

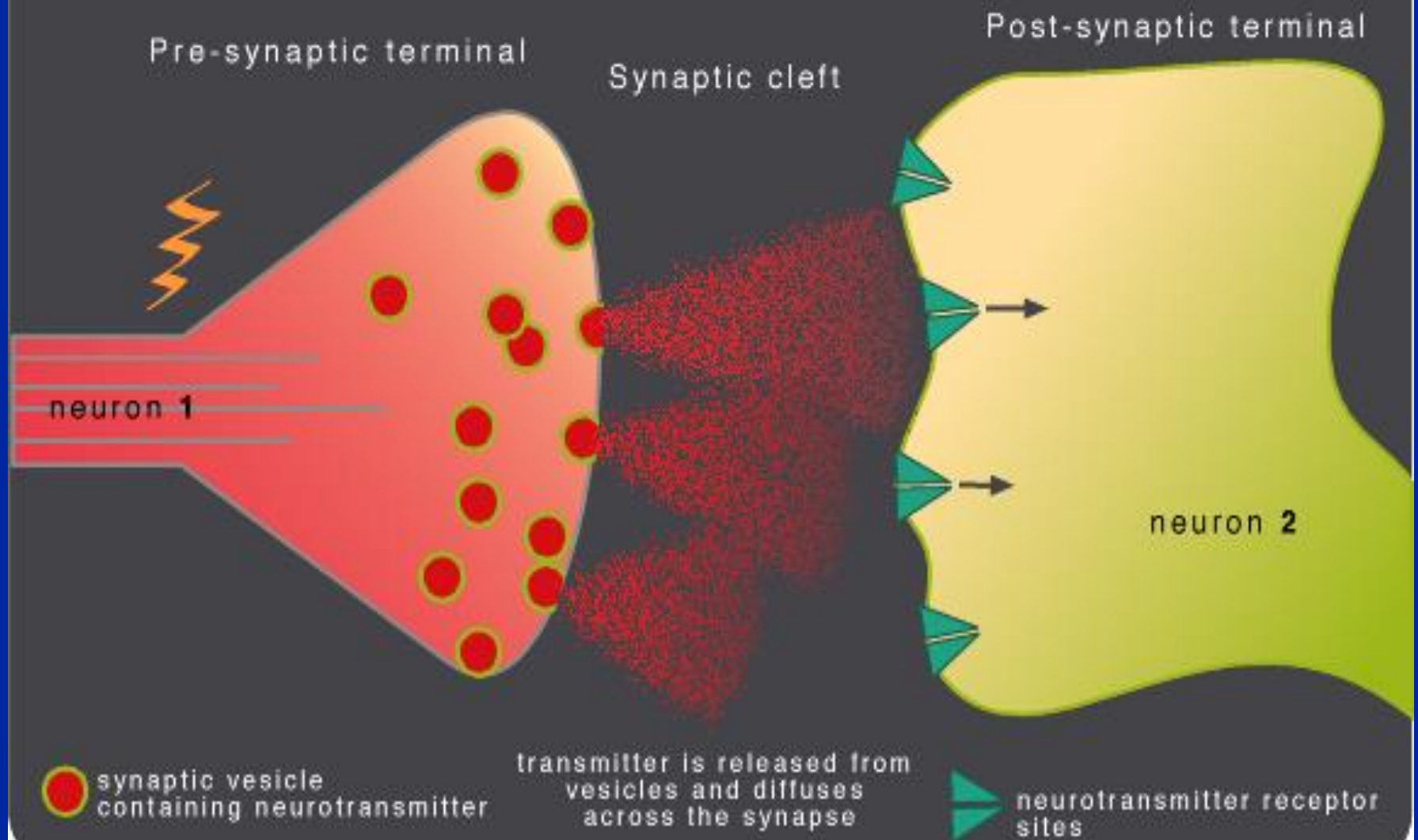
# **Pharmacology of central Neurotransmitters**

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## **- Objectives**

- The main objective of this lecture is to understand the role of neurotransmitters in the etiology and treatment of CNS diseases**

