

# Pharmacology of central Neurotransmitters

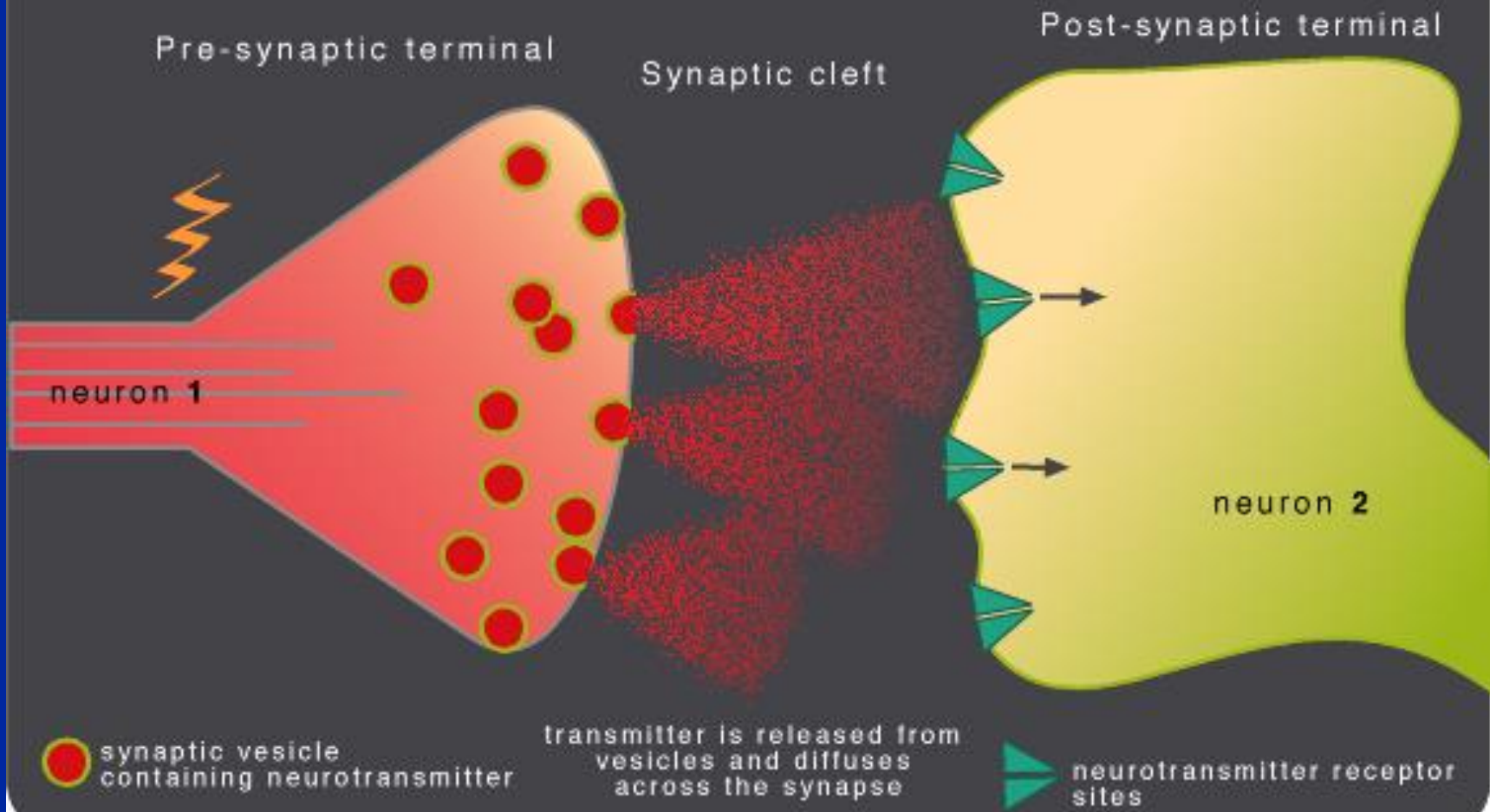
## - Objectives

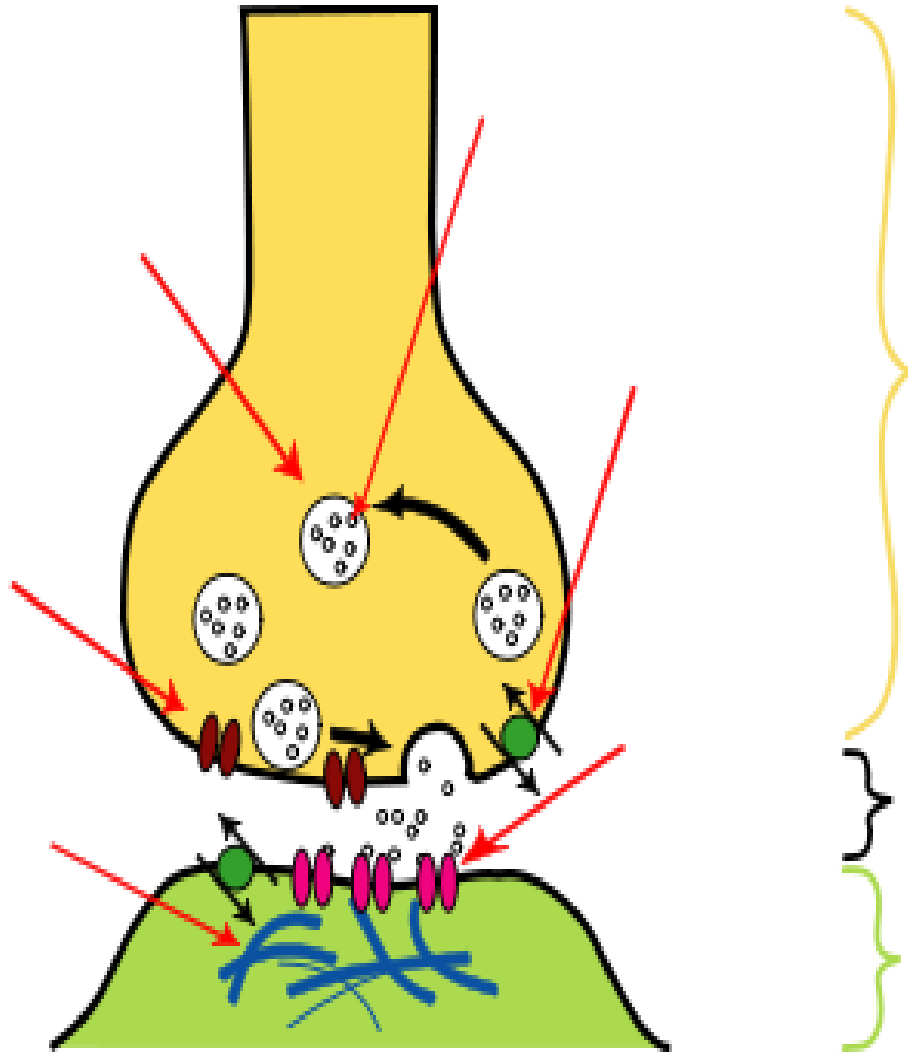
- The main objective of this lecture is to understand the role of neurotransmitters in the etiology and treatment of CNS diseases

# Neurotransmitters

- **Endogenous** chemicals that 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 receptors on the **post synaptic side**.

# THE SYNAPSE





- **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:

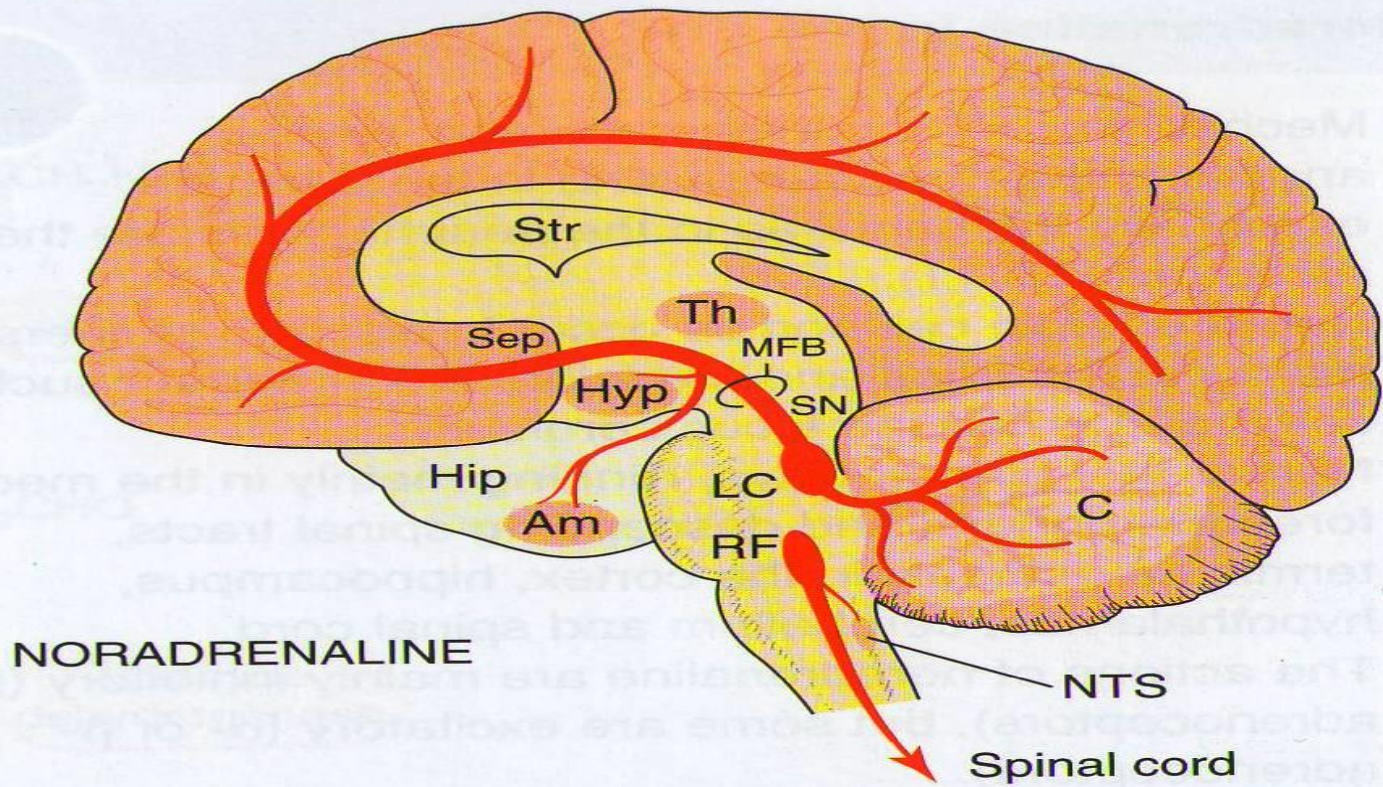
Acetylcholine (Ach)

# **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**



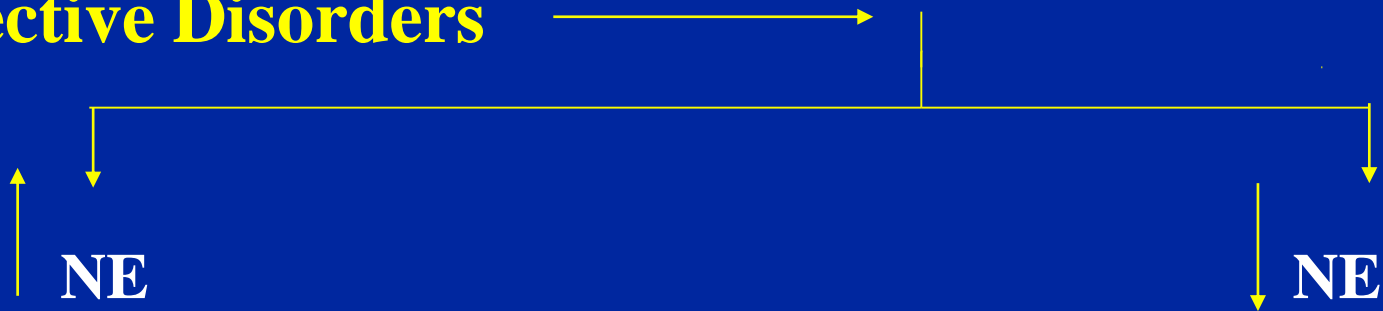




**Fig. 33.1 Noradrenaline pathways in the brain.** The location of the main groups of cell bodies and fibre tracts is shown in red. Pink areas show the location of noradrenergic terminals. (Am, amygdaloid nucleus; C, cerebellum; LC, locus ceruleus; Hip, hippocampus; Hyp, hypothalamus; MFB, medial forebrain 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**

