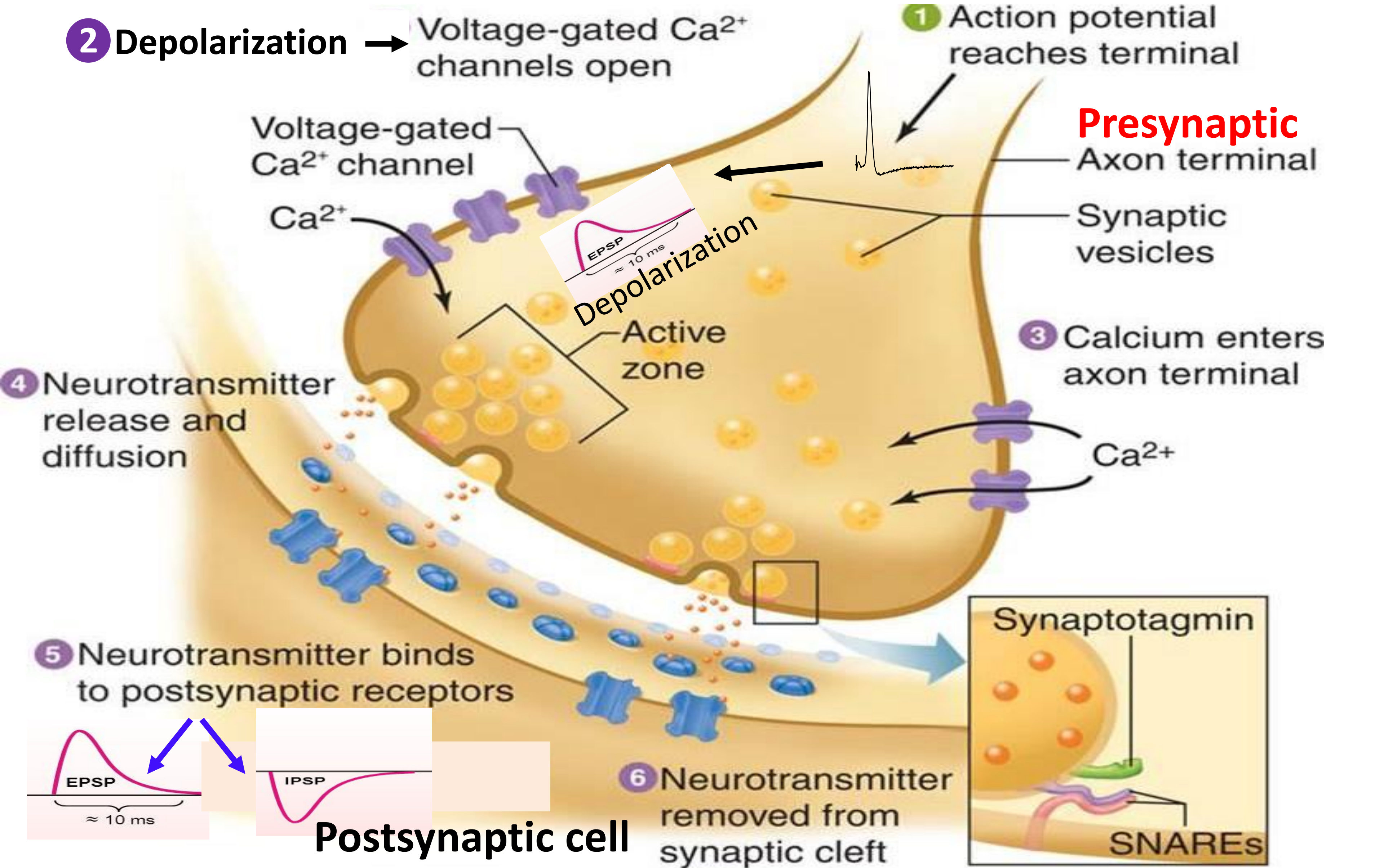
Vesicle fusion and exocytosis.

In the synaptic cleft

The peptides diffuse or degraded by enzymes



How Are Neurotransmitters Released?



Some of NT Systems in the Brain

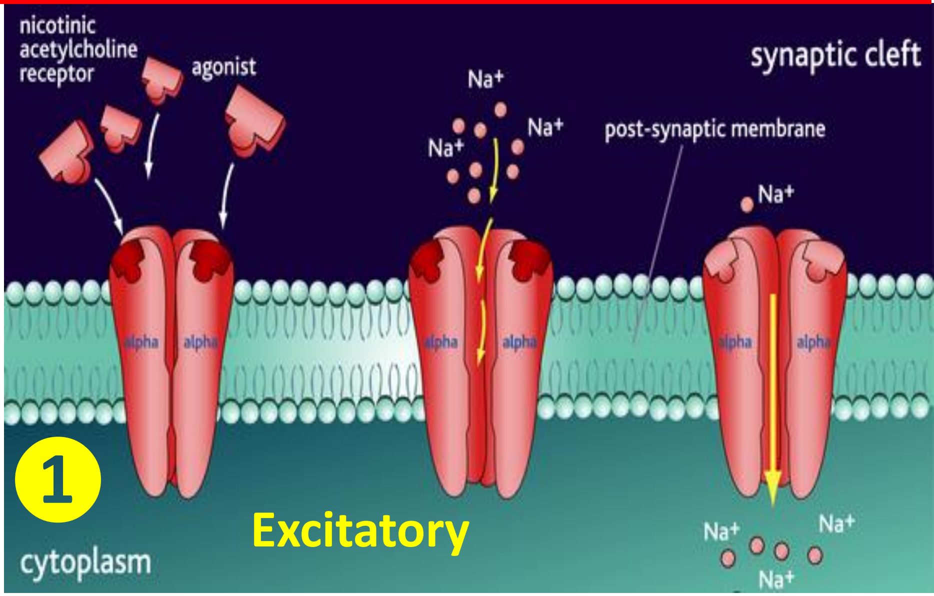
1. Cholinergic system (Acetylcholine)
2. Glutamergic system (Glutamate)
3. GABAergic system (GABA)
4. Noradrenergic system (Noradrenaline)
5. Dopaminergic system (Dopamine)
6. Serotoninergic system (Serotonin)

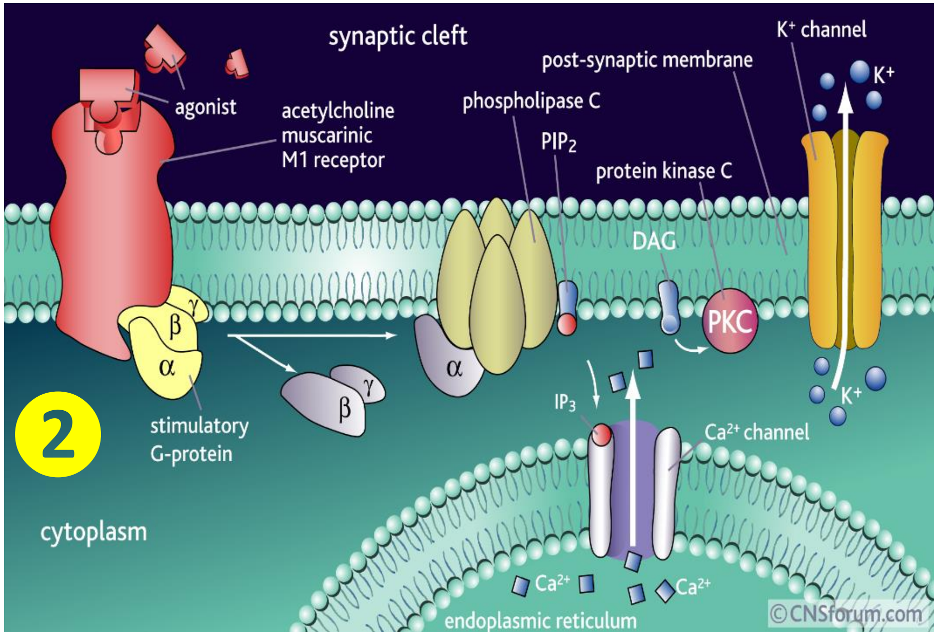
① The Cholinergic System-1

- **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**

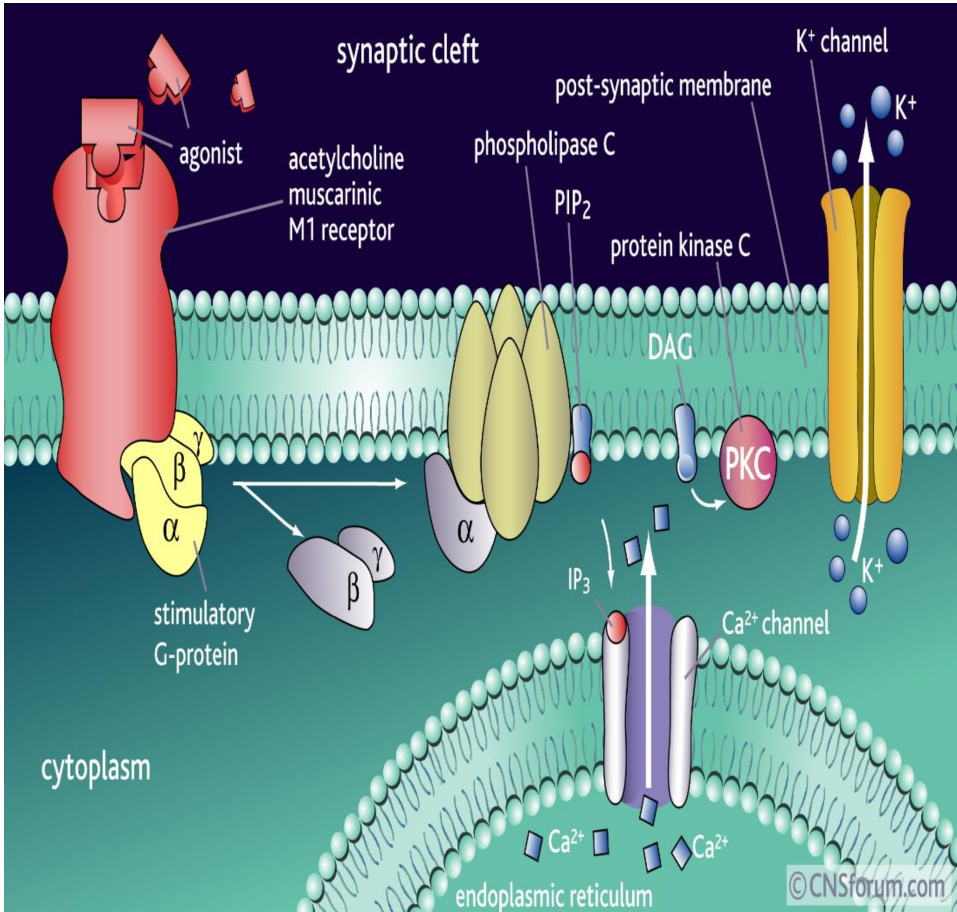
- **Acts on 2 cholinergic receptors:**
① **Nicotinic (ionotropic)** (antagonist-Curare): **excitatory**
② **Muscarinic (metabotropic)** (antagonist-Atropine):
    - **Excitatory** or **inhibitory**
    - Five subtypes (**M1-M5**): all present in the brain