# THE SYNAPSE

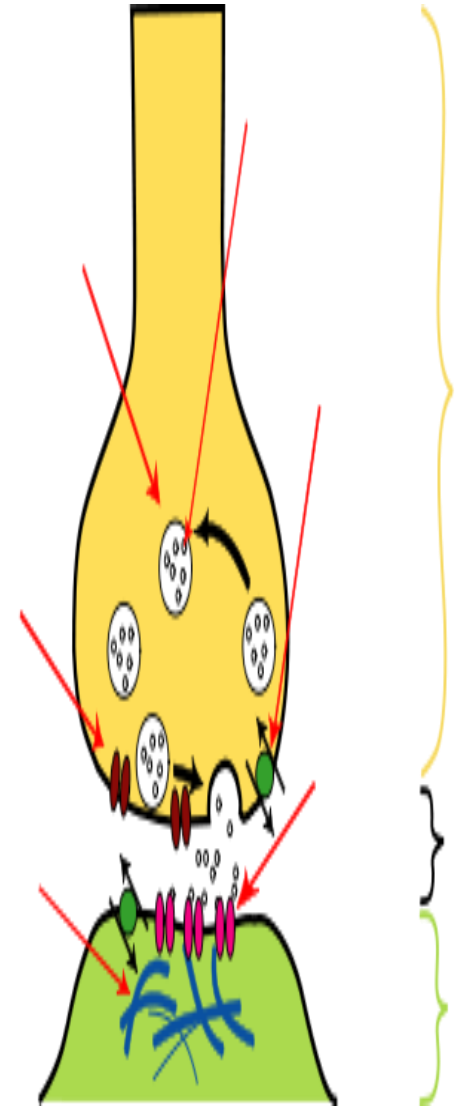


# Neurotransmitters

- **Endogenous** chemicals or chemical messengers that enable neurotransmission (transmit signals from a neuron to a target cell across a synapse).
- They are packed into **synaptic vesicles** under the membrane in the axon terminal, on the **presynaptic side**.
- They are released into & diffuse across the synaptic cleft to bind to a specific receptor on the **post synaptic side**.

- The neurotransmitter-receptor interaction must be terminated quickly to allow rapid, repeated activation of receptors. **One of the following can happen to neurotransmitters that have interacted with receptors:**

- 1- They can be quickly pumped back into the presynaptic nerve terminals by active, ATP-dependent processes (reuptake).
  - 2- They can be destroyed by enzymes near the receptors.
  - 3- They can diffuse into the surrounding area and be removed.
- Neurotransmitters taken up by the nerve terminals are repackaged in vesicles for reuse.



- **Neuropsychopharmacological science seeks to :**
  - ❖ Understand how drugs can affect the CNS selectively to relieve pain, improve attention, induce sleep, reduce appetite, suppress disordered movements ....ect.
  - ❖ To provide the means to develop appropriate drugs to correct pathophysiological events in the abnormal CNS.

# Examples of neurotransmitters

## □ Amino acids:

Glutamate (Glu), gamma aminobutyric acid (GABA)

## □ Monoamines & other biogenic amines:

Dopamine (DA), Norepinephrine (NE), Serotonin (5-HT)

