Pharmacology of central Neurotransmitters

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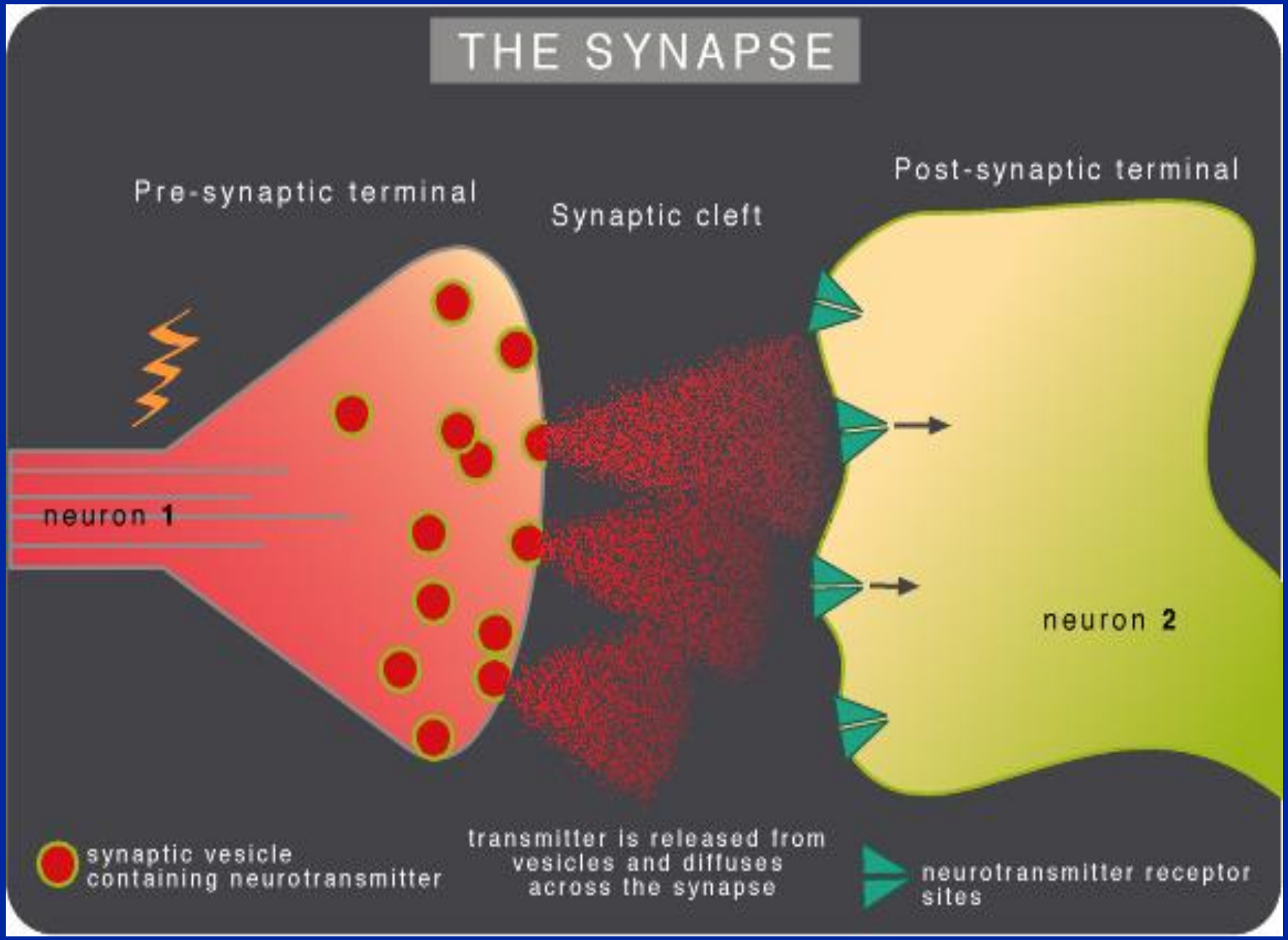
- **Objectives**
  - **The main objective of this lecture is to understand the role of neurotransmitters in the etiology and treatment of CNS diseases**