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



The Cholinergic System-2

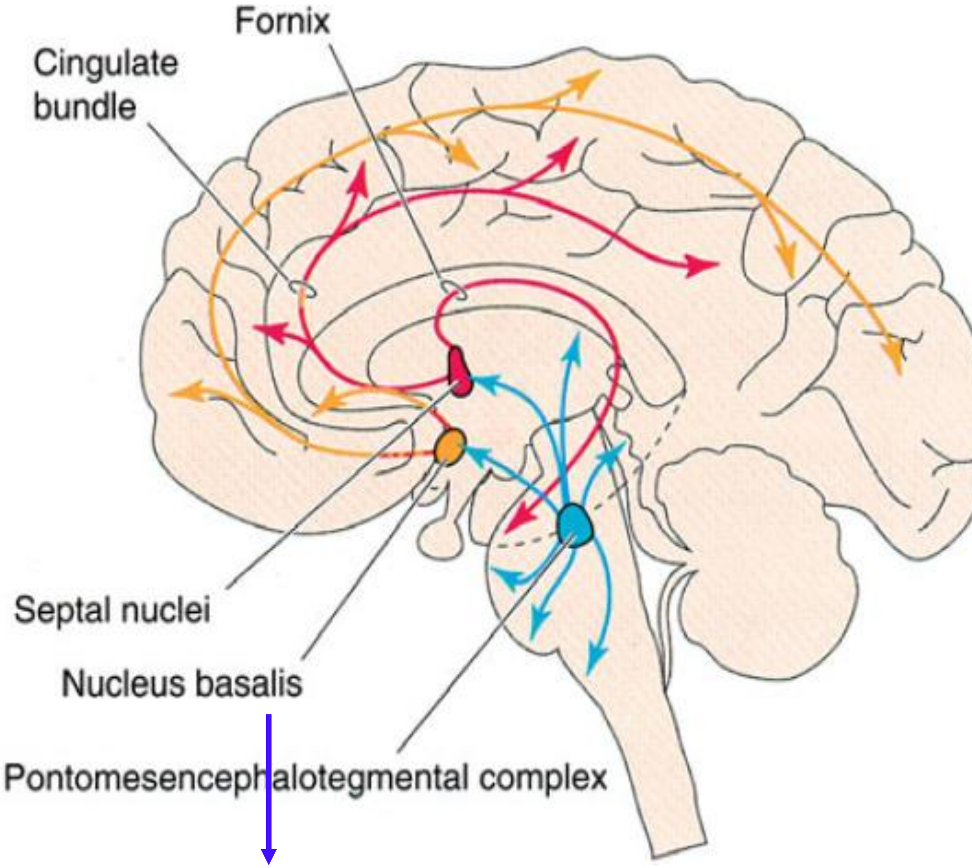
Ach is released from cholinergic neurons of:

❶ 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.

❷ Dorsolateral tegmentum neurons (pons) project to **basal ganglia, thalamus, cerebellum** hypothalamus, reticular formation

May be involved in regulation of sleep-wake states, learning/memory



Degeneration in Alzheimer's disease

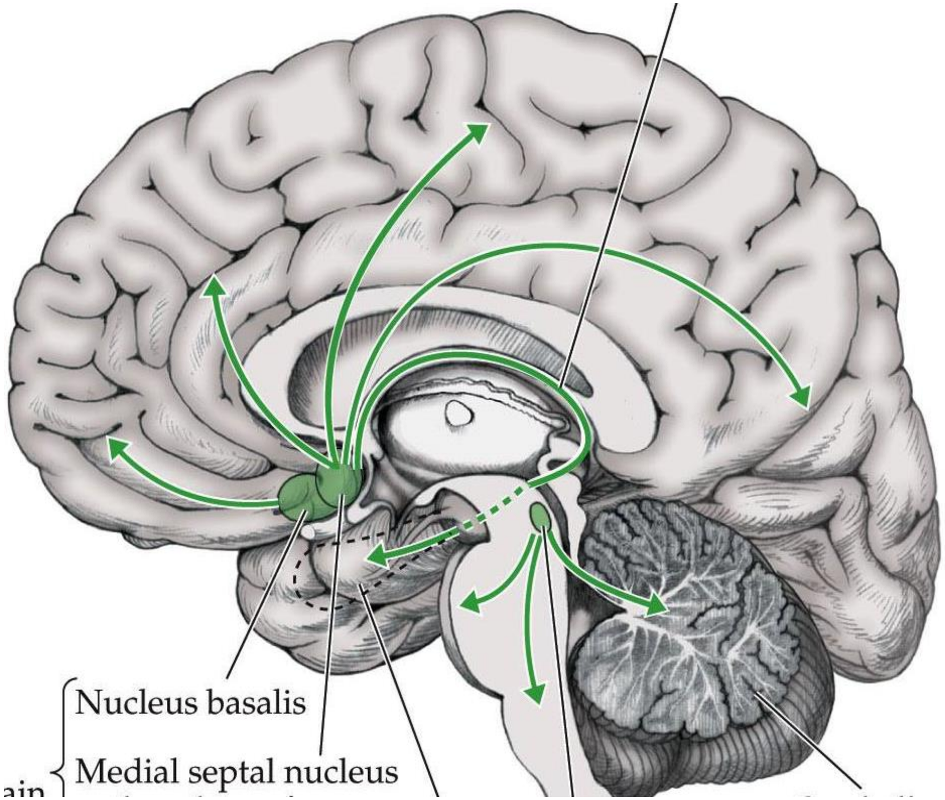
Functions & Disorders of Cholinergic System

Functions

- Learning & Memory
- Dreams & Wakefulness
- Anger & Aggression
- Sexuality & Thirst

Disorders

- **Alzheimer's disease** (death of Ach neurons)
- **Myasthenia gravis**
- **Mood swings**
- **Depression**



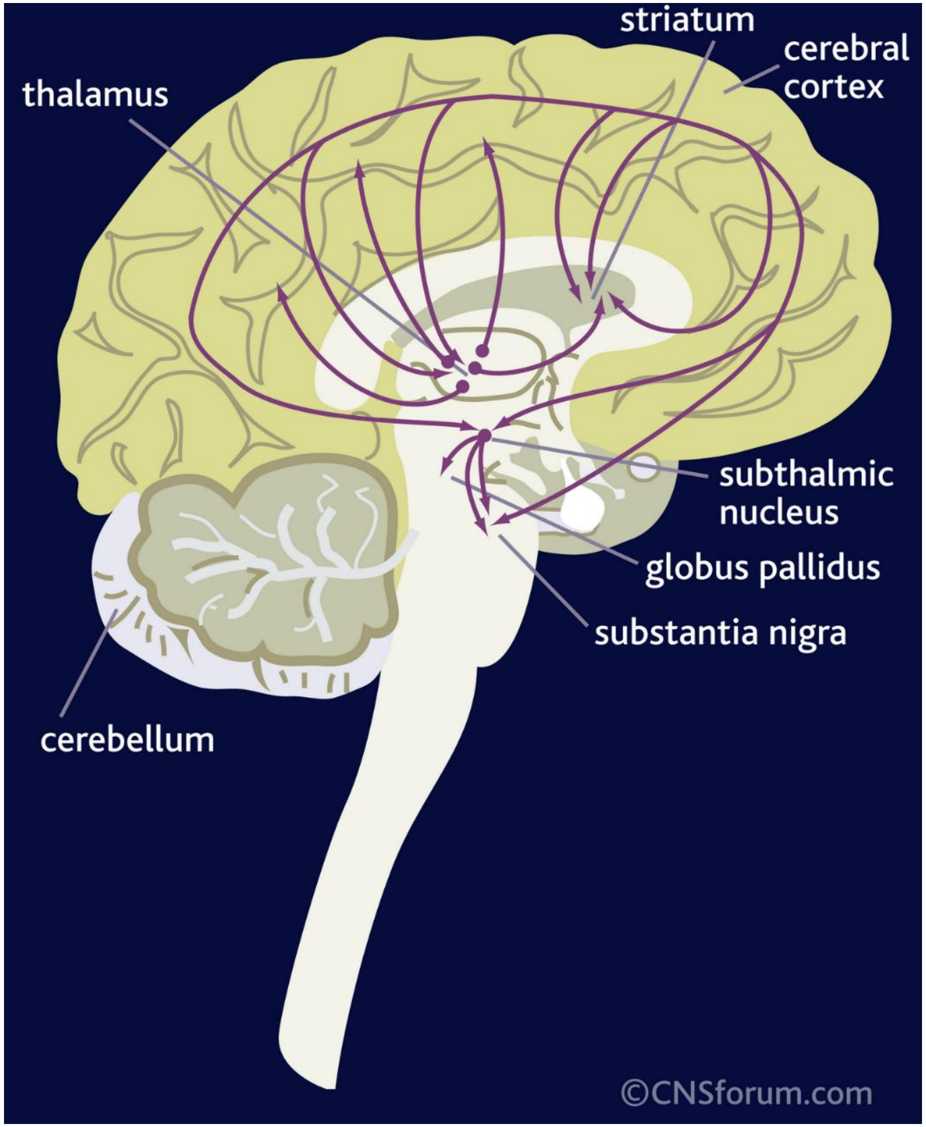
Inhibitors of acetylcholinesterase in the brain are the main drugs used to treat Alzheimer's disease.

2 The Glutaminergic System

- Glutamate is the most commonly found NT in the brain (**king** of NTs, ~50% neurons).