## □ Peptides:

Somatostatin

## □ Others:

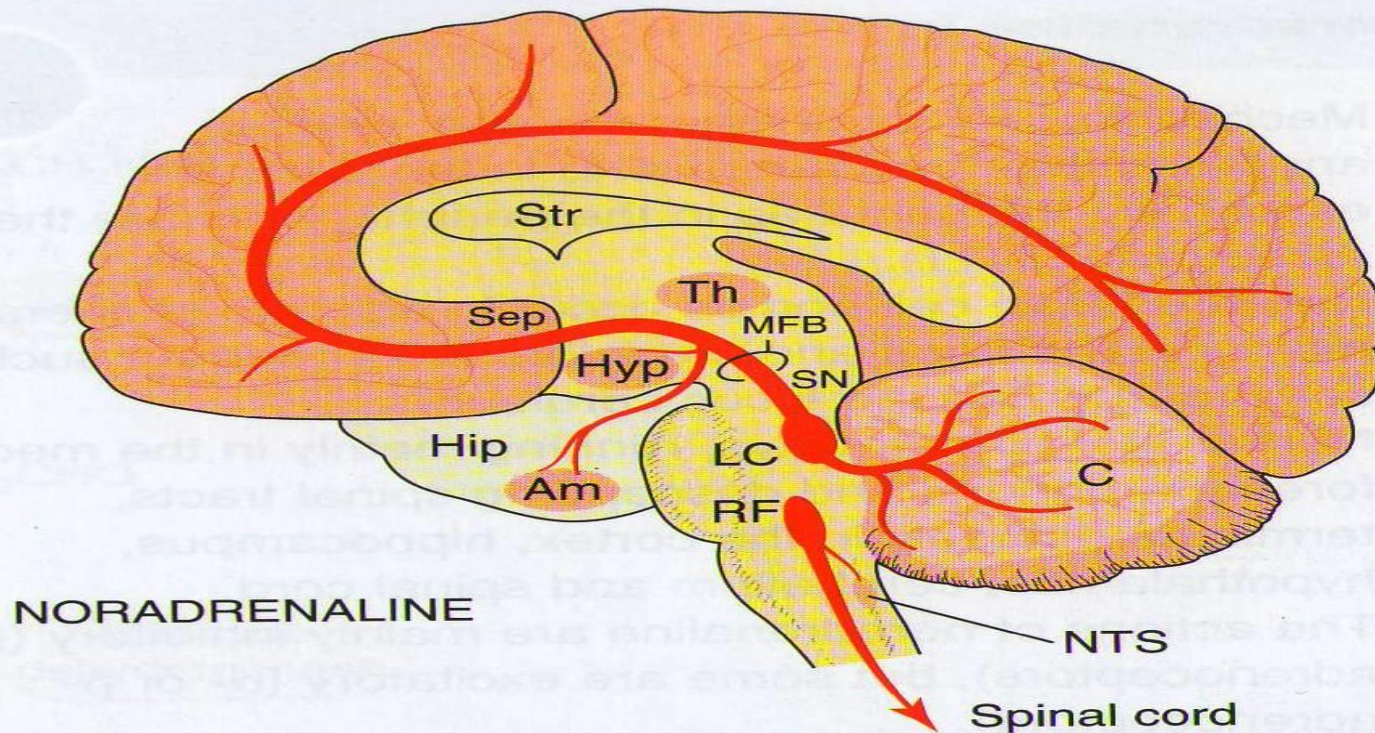
Acetylcholine (Ach)

# **What is the importance of understanding neurotransmitters**

- ❖ To understand the etiology of diseases**
- ❖ To suggest the best drugs to be used**
- ❖ To understand the other clinical uses of any particular drug**



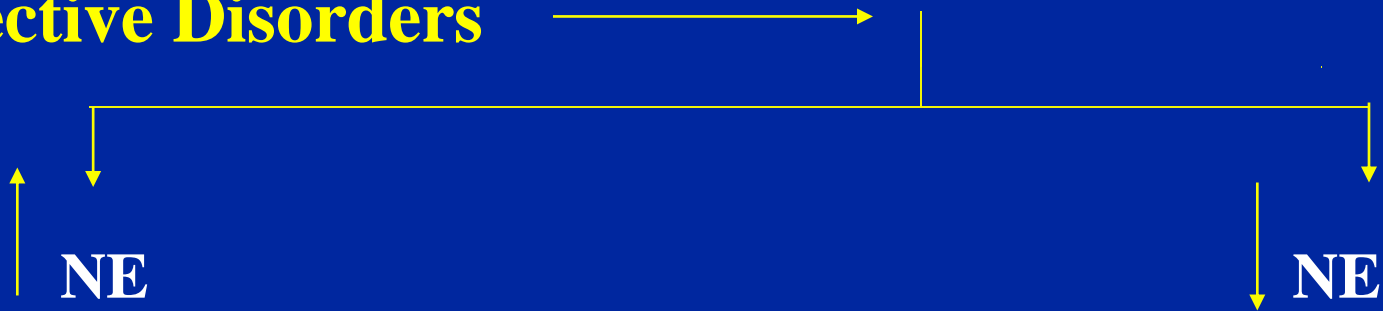
# Norepinephrine ( NE)



**Fig. 33.1** Noradrenaline pathways in the brain. The location of the main groups of cell bodies and fibre tracts is shown in red. Pink areas show the location of noradrenergic terminals. (Am, amygdaloid nucleus; C, cerebellum; LC, locus ceruleus; Hip, hippocampus; Hyp, hypothalamus; MFB, medial forebrain bundle; NTS, nucleus of the tractus solitarius (vagal sensory nucleus); RF, brainstem reticular formation; Sep, septum; SN, substantia nigra; Str, corpus striatum; Th, thalamus.)