THE SYNAPSE
Pre-synaptic terminal
Synaptic cleft
Post-synaptic terminal
neuron 1
neuron 2
synaptic vesicle containing neurotransmitter
transmitter is released from vesicles and diffuses across the synapse
neurotransmitter receptor sites

Neurotransmitters

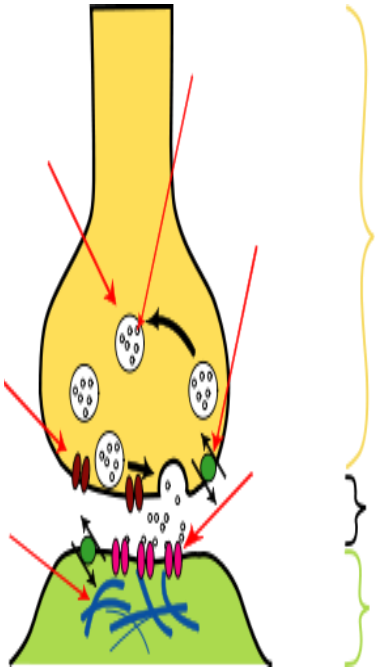
- **Endogenous chemicals or chemical messengers that enable neuro-transmission (transmit signals from a neuron to a target cell across a synapse).**
- **They packed into synaptic vesicles under the membrane in the axon terminal, on the presynaptic side.**
- **They are released into & diffuse across the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

- The 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) Neurotransmitters taken up by the nerve terminals are repackaged in vesicles for reuse.

2- They can be destroyed by enzymes near the receptors.

3- They can diffuse into the surrounding area and be removed.



- **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 aminobutryic 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)