- 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**



Glutamate Receptors

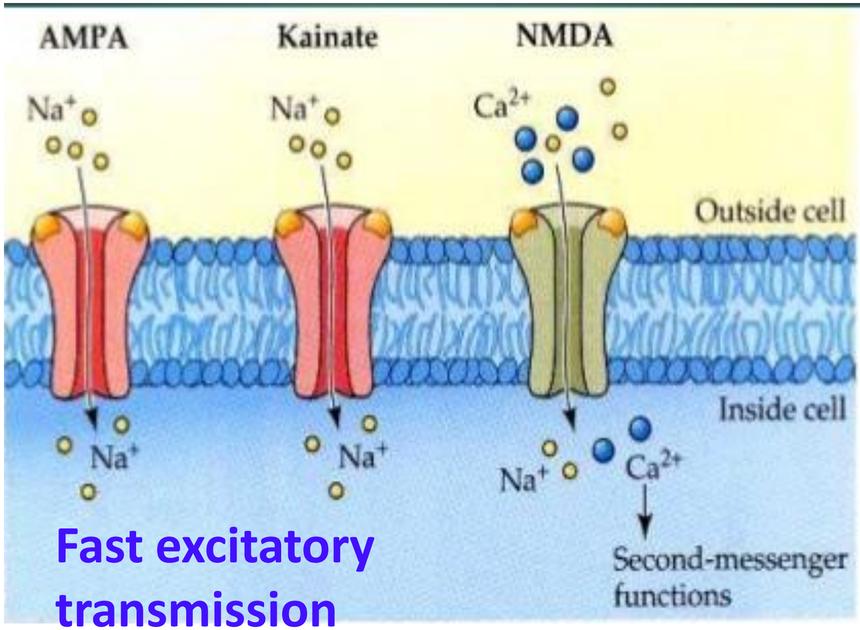
- **Are widely distributed in the brain; they are of two types:**

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:

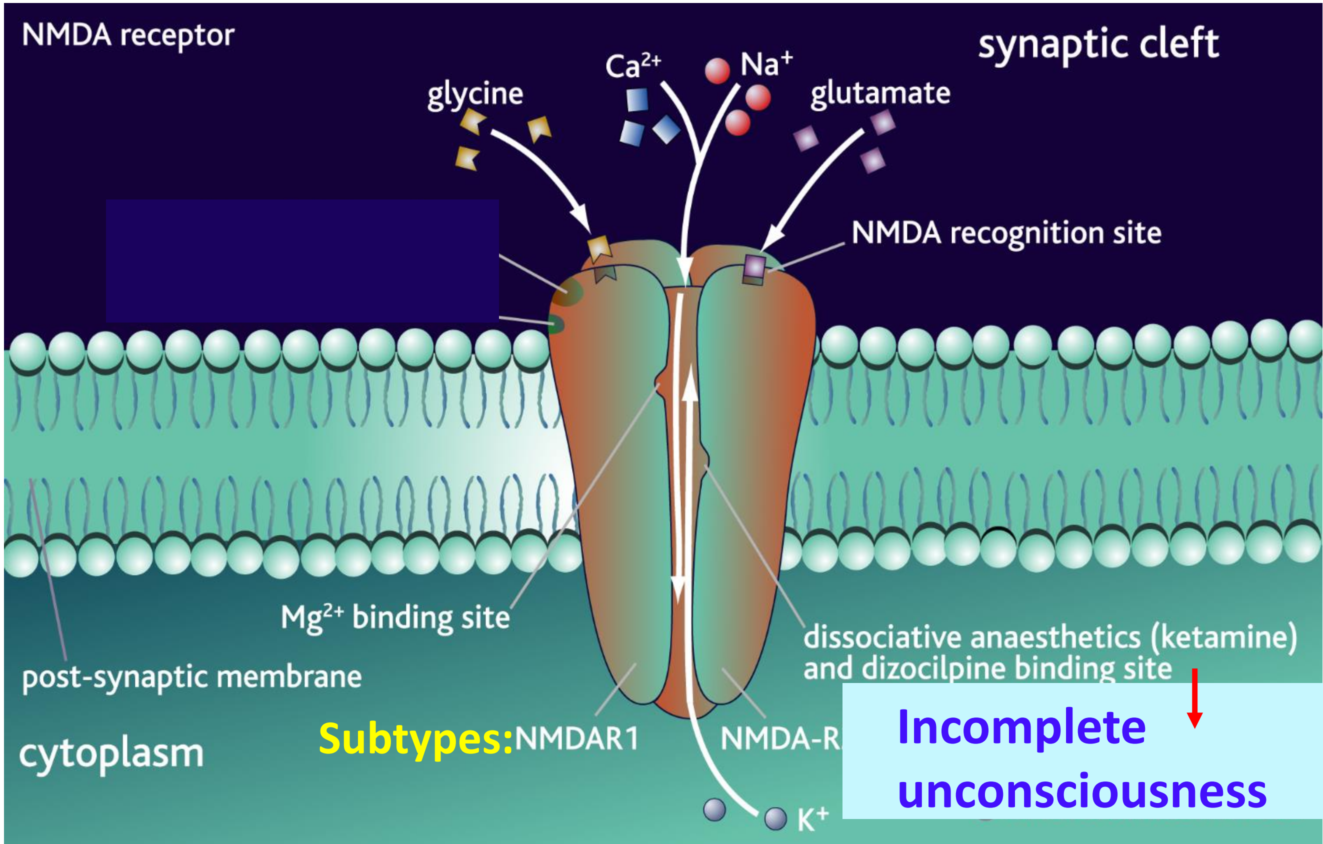
- **AMPA receptors** (α-amino-3-hydroxy-5-methylisoxazole-4-propionate)
- **Kainate receptors** (kainate is an acid isolated from seaweed),
- **NMDA receptors** (for N-methyl-D-aspartate); **play a role in synaptic plasticity related to learning and memory**



slow transmission

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



Incomplete unconsciousness ↓

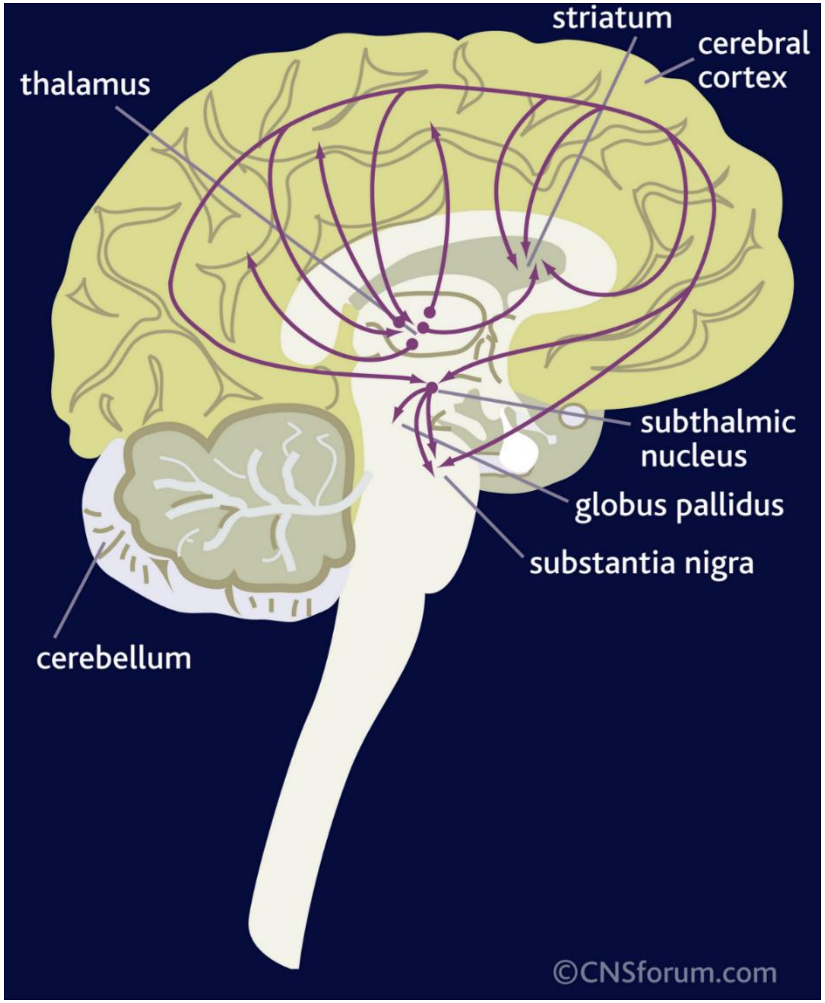
Functions & Disorders of Glutaminergic System

Functions

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

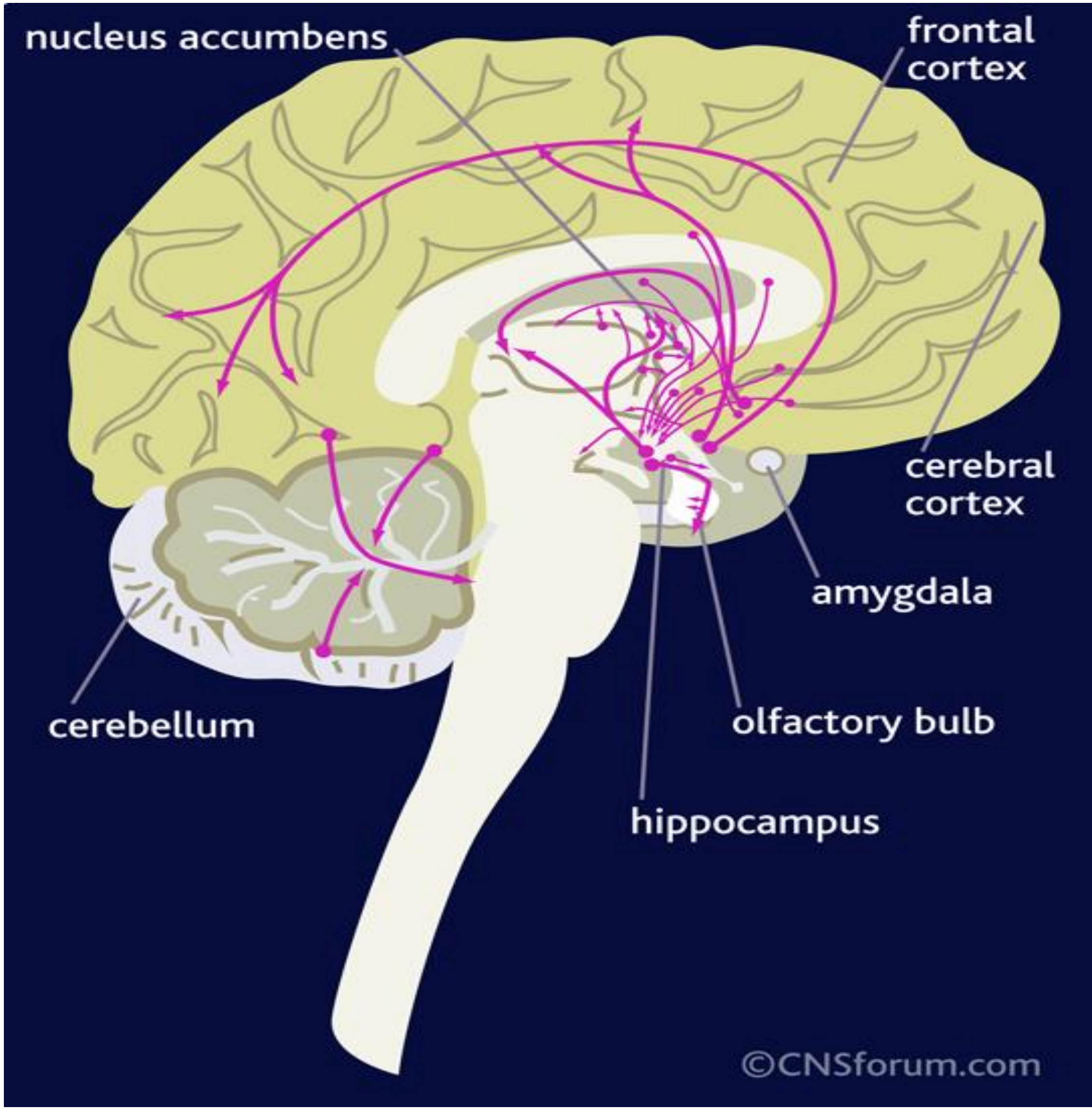
Disorders

- **Alzheimer's disease**
- **Schizophrenia**
- **Reduced levels in stroke and autism**