# Mood disorders and NE

**Affective Disorders**



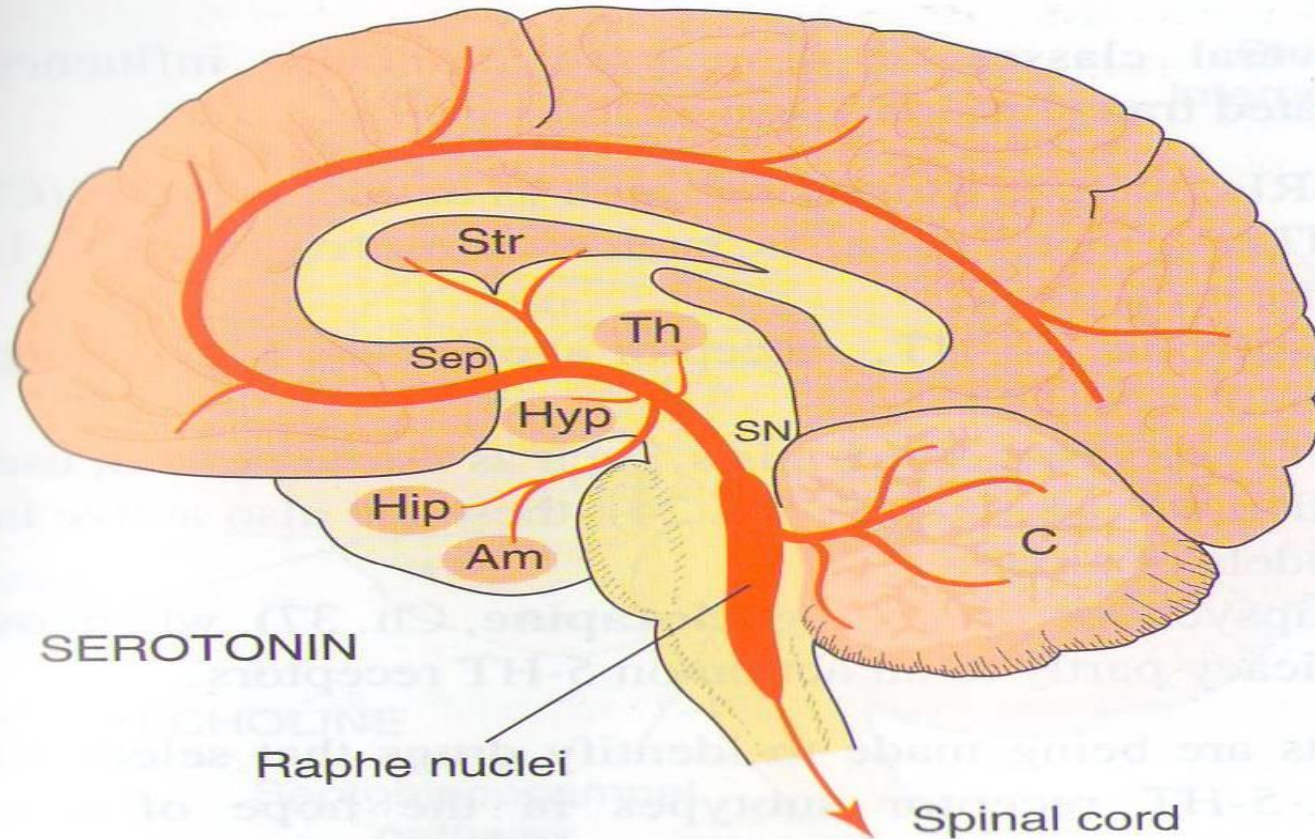
**Mania**

**Depression**

**Rx** Drugs that decrease NE

Drugs that increase NE

# Serotonin (5-HT)



**Fig. 33.5** 5-Hydroxytryptamine (serotonergic) pathways in the brain. (Abbreviations and drawn as in Fig. 33.1.)

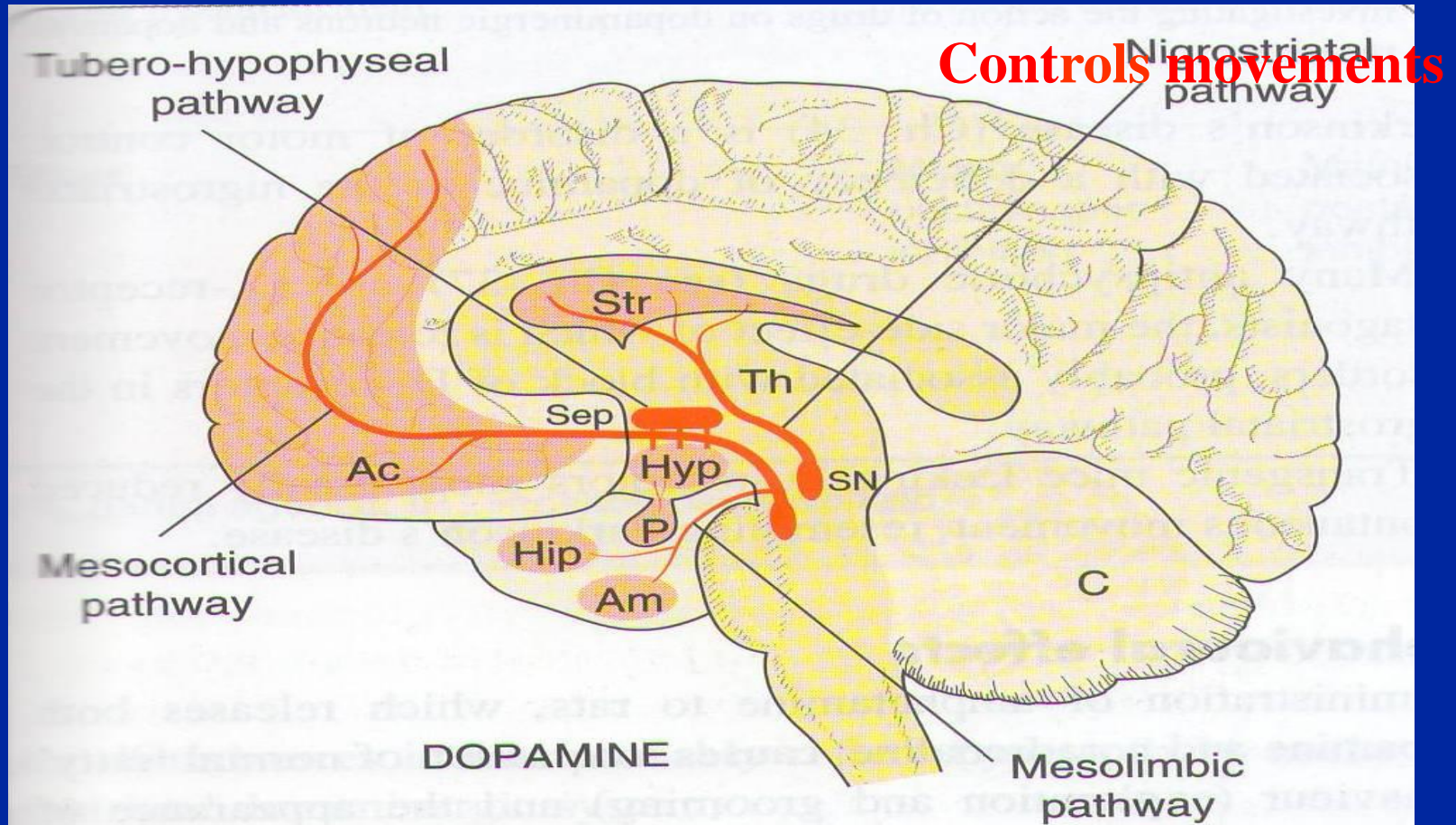
# Serotonin ( 5HT)

- Primarily found in the CNS , GIT, platelets, .....
- It is a popular thought that serotonin is responsible for feeling of **well-being & happiness.**
- **Serotonin** plays an important role :  
in regulation of ; **Mood ; sleep;**  
**appetite and pain perception**