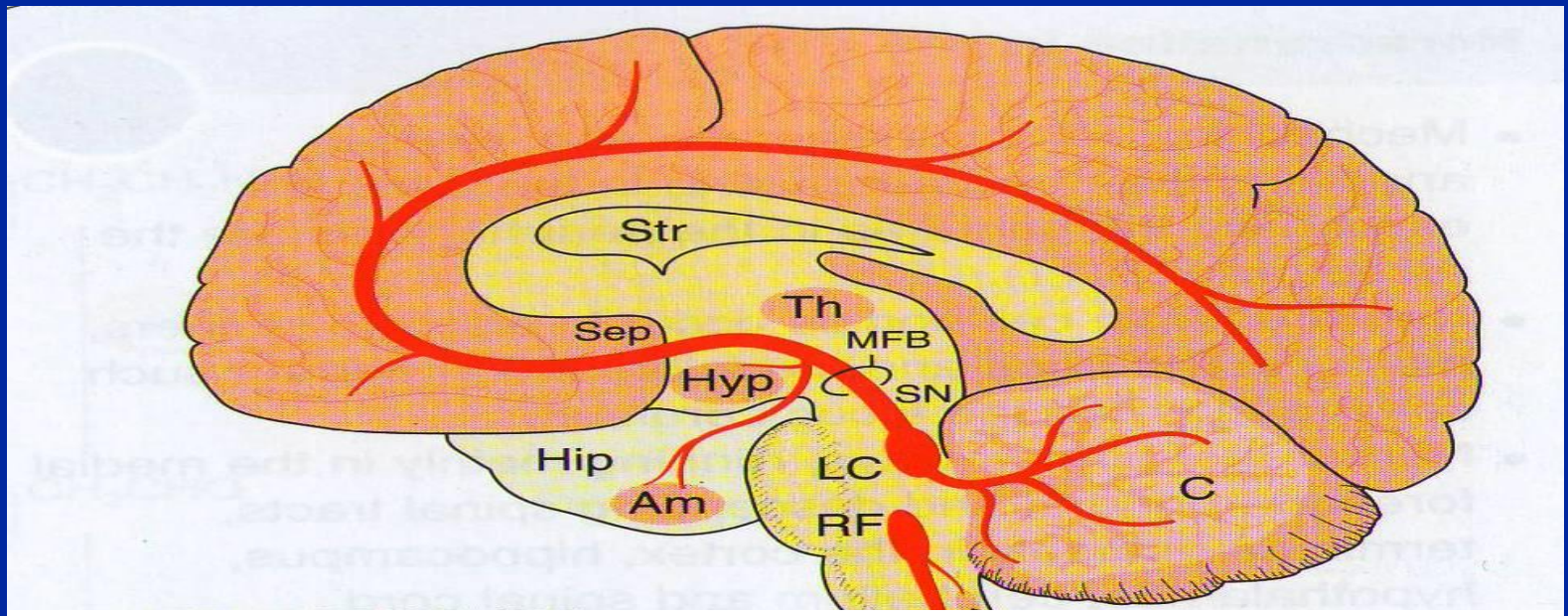


Fig. 33.1 Noradrenaline pathways in the brain. The location of the main groups of cell bodies and fibre tracts is shown in red. Pink areas show the location of noradrenergic terminals. (Am, amygdaloid nucleus; C, cerebellum; LC, locus ceruleus; Hip, hippocampus; Hyp, hypothalamus; MFB, medial forebrain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

- **also called noradrenaline , belongs to catecholamines, the direct precursor of NE is dopamine**
- **The CNS effects of NE are manifested in alertness, arousal , and readiness for action.**
- **A variety of medically important drugs work by altering the actions of NE e.g., for treatment of CV problems and some of psychiatric conditions.**

Mood disorders and NE

Affective Disorders

Mania **Depression**

Rx **Drugs that decrease NE** **Drugs that increase NE**

Serotonin (5-HT)