3 The GABAergic System-1

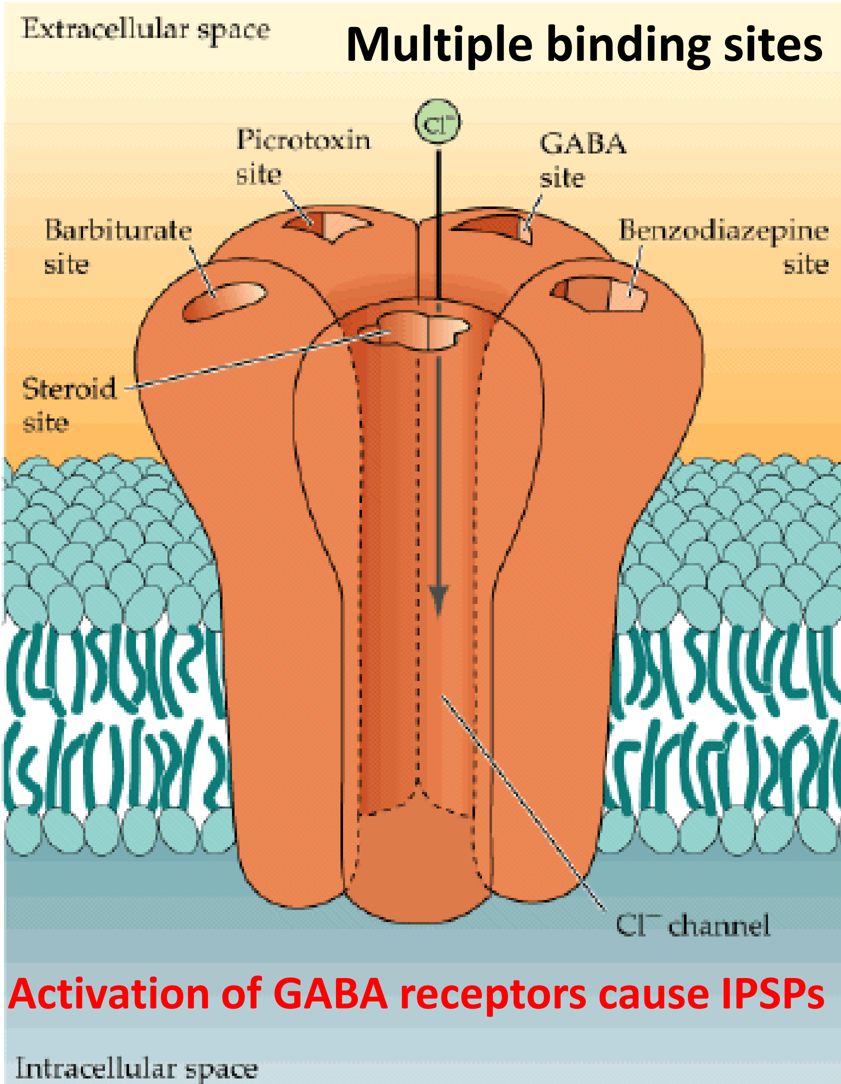
- **GABA** is the main inhibitory NT in CNS.
- **GABAergic inhibition** is seen at all levels of the CNS:
  - Cerebral cortex
  - Cerebellar cortex
  - Hypothalamus
  - Hippocampus
- GABA interneurons are abundant in the brain, with **50%** of inhibitory synapses in the brain being **GABAergic**.



The GABAergic System-2

- Formed by decarboxylation of glutamate.
- **Three types of GABA receptors**:
  GABA A, B & C .
- GABA A & B receptors are widely distributed in CNS.
- GABA C receptors (in retina only)
- GABA B are **metabotropic** (G-protein) receptors (**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^+)

The fabulous GABA receptor



Functions & Disorders of GABAergic System

Functions

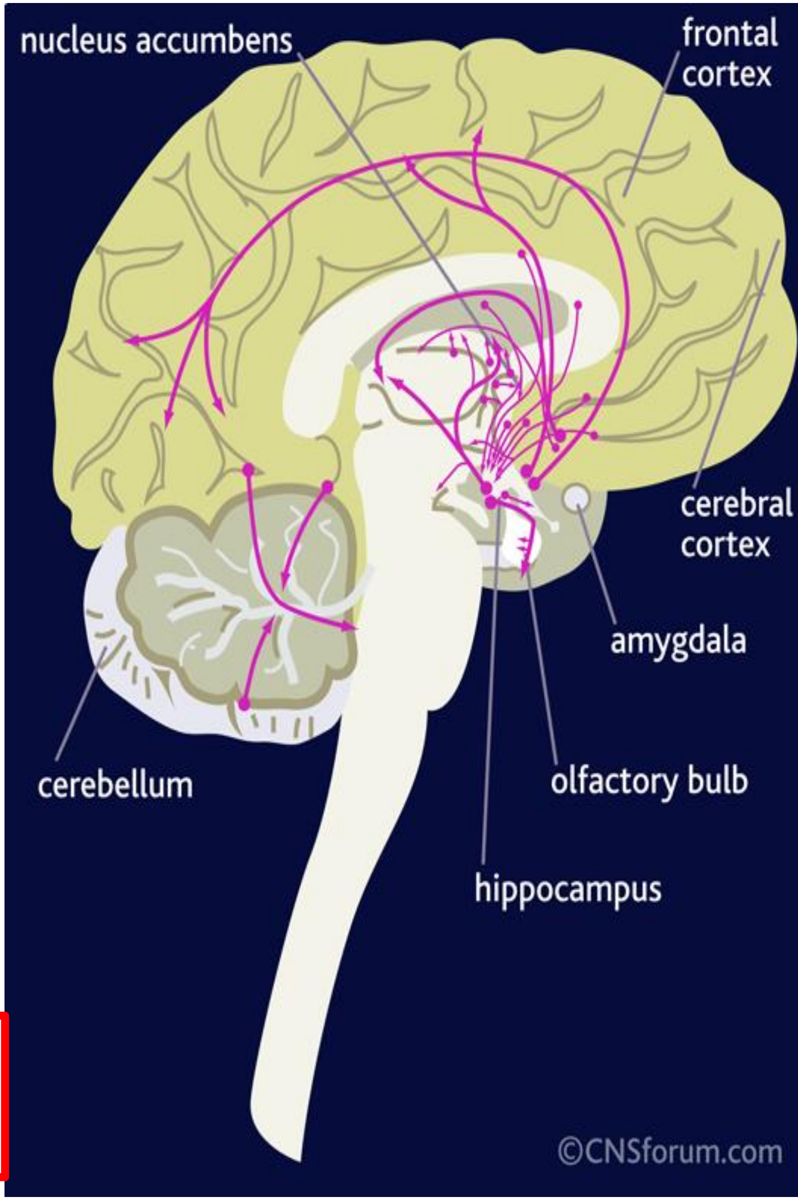
- Presynaptic inhibition
- GABAA receptors in the CNS are chronically stimulation to regulate neuronal excitability

Disorders

- **Seizures**

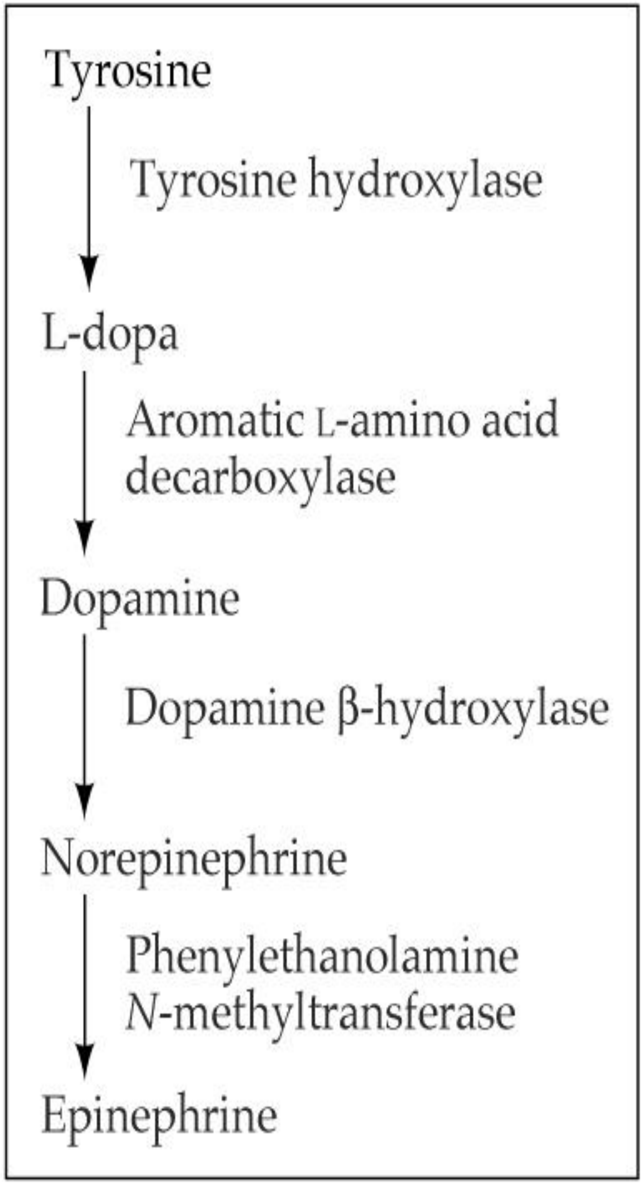
(under activity of GABA)

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



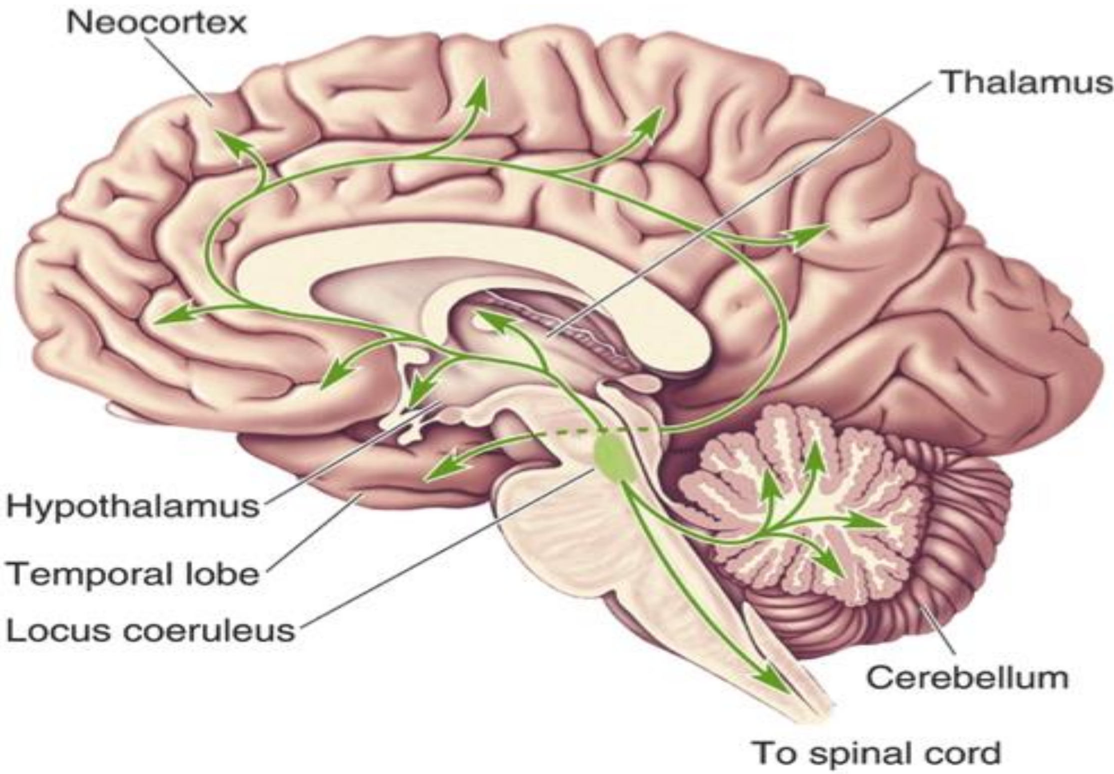
④ The Noradrenergic System-1

- **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.**



The Noradrenergic System-2

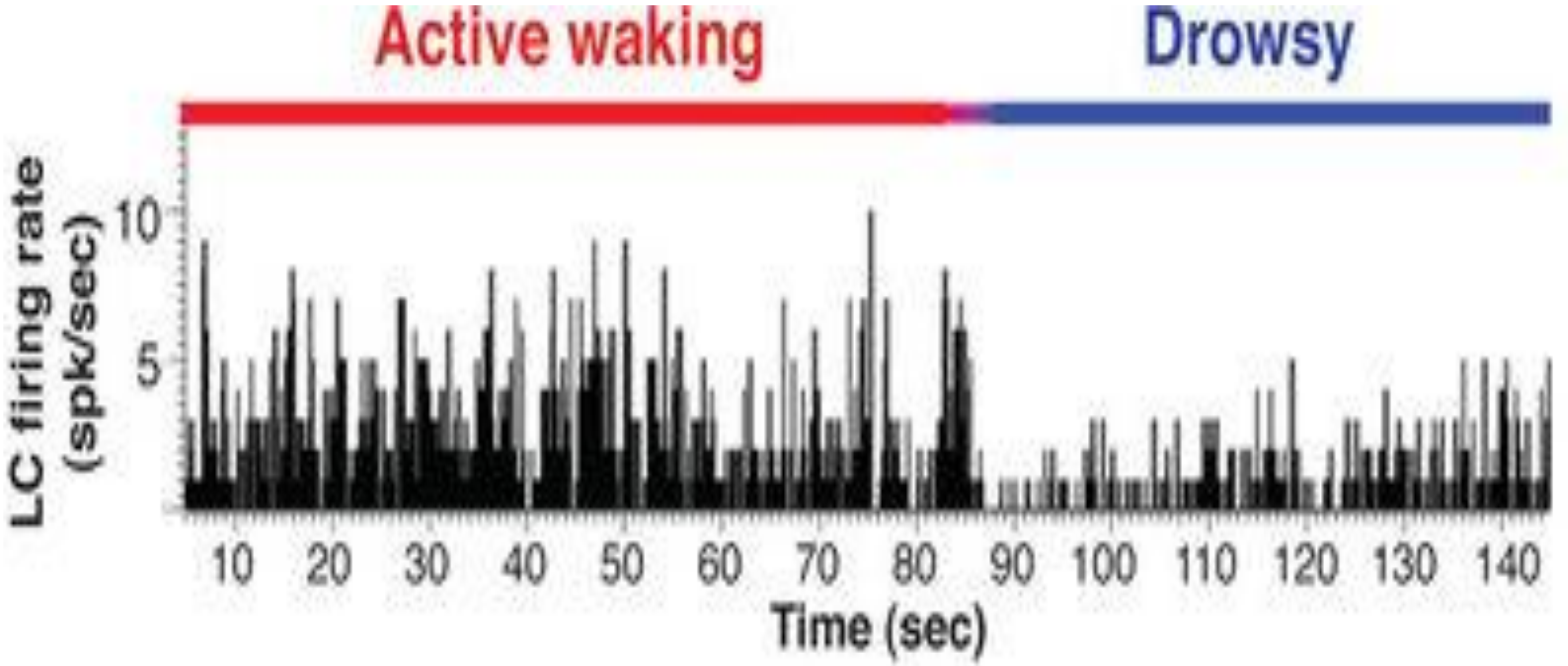
- **Noradrenergic neurons are located in locus coeruleus (LC) which projects to:**
  - **Spinal cord (pain)**
  - **Cerebellum**
  - **Thalamus & amygdala**
  - **Hypothalamus**
  - **Cerebral cortex**
  - **Autonomic brainstem centers**
- It constitutes part of the Reticualr Activating System (RAS) → **alertness**



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

The Noradrenergic System-3

- LC neurons fire as a function of **vigilance** and **arousal**
- Irregular firing during **quiet wakefulness**
- Firing of LC neurons decreases markedly during slow-wave sleep & virtually disappears during REM sleep.
- **Stress causes very high levels of LC activity**



The Noradrenergic System-4

Functions

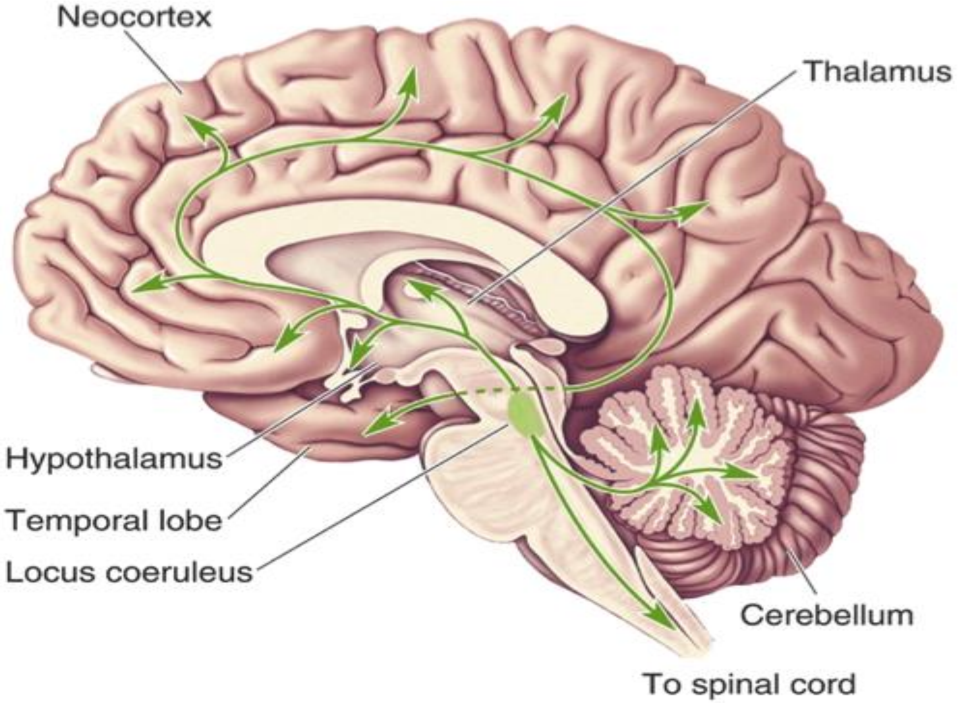
- Attentiveness & Vigilance
- Learning
- Aggressive behaviour
- Fight-or-Flight response

Disorders

- Depression & Panic disorders

Deficiencies in NA

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

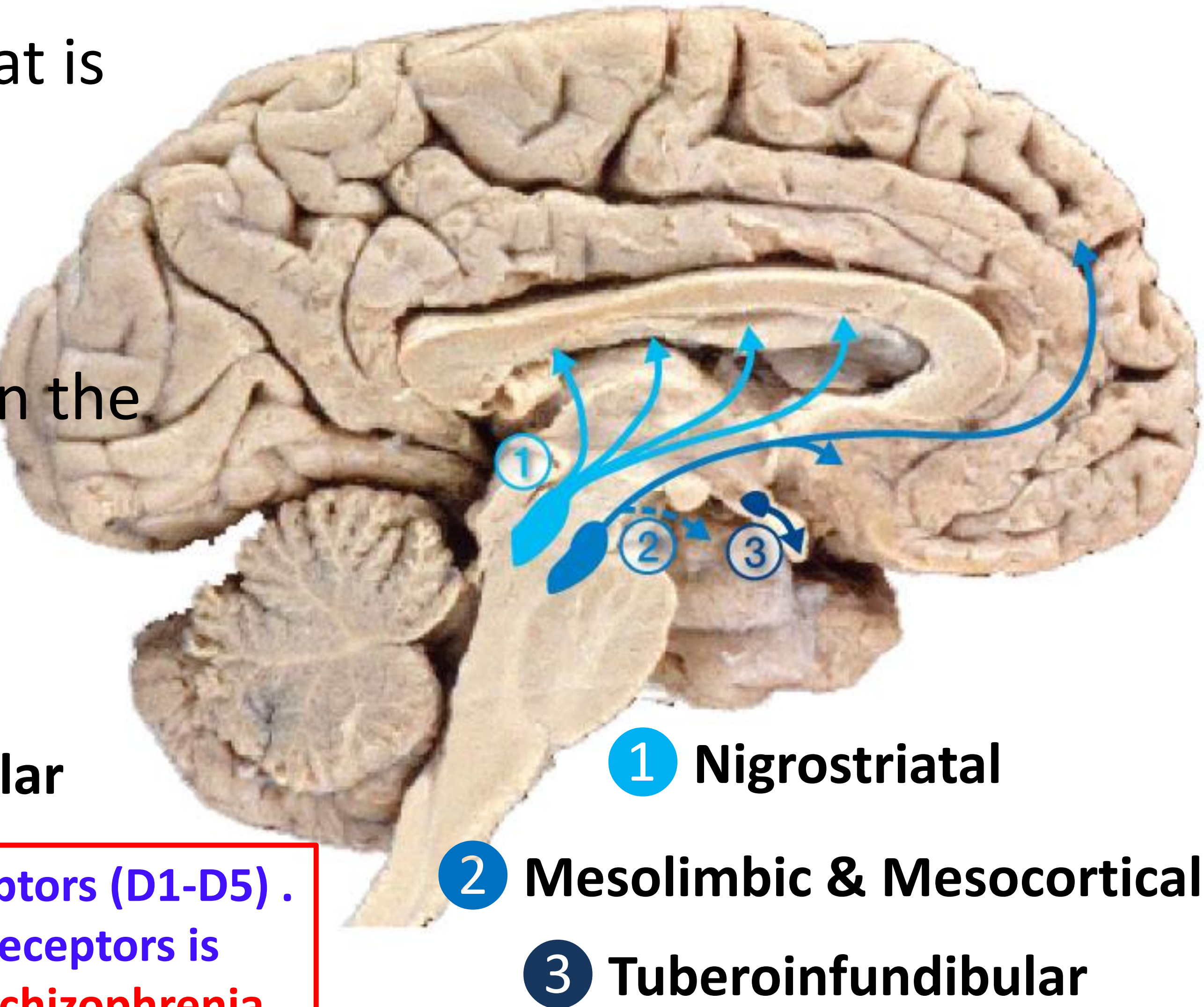


✓ Drugs that suppress LC have a powerful sedating effect because LC controls arousal level