**- Diseases that are influenced by changes in 5-HT brain content:**

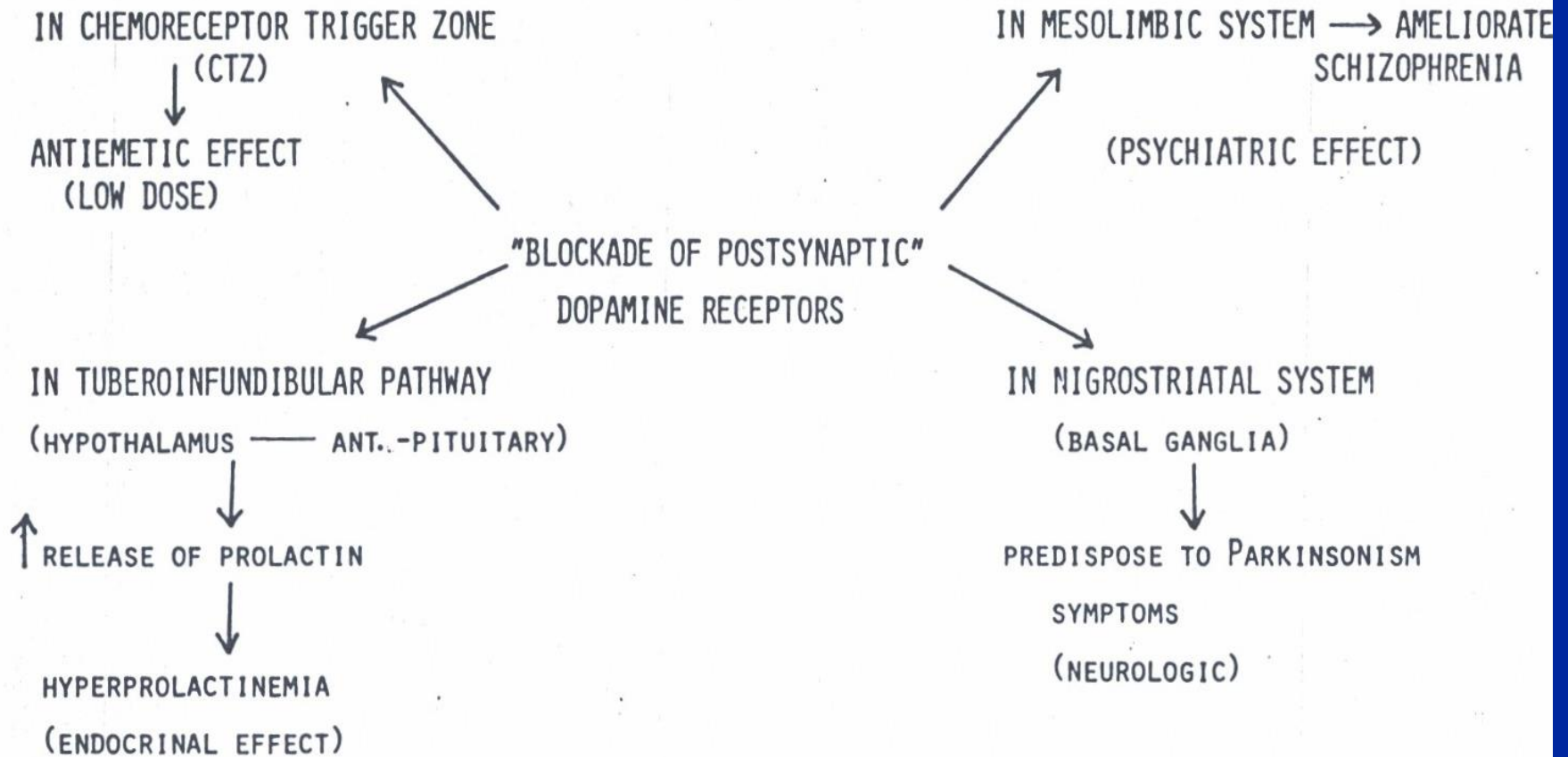
- **Depression**
- **Social phobia**
- **Obsessive Compulsive Disorders (OCDs)**
- **Generalized Anxiety**
- **Schizophrenia**
- **Vomiting**

# Dopamine



**Fig. 33.3 Dopamine pathways in the brain (drawn as in Fig. 33.1).** The pituitary gland (P) is shown, innervated with dopaminergic fibres from the hypothalamus. (Ac, nucleus accumbens; other abbreviations as in Fig. 33.1.)

## EFFECTS ON DOPAMINERGIC SYNAPSES

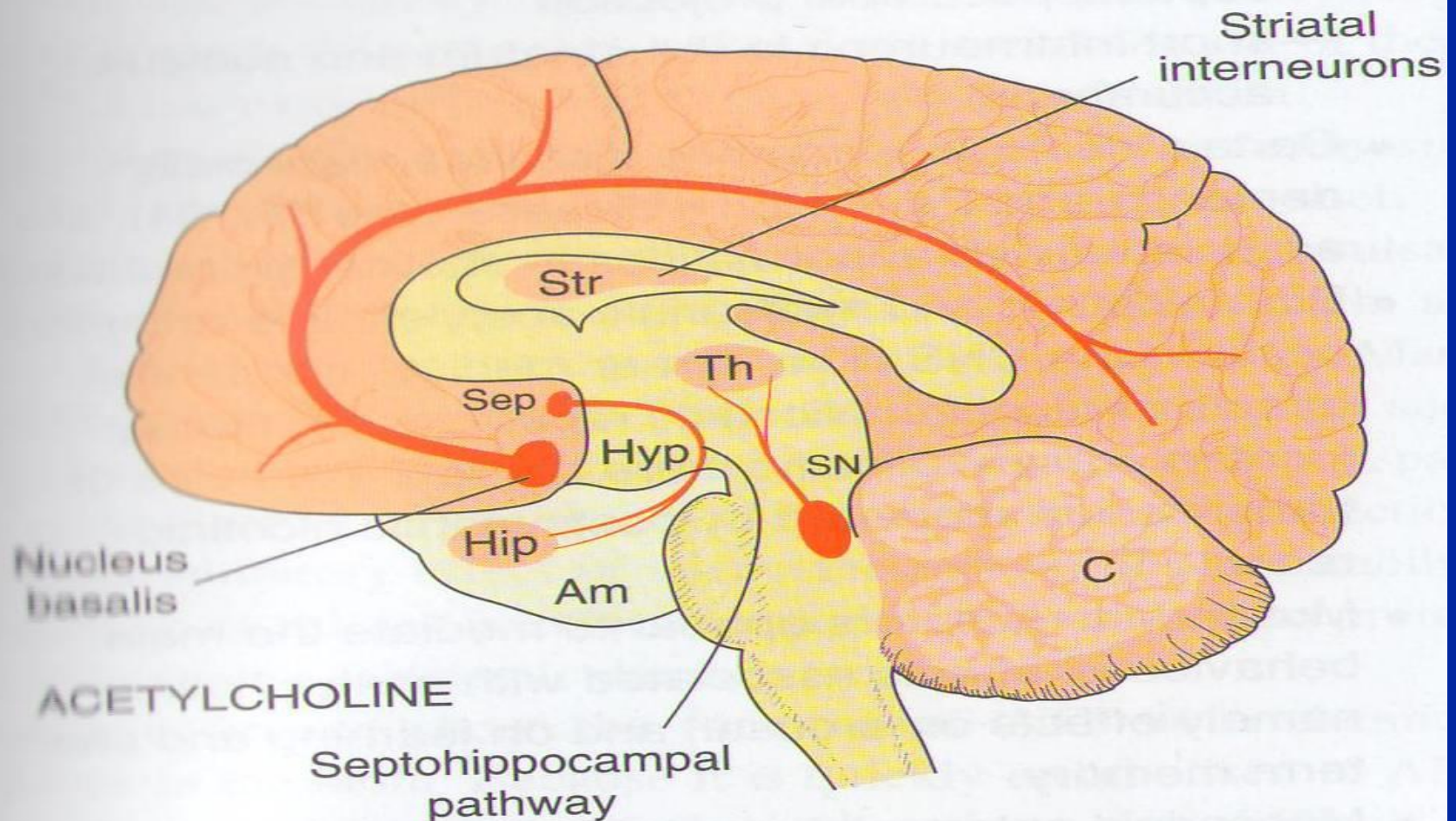


THE SAME PHARMACODYNAMIC ACTION MAY HAVE DISTINCT PSYCHIATRIC "NEUROLOGIC" AND ENDOCRINE EFFECTS.

- **What are the diseases that influenced by dopamine level ?**
- **Attention deficit hyperactivity disorder (ADHD)**
- **Schizophrenia**
- **Depression**
- **Drug addiction**
- **Parkinson's disease**



# Acetylcholine



**Fig 33.6 Acetylcholine pathways in the brain.**  
(Abbreviations and drawn as in Fig. 33.1.)

- Acetylcholine, the first neurotransmitter discovered
- Inside the brain Ach functions as a **neuro-modulator**—a chemical that alters the way other brain structures process information rather than a chemical used to transmit information from point to point
- Is Ach an inhibitory or excitatory neurotransmitter?

# Role of Acetylcholine in the CNS

Ach is thought to be involved in cognitive functions such as :

- **Memory**
- **Arousal**
- **Attention**

# What are the CNS diseases that linked to ACh derangement ?

- Damage to cholinergic receptors ( muscarinic) is associated with memory deficits as in **Alzheimer's disease.**
- Muscarinic antagonists as hyoscine cause **amnesia.**
- Increased brain level of ACh predispose to **Parkinson's disease**

- **Schizophrenia** may be due to imbalance between Ach & dopamine brain levels.
- **Depression** may be a manifestation of a central cholinergic predominance.

# Glutamic acid

- is an **excitatory** neurotransmitter
- An increase in its level predispose to **epilepsy**

# Potential therapeutic effect of glutamate antagonists

- Reduction of brain damage following strokes & head injury
- Treatment of epilepsy
- Drug dependence
- Schizophrenia

# Gamma amino butyric acid “GABA”

- **GABA** is the main inhibitory neurotransmitter in the brain
- Present throughout the brain; there is very **little** in peripheral tissues



# Pathophysiological role of GABA

Decrease GABA brain content is associated with :

- Epilepsy
- Anxiety
- Convulsions
- Insomnia

Neurotransmitter pharmacology in the central nervous system.\*

Transmitter	Anatomic Distribution	Receptor Subtypes	Receptor Mechanisms
Acetylcholine	Cell bodies at all levels, short and long axons	Muscarinic, M <sub>1</sub> ; blocked by pirenzepine and atropine	Excitatory; ↓ in K <sup>+</sup> conductance; ↑ IP <sub>3</sub> and DAG
		Muscarinic, M <sub>2</sub> ; blocked by atropine	Inhibitory; ↑ K <sup>+</sup> conductance; ↓ cAMP
	Motoneuron–Renshaw cell synapse	Nicotinic, N	Excitatory; ↑ cation conductance
Dopamine	Cell bodies at all levels, short, medium, and long axons	D <sub>1</sub> ; blocked by phenothiazines	Inhibitory; ↑ cAMP
		D <sub>2</sub> ; blocked by phenothiazines and haloperidol	Inhibitory (presynaptic); ↓ Ca <sup>2+</sup> conductance; Inhibitory (postsynaptic); ↑ K <sup>+</sup> conductance; ↓ cAMP
Norepinephrine	Cell bodies in pons and brain stem project to all levels	Alpha <sub>1</sub> ; blocked by prazosin	Excitatory; ↓ K <sup>+</sup> conductance; ↑ IP <sub>3</sub> and DAG
		Alpha <sub>2</sub> ; activated by clonidine	Inhibitory (presynaptic); ↓ Ca <sup>2+</sup> conductance
			Inhibitory (postsynaptic); ↑ K <sup>+</sup> conductance; ↓ cAMP
		Beta <sub>1</sub> ; blocked by propranolol	Excitatory; ↓ K <sup>+</sup> conductance; ↑ cAMP
Beta <sub>2</sub> ; blocked by propranolol	Inhibitory; ? increase in electrogenic sodium pump; ↑ cAMP		

Serotonin (5-hydroxy-tryptamine)	Cell bodies in midbrain and pons project to all levels	5-HT <sub>1A</sub> ; buspirone is a partial agonist	Inhibitory; ↑ K <sup>+</sup> conductance, ↓ cAMP
		5-HT <sub>2A</sub> ; blocked by clozapine, risperidone, and olanzapine	Excitatory; ↓ K <sup>+</sup> conductance; ↑ IP <sub>3</sub> and DAG
		5-HT <sub>3</sub> ; blocked by ondansetron	Excitatory; ↑ cation conductance
		5-HT <sub>4</sub>	Excitatory; ↓ K <sup>+</sup> conductance
GABA	Supraspinal interneurons; spinal interneurons involved in presynaptic inhibition	GABA <sub>A</sub> ; facilitated by benzodiazepines and zolpidem	Inhibitory; ↑ Cl <sup>-</sup> conductance
		GABA <sub>B</sub> ; activated by baclofen	Inhibitory (presynaptic); ↓ Ca <sup>2+</sup> conductance Inhibitory (postsynaptic); ↑ K <sup>+</sup> conductance
Glutamate	Relay neurons at all levels	Four subtypes; NMDA subtype blocked by phencyclidine	Excitatory; ↑ Ca <sup>2+</sup> or cation conductance
		Metabotropic subtypes	Inhibitory (presynaptic); ↓ Ca <sup>2+</sup> conductance, ↓ cAMP Excitatory (postsynaptic); ↓ K <sup>+</sup> conductance, ↑ IP <sub>3</sub> and DAG
Glycine	Interneurons in spinal cord and brain stem	Single subtype; blocked by strychnine	Inhibitory; ↑ Cl <sup>-</sup> conductance
Opioid peptides	Cell bodies at all levels	Three major subtypes: mu, delta, kappa	Inhibitory (presynaptic); ↓ Ca <sup>2+</sup> conductance; ↓ cAMP
			Inhibitory (postsynaptic); ↑ K <sup>+</sup> conductance; ↓ cAMP

## - **Conclusion:**

- Without understanding the involvement of **neurotransmitters** in the **etiology** of **CNS diseases**, doctors could not select the proper drug for any particular disease.