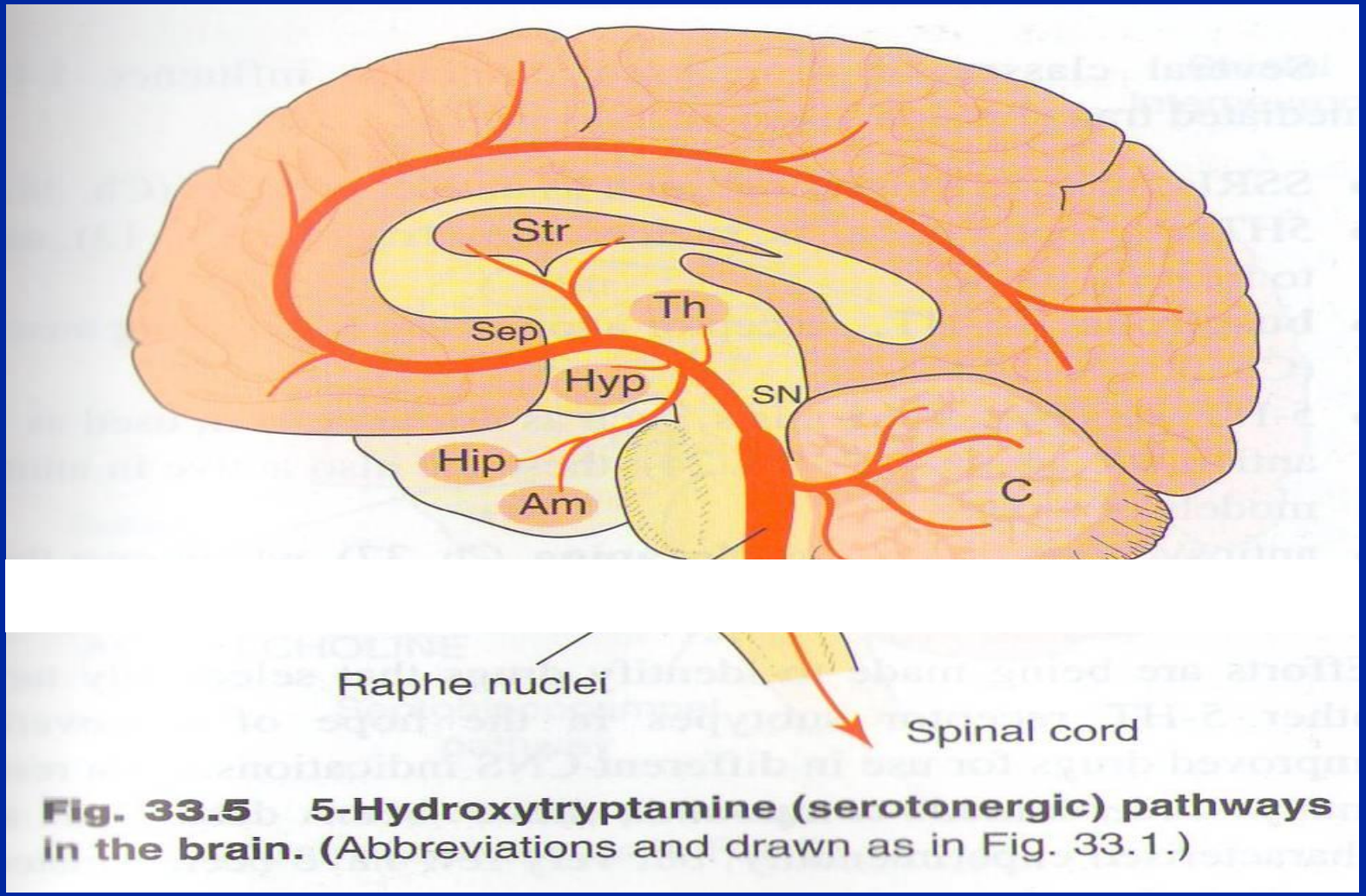


Fig. 33.5 5-Hydroxytryptamine (serotonergic) pathways in the brain. (Abbreviations and drawn as in Fig. 33.1.)

Serotonin (5HT)

- 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter found in the CNS, GIT, platelets
- a contributor to feelings of well-being & happiness.
- Serotonin plays an important role in the regulation of mood, sleep; appetite, pain perception and some cognitive functions, including memory and learning.

➢ Modulation of serotonin at synapses is a major action of several classes of antidepressants eg selective serotonin re-uptake inhibitors (SSRIs).