⑤ The Dopaminergic System-1

- **Dopamine** is a catecholamine that is synthesized from **tyrosine**
- It is present in 3 principal circuits in the brain:

❶ **Nigrostriatal**
❷ **Mesolimbic & Mesocortical**
❸ **Tuberoinfundibular**

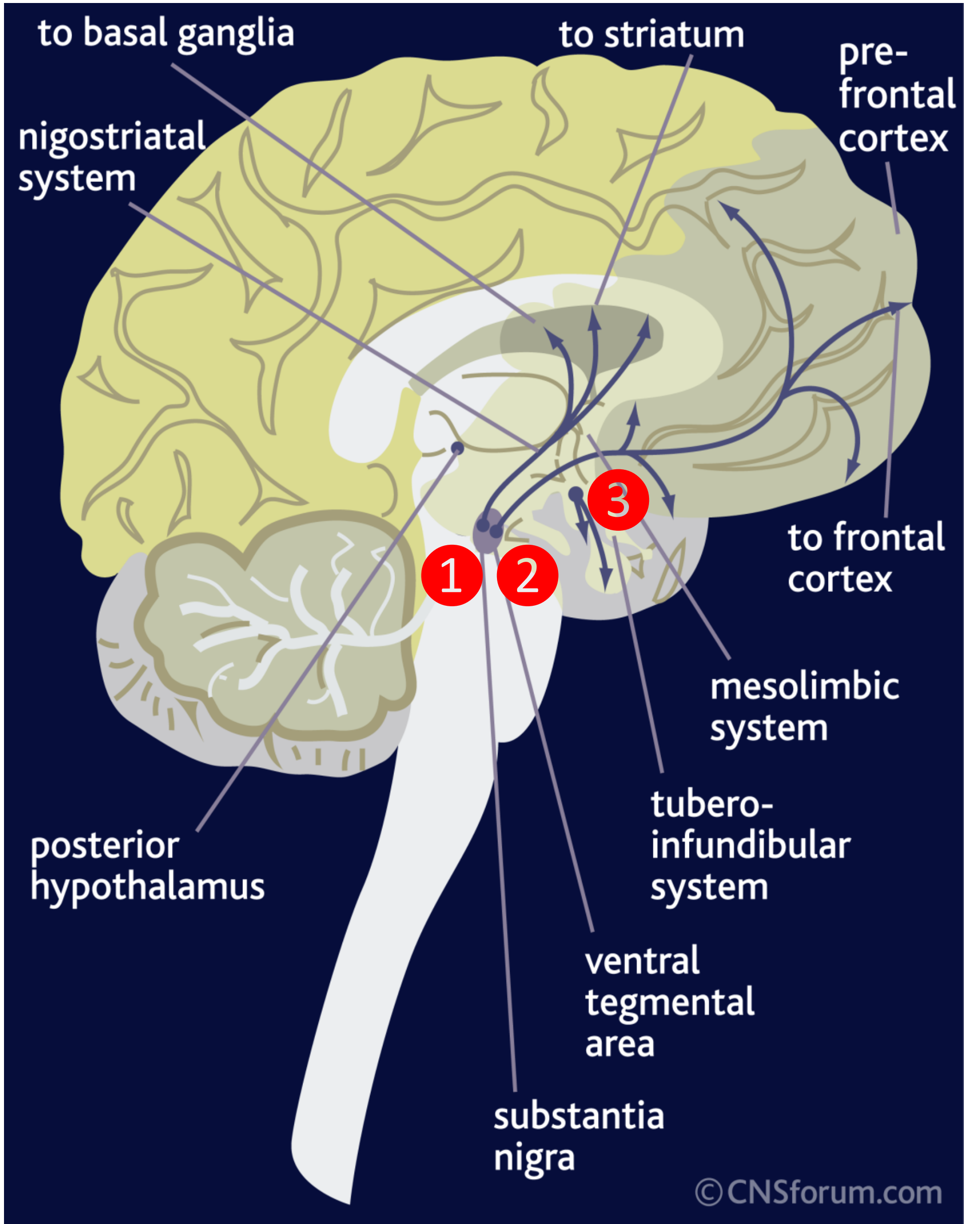


- **Five dopaminergic receptors (D1-D5) .**
- **Overstimulation of D2 receptors is thought to be related to schizophrenia**

The Dopaminergic System-2

❶ **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**

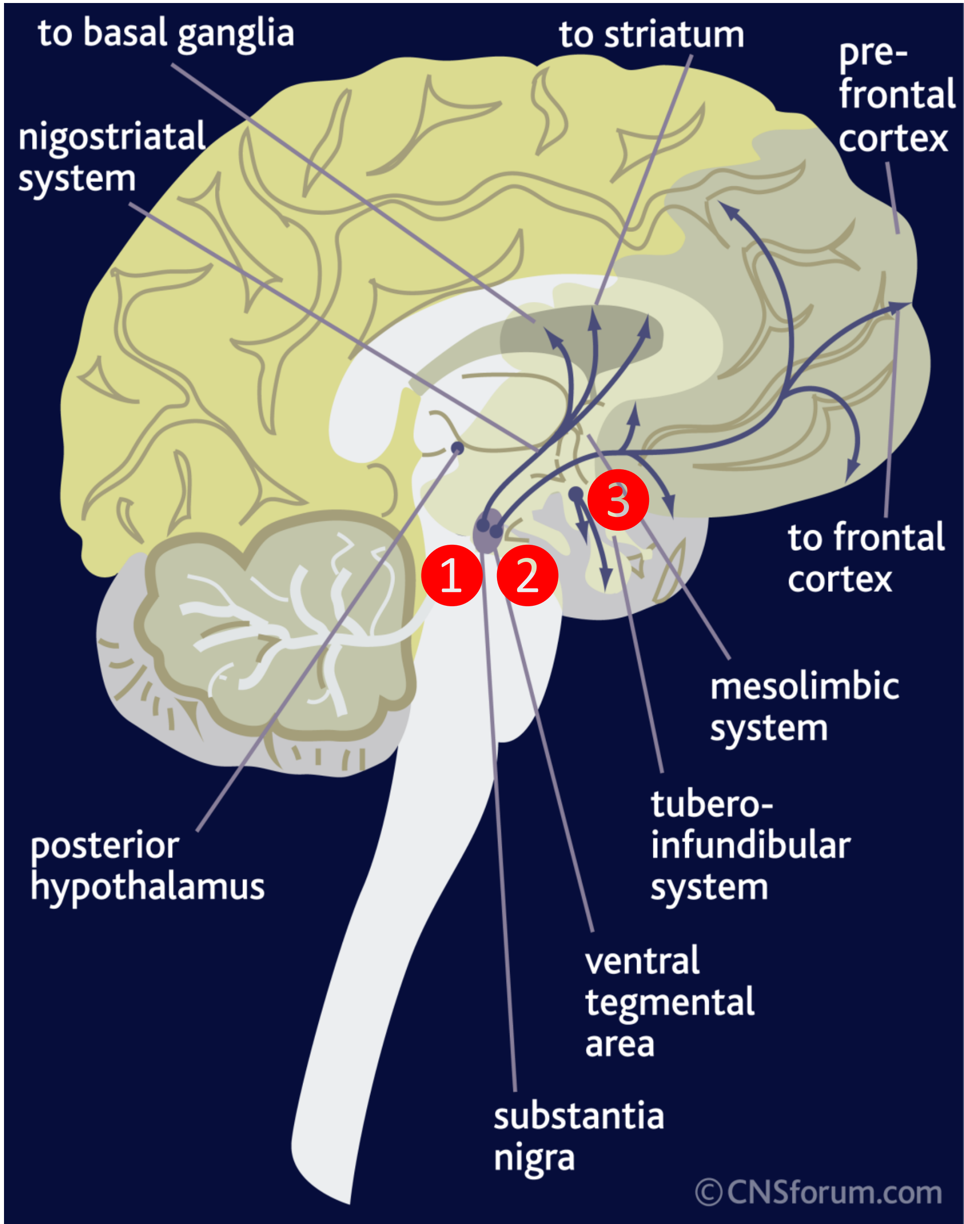


The Dopaminergic System-3

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**

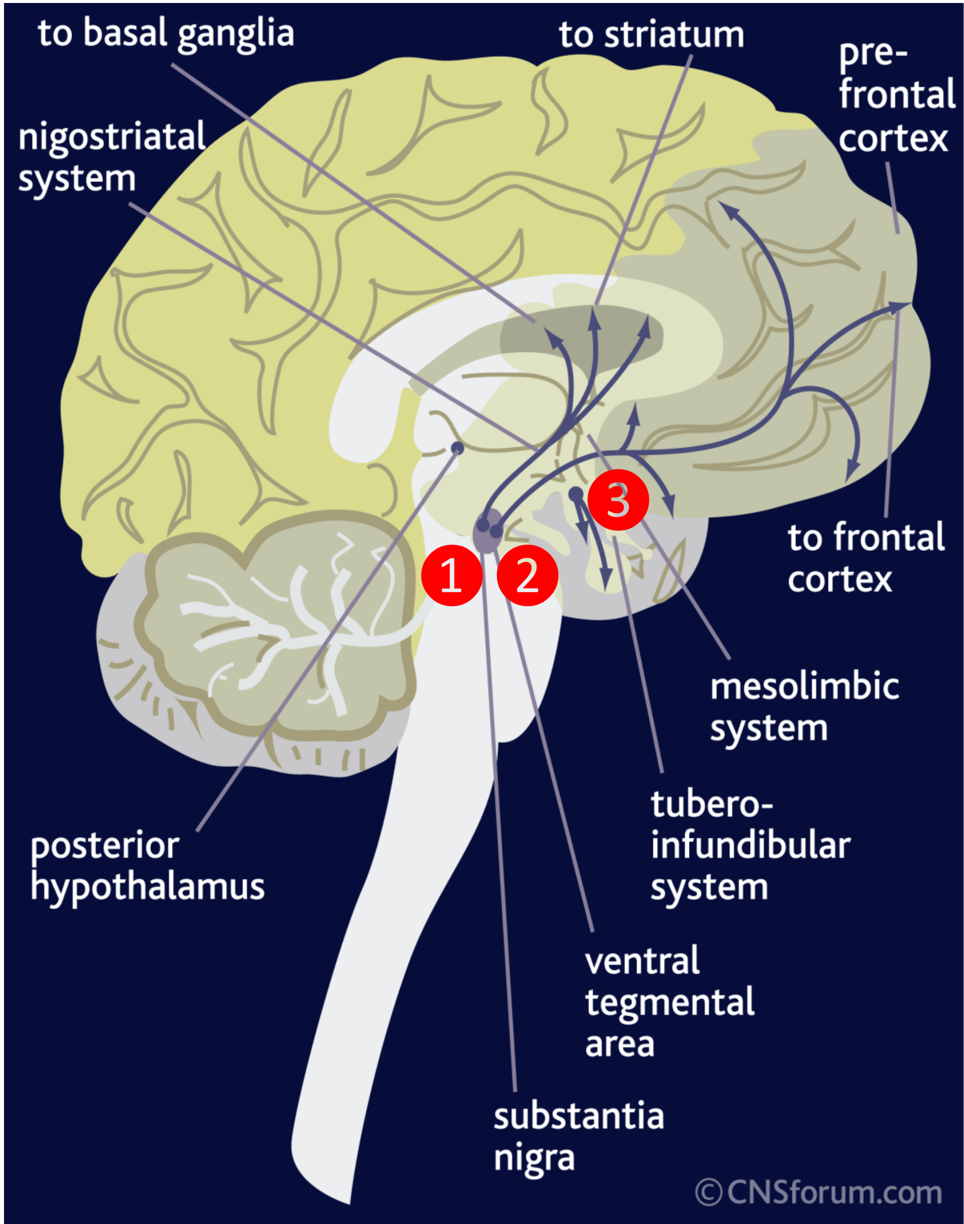


The Dopaminergic System-4

❸ **Tuberoinfundibular system** extends from infundibular region (**median eminence of hypothalamus**) to:

- **Pituitary gand**

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



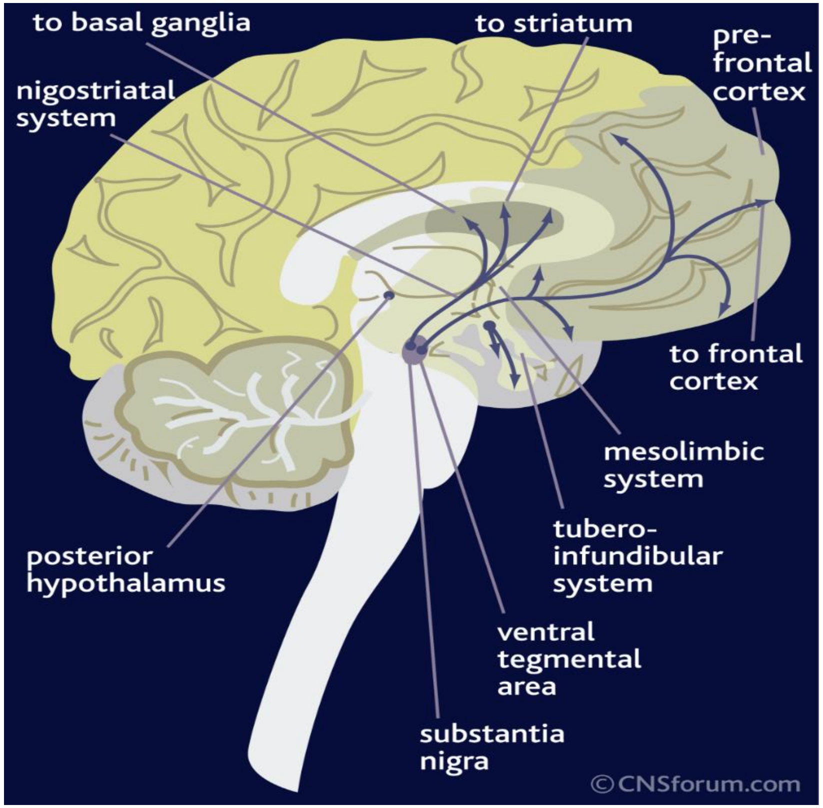
Functions & Disorders of Dopaminergic System