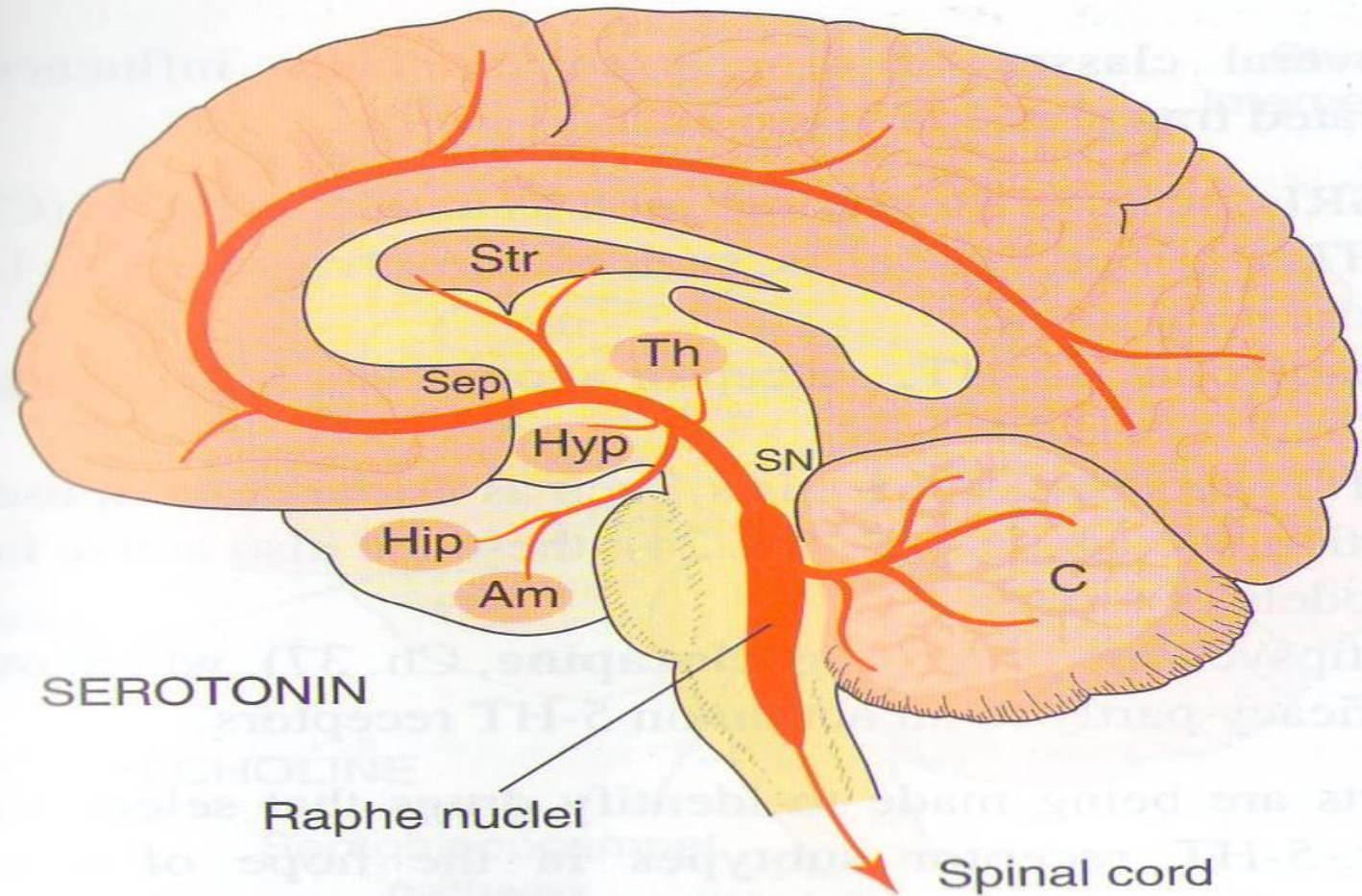
**Depression**

**Rx** Drugs that decrease NE

Drugs that increase NE







**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**

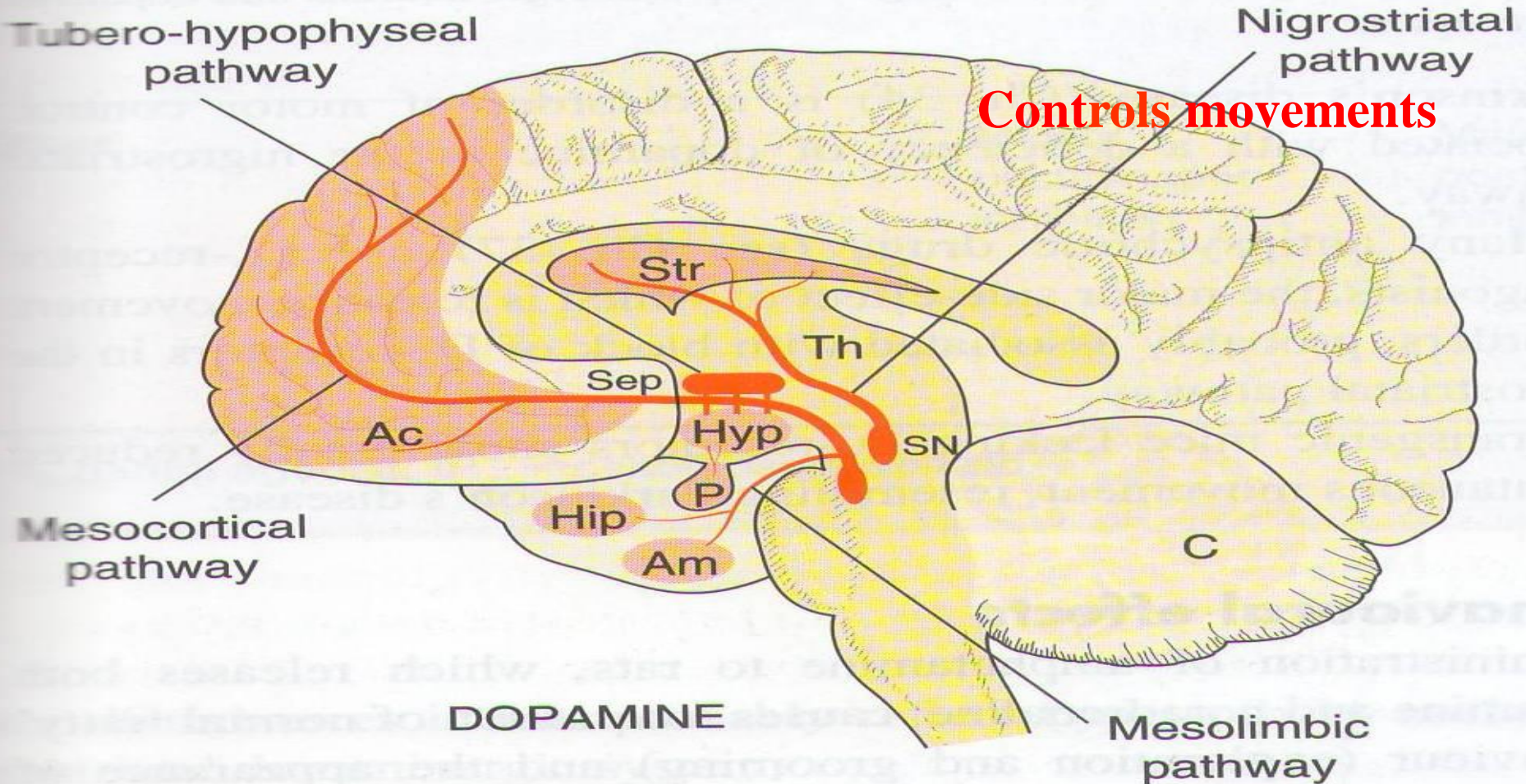
**- Diseases that are influenced by changes in 5-HT brain content:**

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



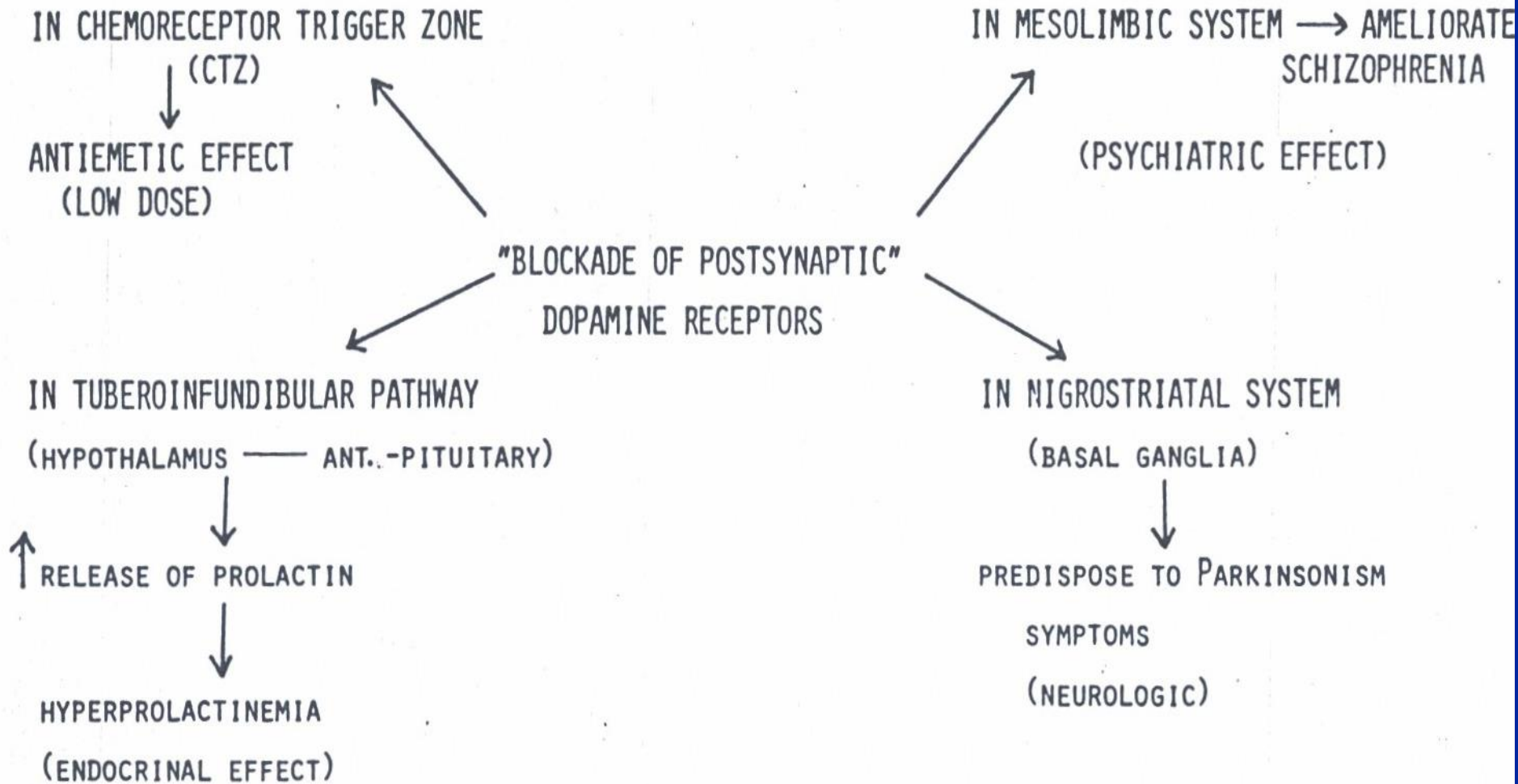


# Dopaminergic Pathways



**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



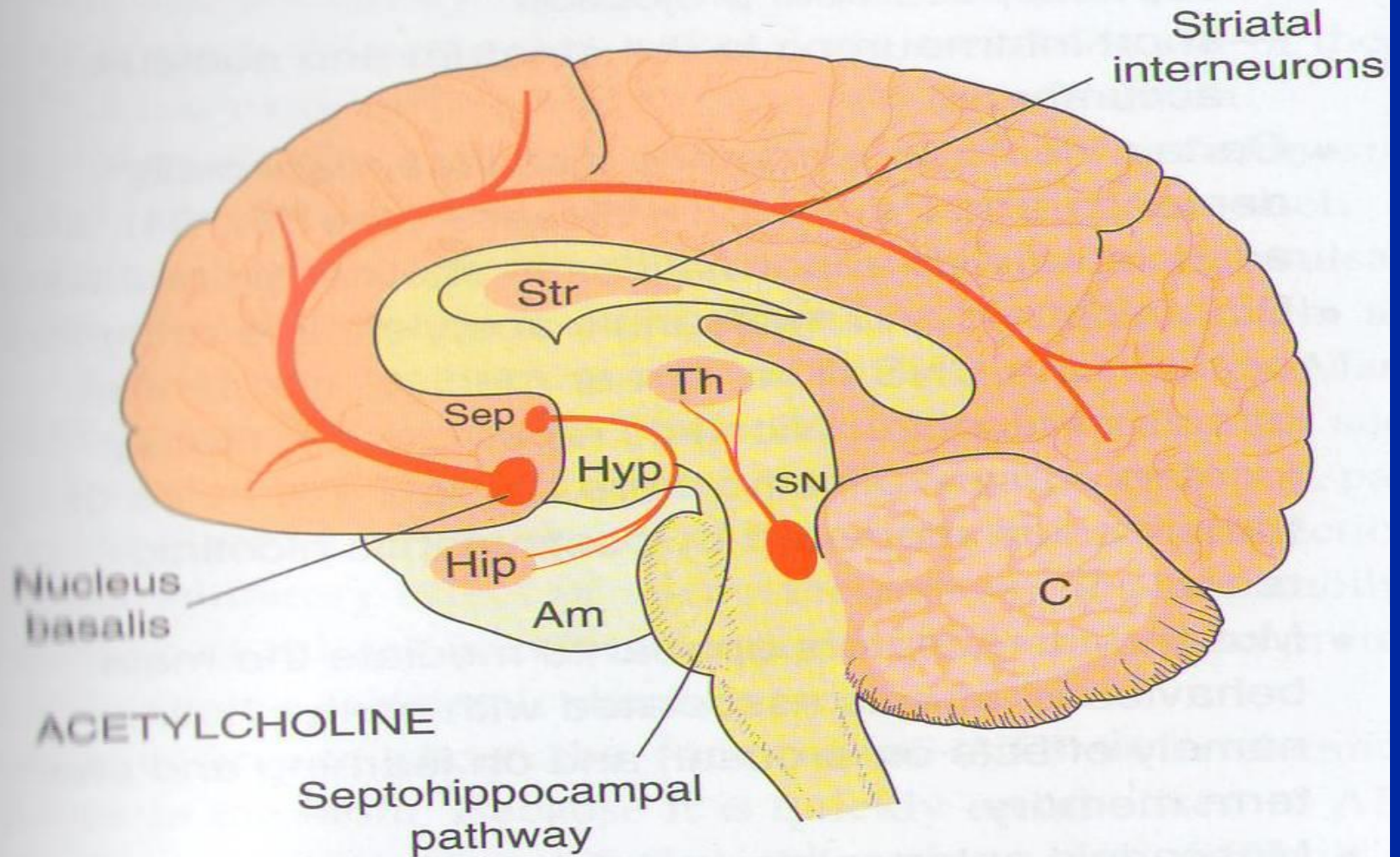
THE SAME PHARMACODYNAMIC ACTION MAY HAVE DISTINCT PSYCHIATRIC "NEUROLOGIC" AND ENDOCRINE EFFECTS.

**What are the diseases that  
influenced by dopamine level ?**

Parkinson's disease, attention  
deficit hyperactivity disorder,  
schizophrenia, depression and  
drug addiction







**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** الإثارة
- **Attention** انتباه

# 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

- **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

# GABA

- **is the main inhibitory transmitter 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.\***

<b>Transmitter</b>	<b>Anatomic Distribution</b>	<b>Receptor Subtypes</b>	<b>Receptor Mechanisms</b>
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-hydroxytryptamine)	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 Metabotropic subtypes	Excitatory; ↑ Ca <sup>2+</sup> or cation conductance  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



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## **- Conclusion:**

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