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

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

Dopamine

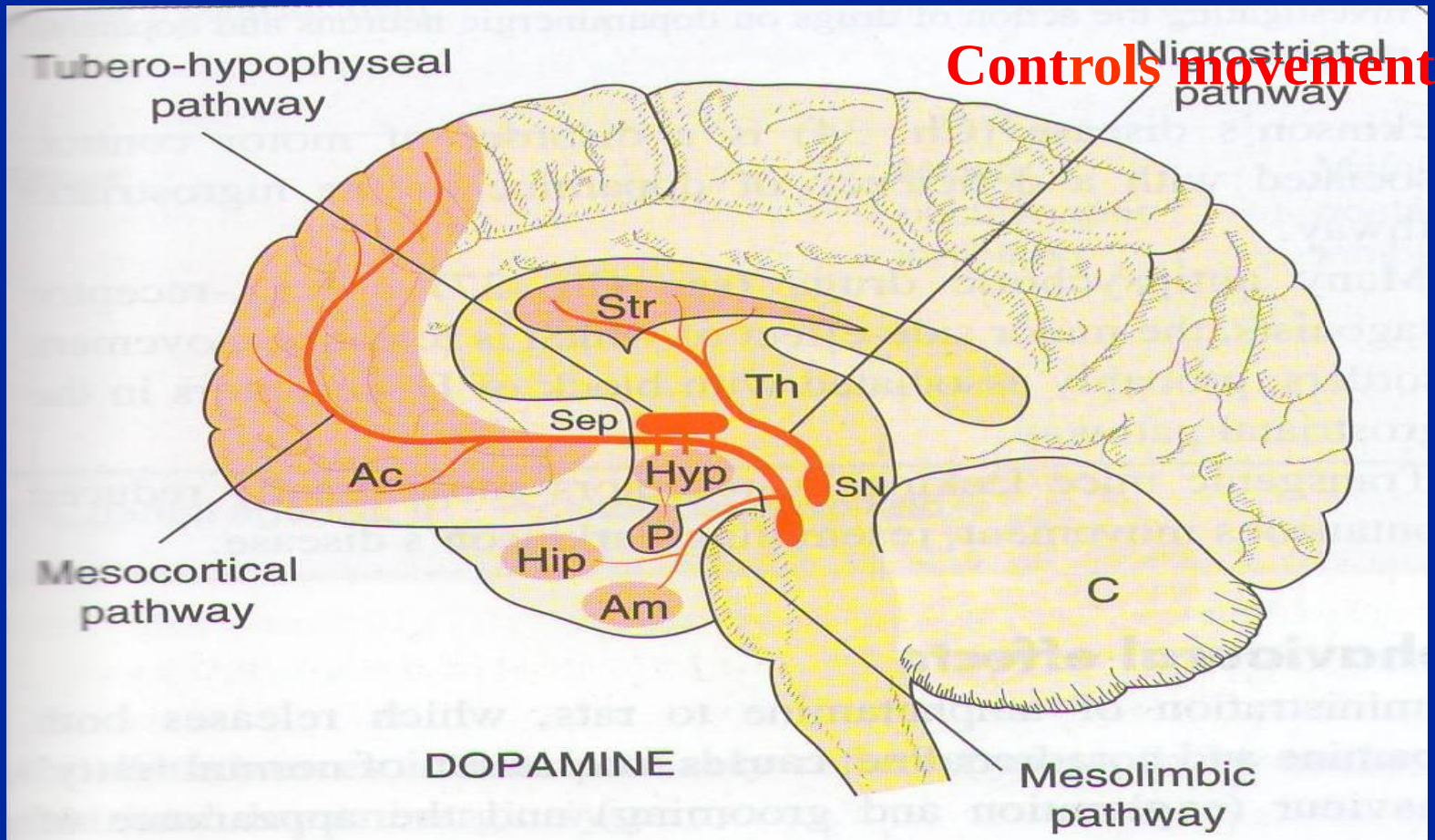