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**

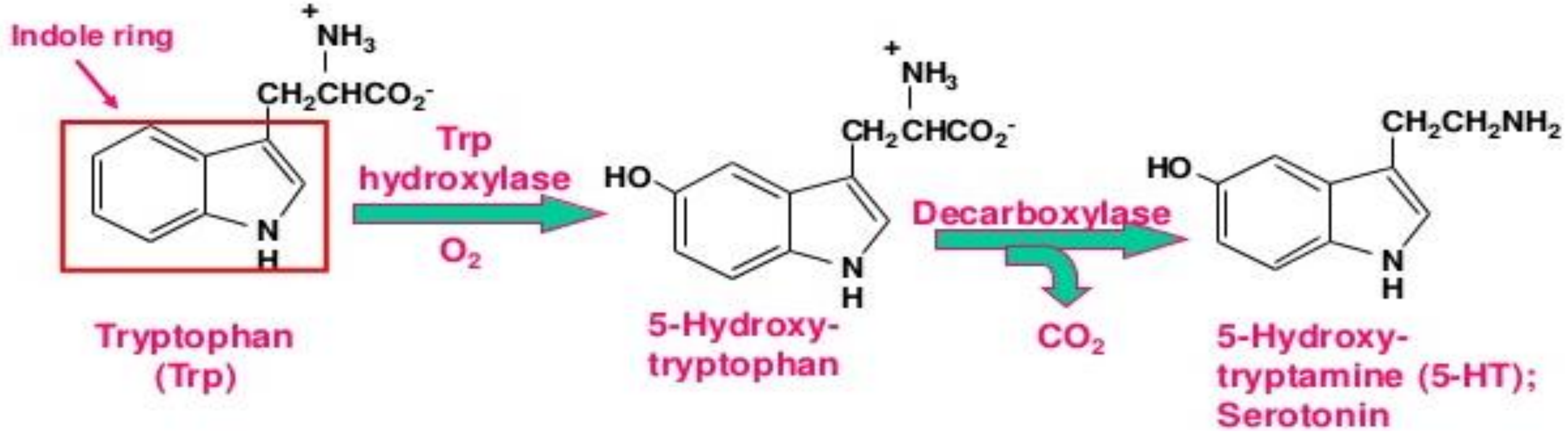


✓ **Cocaine elevate activity at dopaminergic synapses**

EUPHORIA

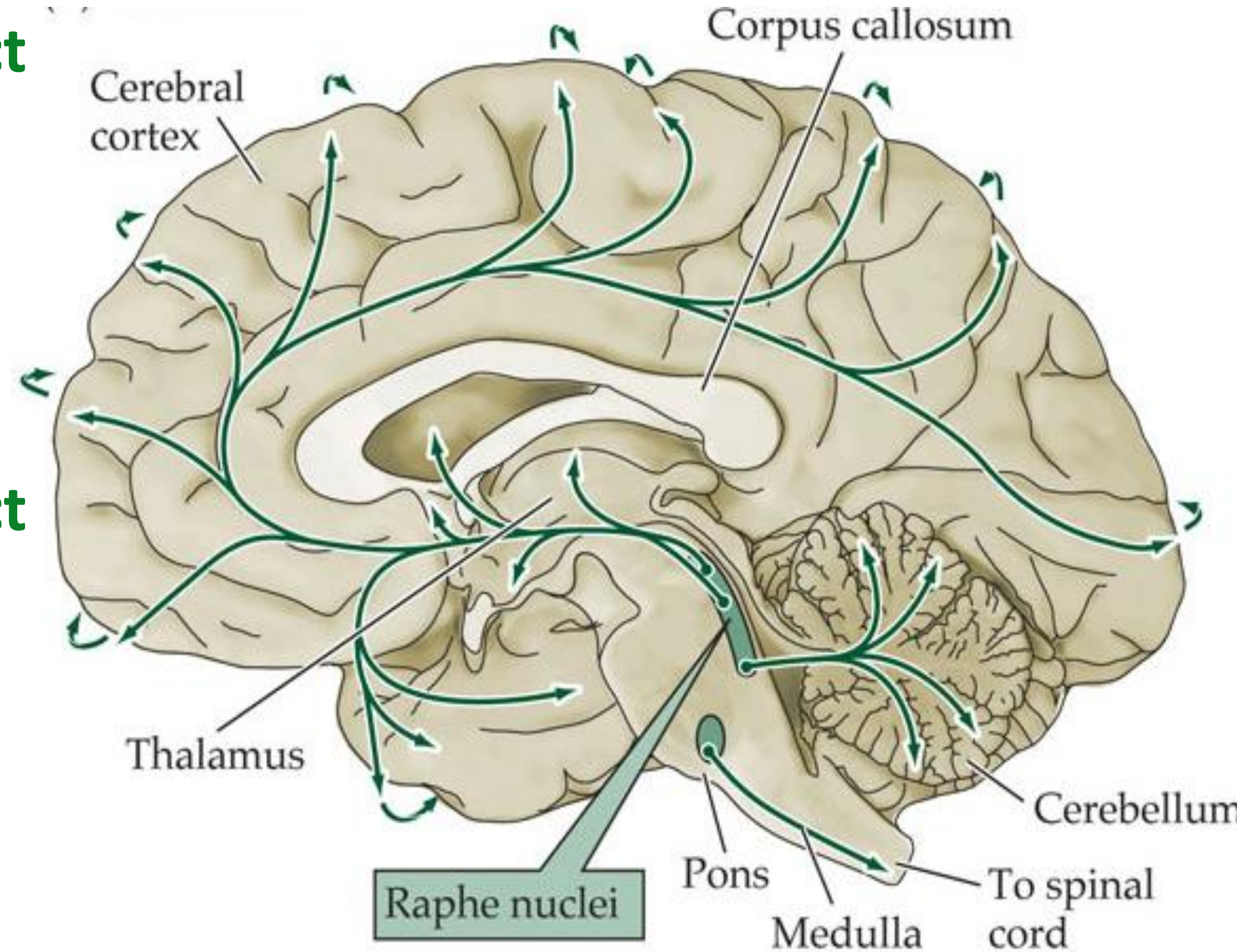
6 The Serotonin System-1

- 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-2

- **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



Serotonin innervates the entire CNS

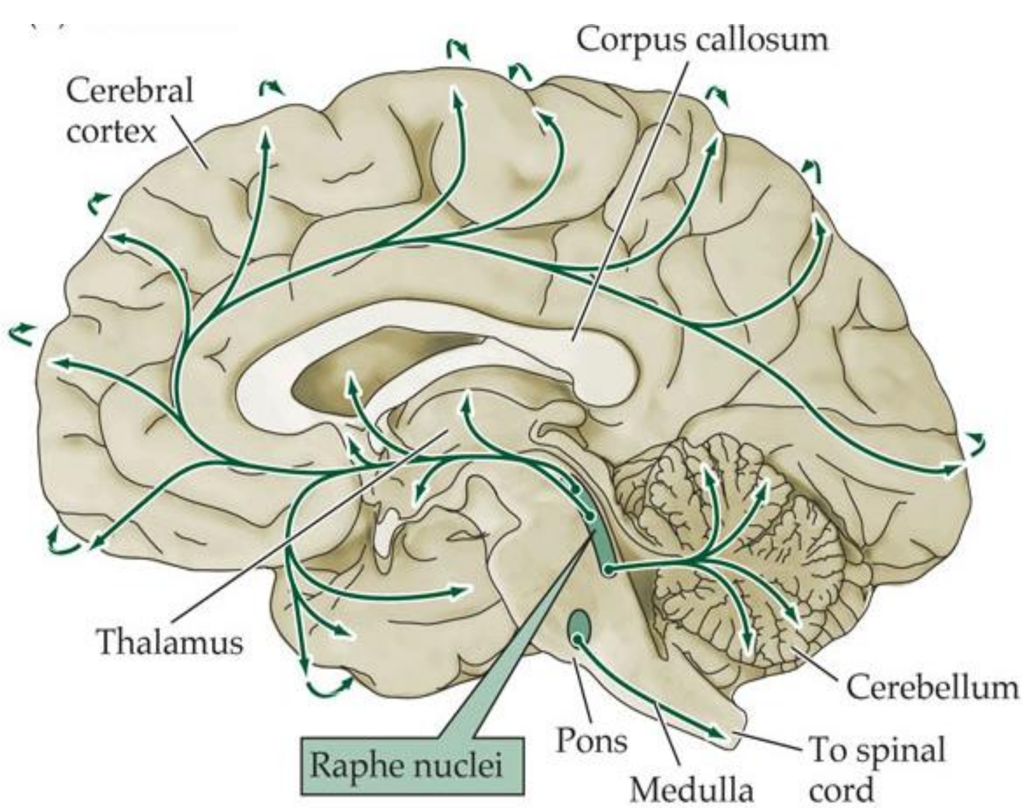
Functions & Disorders of Serotonin System

Functions

- Mood & appetite
- Sleep & pain
- Sexual function
- Cognition

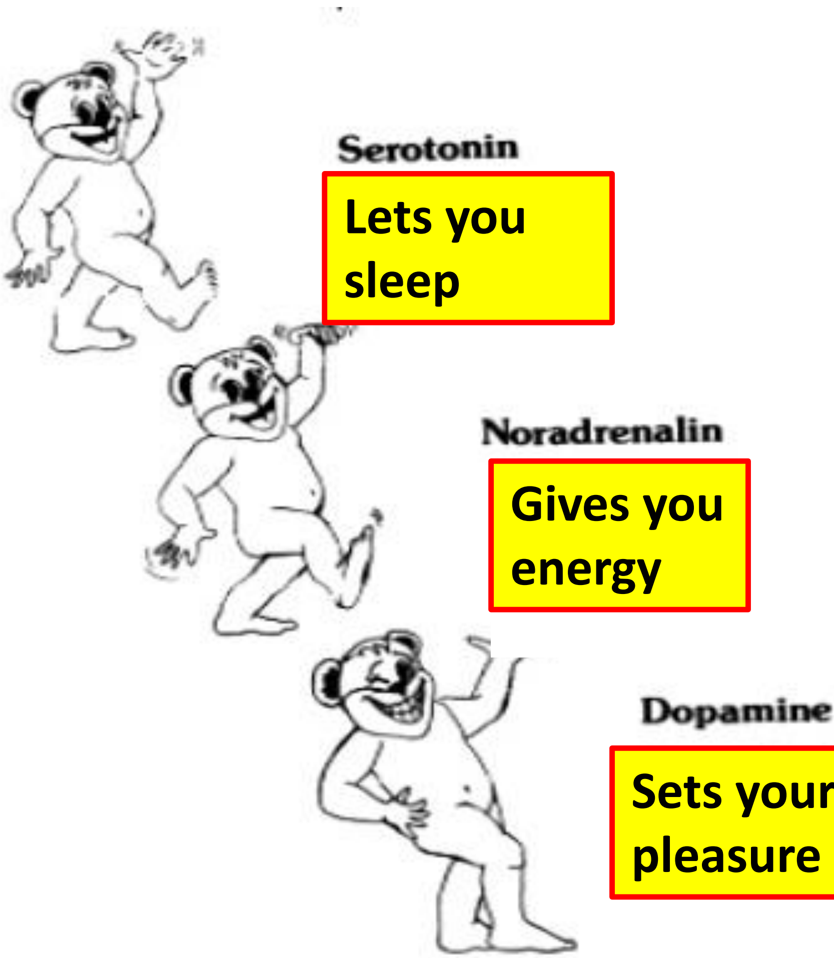
Disorders

- Depression
- Anxiety and suicide
- Aggressiveness



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

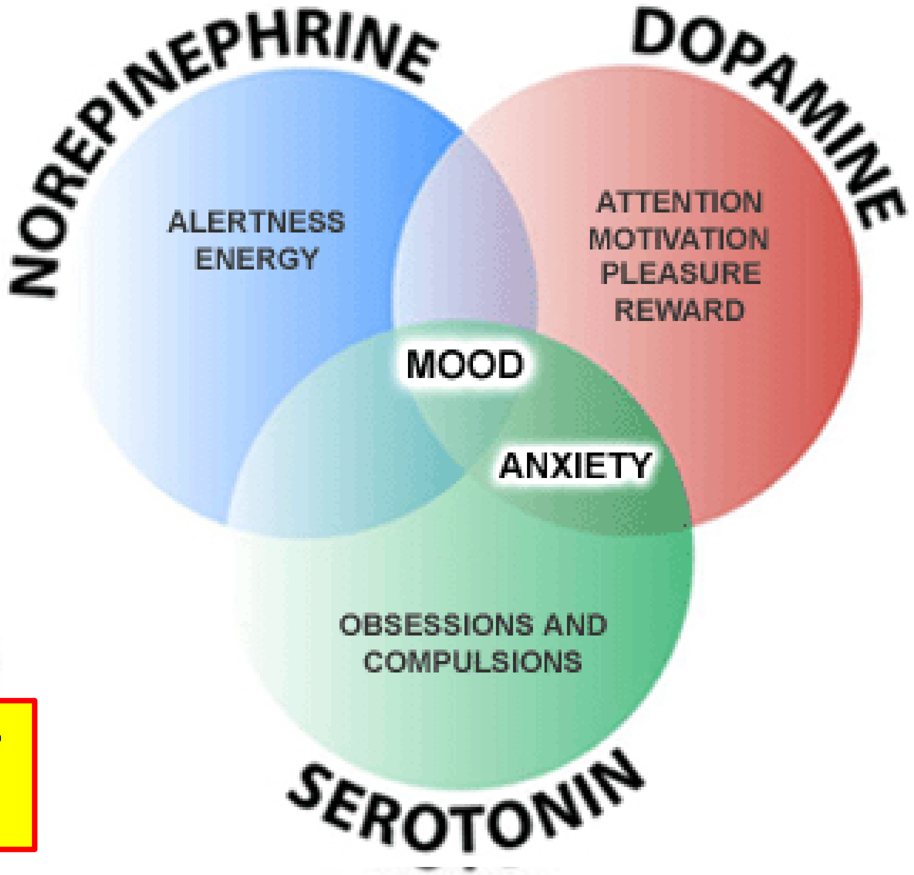
The Three Happy Neurotransmitters



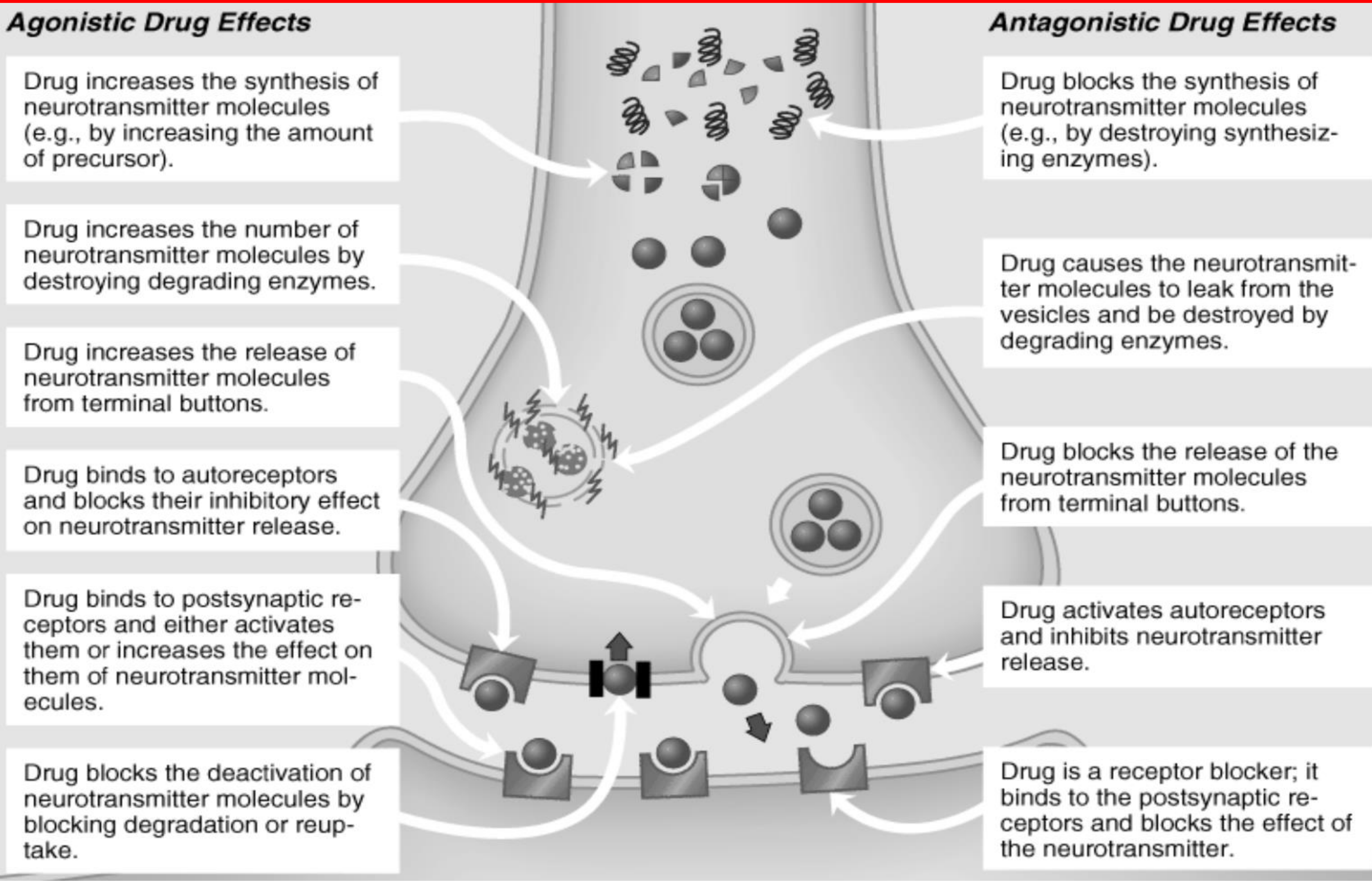
Lets you sleep

Gives you energy

Sets your pleasure



Some Mechanisms of Drug Action

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