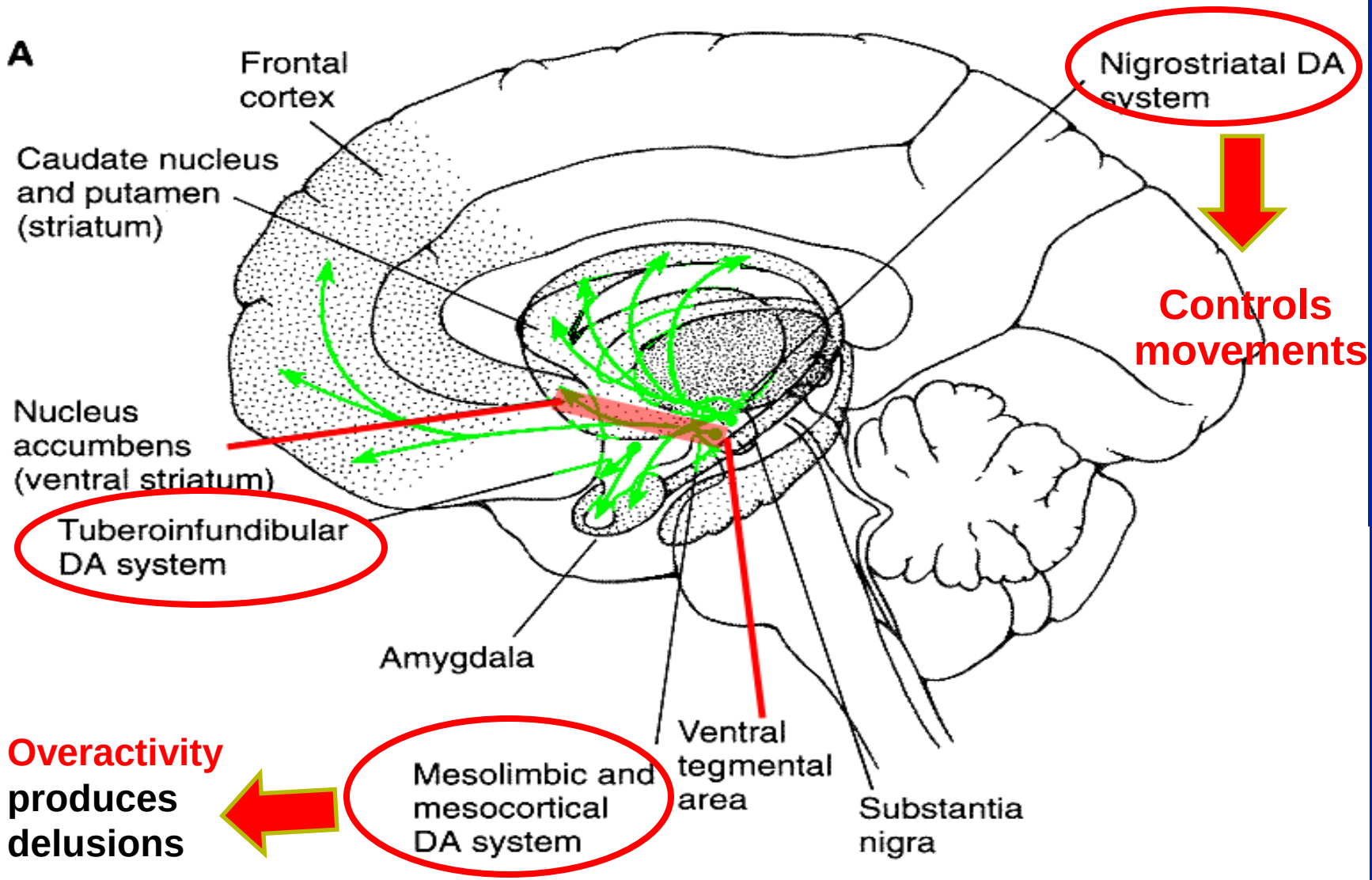
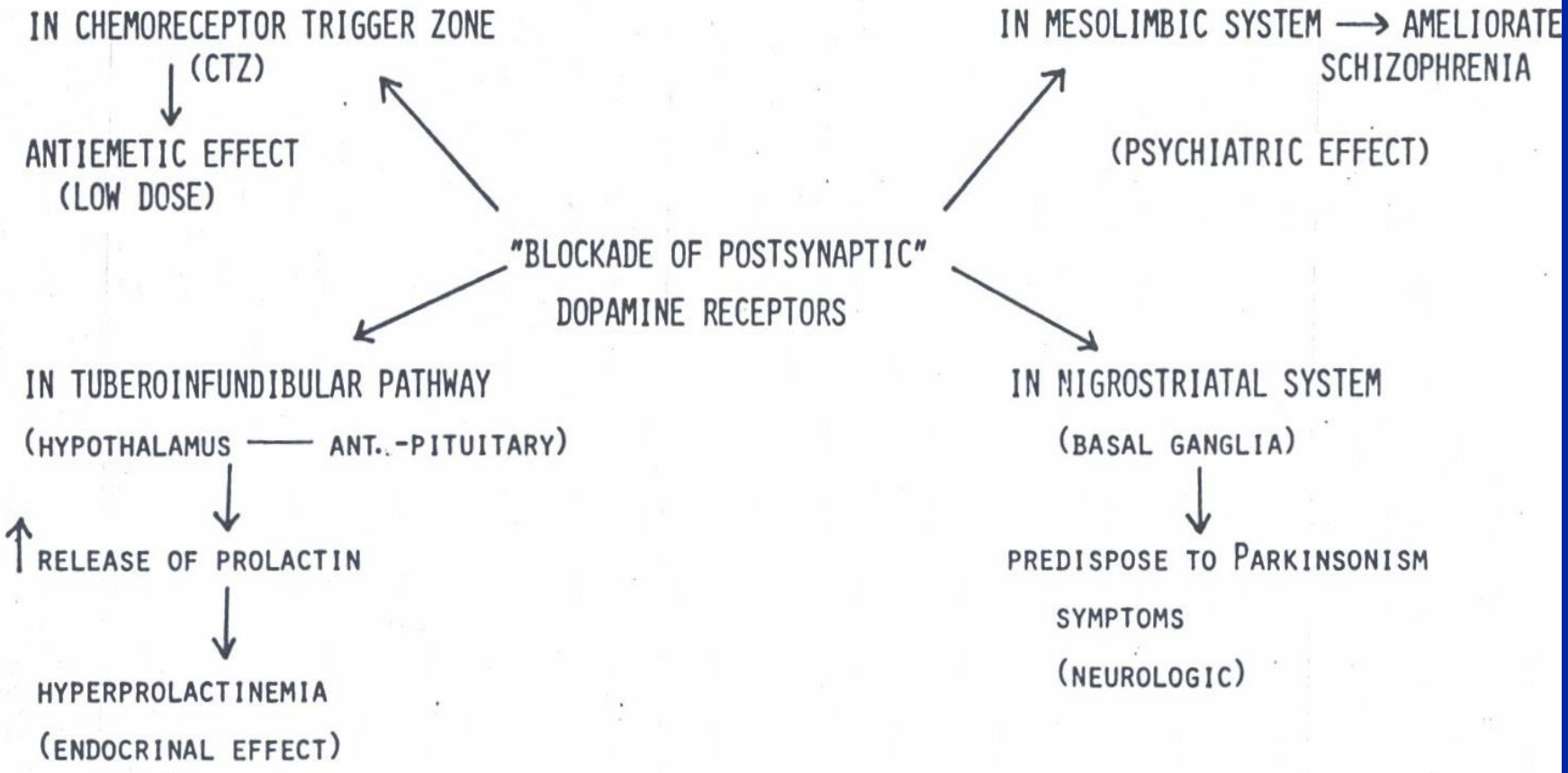


Fig. 33.3 Dopamine pathways in the brain (drawn as in Fig. 33.1). The pituitary gland (P) is shown, innervated with dopaminergic fibres from the hypothalamus. (Ac, nucleus accumbens; other abbreviations as in Fig. 33.1.)

Dopamine Pathways



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

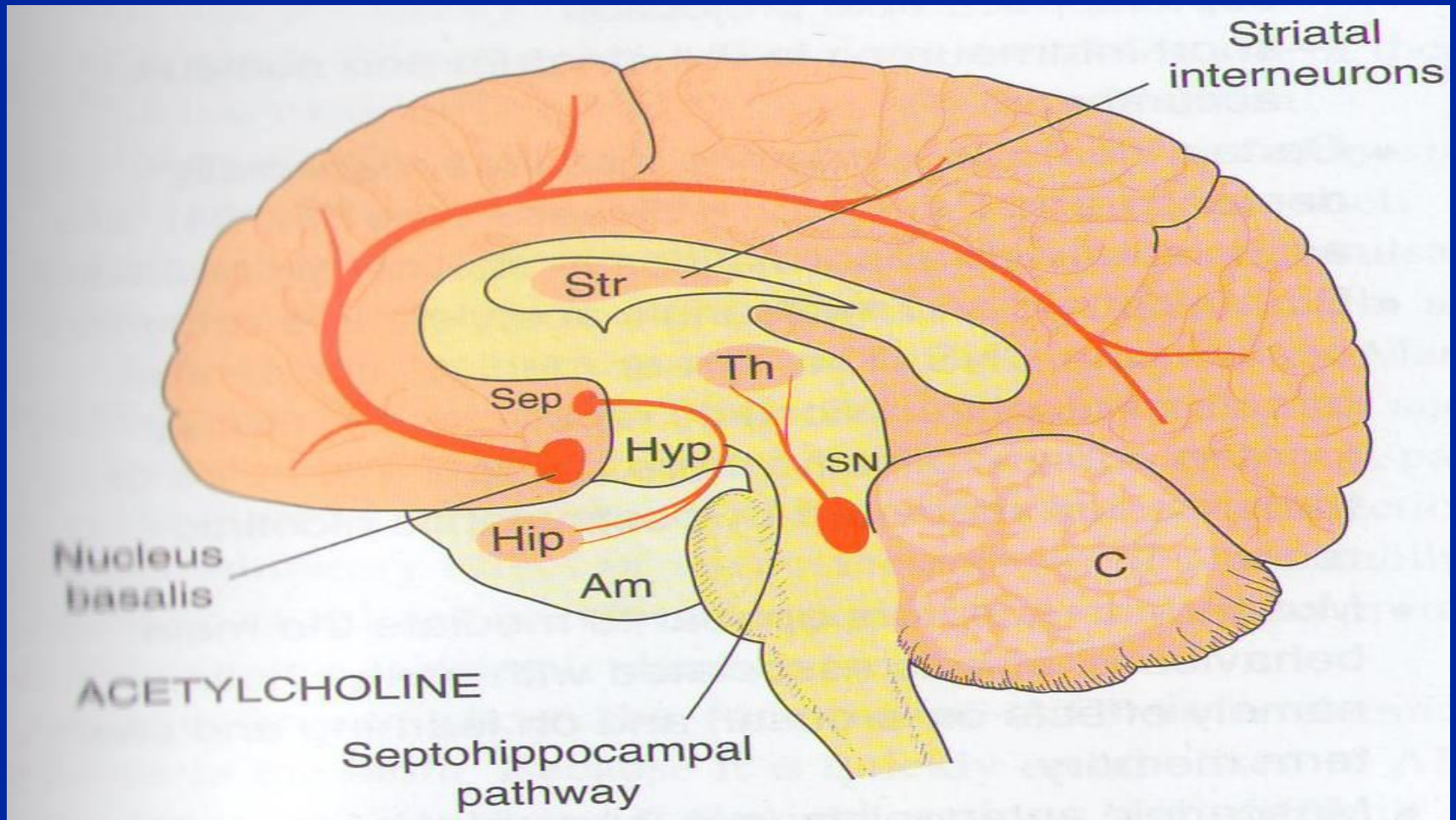


Fig 33.6 Acetylcholine pathways in the brain.
(Abbreviations and drawn as in Fig. 33.1.)

- **Acetylcholine (Ach), 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 (Cholinomimetics are used as therapy of Alzheimer).
- Increased brain level of Ach predispose to Parkinson's disease (anticholinergic drugs are used as therapy)
- Depression may be a manifestation of a

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**
- **Benzodiazepine (diazepam) enhances GABA function and used in treatment of above diseases.**

- **Conclusion:**

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

- **Self reading**

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_1; blocked by pirenzepine and atropine	Excitatory; ↓ in K^+ conductance; ↑ IP_3 and DAG
		Muscarinic, M_2; blocked by atropine	Inhibitory; ↑ K^+ conductance; ↓ cAMP
	Motoneuron–Renshaw cell synapse	Nicotinic, N	Excitatory; ↑ cation conductance
Dopamine	Cell bodies at all levels, short, medium, and long axons	D_1; blocked by phenothiazines	Inhibitory; ↑ cAMP
		D_2; blocked by phenothiazines and haloperidol	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
Norepinephrine	Cell bodies in pons and brain stem project to all levels	$Alpha_1$; blocked by prazosin	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		$Alpha_2$; activated by clonidine	Inhibitory (presynaptic); ↓ Ca^{2+} conductance Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
		$Beta_1$; blocked by propranolol	Excitatory; ↓ K^+ conductance; ↑ cAMP
		$Beta_2$; 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_{1A}; buspirone is a partial agonist	Inhibitory; ↑ K^+ conductance, ↓ cAMP
		5-HT_{2A}; blocked by clozapine, risperidone, and olanzapine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		5-HT_3; blocked by ondansetron	Excitatory; ↑ cation conductance
		5-HT_4	Excitatory; ↓ K^+ conductance
GABA	Supraspinal interneurons; spinal interneurons involved in presynaptic inhibition	$GABA_A$; facilitated by benzodiazepines and zolpidem	Inhibitory; ↑ Cl^- conductance
		$GABA_B$; activated by baclofen	Inhibitory (presynaptic); ↓ Ca^{2+} conductance Inhibitory (postsynaptic); ↑ K^+ conductance
Glutamate	Relay neurons at all levels	Four subtypes; NMDA subtype blocked by phencyclidine	Excitatory; ↑ Ca^{2+} or cation conductance
		Metabotropic subtypes	Inhibitory (presynaptic); ↓ Ca^{2+} conductance, ↓ cAMP Excitatory (postsynaptic); ↓ K^+ conductance, ↑ IP_3 and DAG
Glycine	Interneurons in spinal cord and brain stem	Single subtype; blocked by strychnine	Inhibitory; ↑ Cl^- conductance
Opioid peptides	Cell bodies at all levels	Three major subtypes: mu, delta, kappa	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; ↓ cAMP
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP