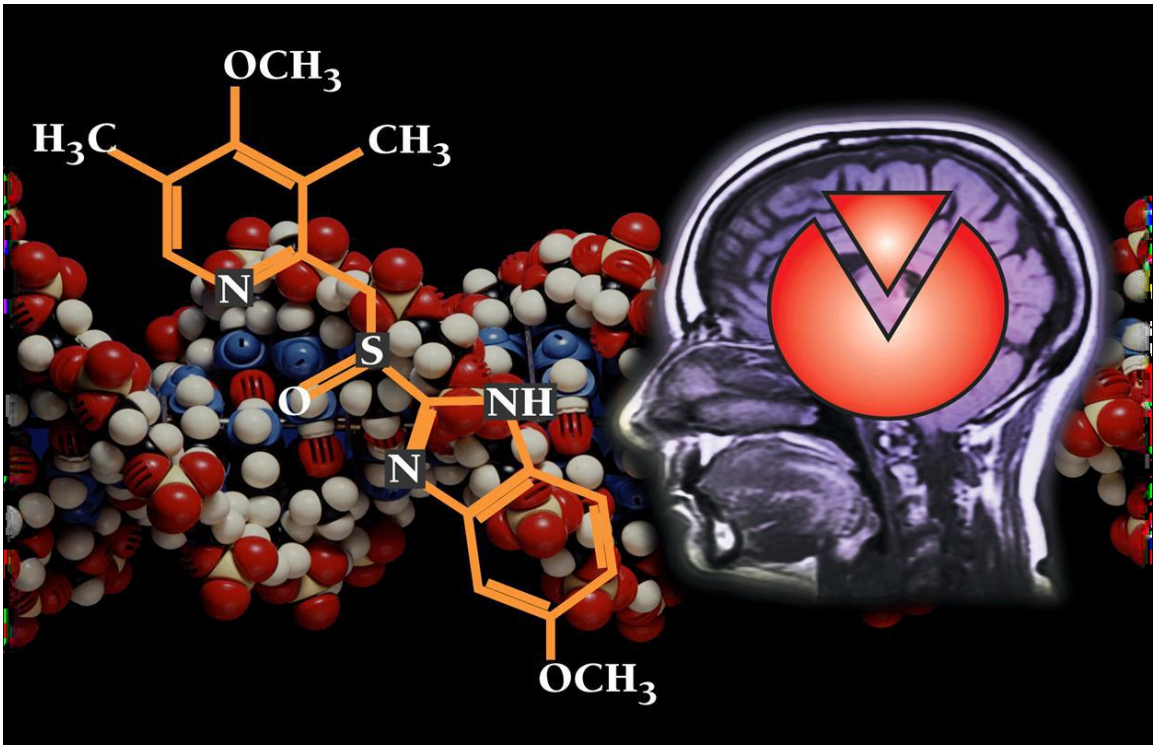
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Neurotransmitters



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« Neurotransmitters »

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

What is the importance of understanding the type of neurotransmitters in the CNS?

- To understand the etiology of diseases.
- To suggest the best drug to be used.
- To understand the clinical uses of any particular drug.

Note: Remember that in neurotransmission **K+ and Cl-** are inhibitory in nature, while **Na+ and Ca+** are excitatory in nature.

1- Norepinephrine (NE): both inhibitory and excitatory neurotransmitter and it works on the adrenergic receptors (alpha and beta) in the CNS .

- The Increase of Norepinephrine(NE) Causes Mania, and is treated with drugs that decrease Norepinephrine, such as (**Lithium which is one of the neuroleptic drugs**).

- The decrease of Norepinephrine(NE) Causes Depression, and is treated with drugs that Increase Norepinephrine, such as (**Tricyclic which is one of the antidepressant drugs**).

Note: Alpha 2 agonists (e.g. methyldopa) decrease the release of norepinephrine. Amphetamines increase the release of norepinephrine.

2- Serotonin (5HT): both inhibitory and excitatory neurotransmitter and it works on 4 types of receptors. Three of these receptors are known:

5HT1 → has inhibitory effect

5HT2 → has excitatory effect

5HT3 → responsible for the nausea and vomiting

Although the CNS contains less than 2% of the total **serotonin** in the body**, serotonin** plays a very important role in a range of brain functions including:

A) Mood control.
B) Regulation of sleep.
C) Pain perception.

Note: Serotonin has a synergism effect with the analgesics if its level is normal or high, but in low level of serotonin will antagonize the analgesic's actions.(high doses of analgesics are recommended in case of low levels of serotonin)

D) Appetite and weight gain. (In the new generation of anti-psychotic drugs)

- Diseases that are influenced by derangement of **5-HT**:

  - Affective Disorders (Mania and Depression) (low serotonin levels)
  - Schizophrenia.(serotonin levels are low)
  - Obsessive Compulsive Disorders (Serotonin levels are low)
  - Generalized Anxiety. (low serotonin levels)
  - Nausea and Vomiting (use 5-HT3 antagonists as therapy)

Note: high serotonin levels may cause shivering, headaches, vomiting, or seizures

Note: In affective disorders, schizophrenia, obsessive compulsive disorder, or generalized anxiety serotonin levels are low. **(Serotonin agonists are used as a treatment).** In Nausea and vomiting, serotonin levels are high. **(use 5-HT3 antagonists as therapy).**

3- Dopamine: an inhibitory neurotransmitter. It has five receptors but the most important, first discovered, and the site of drugs actions is D2 receptor

Diseases which are influenced by the level of **Dopamine**:

- Parkinson Disease.
- Psychosis (Schizophrenia).
- Nausea and vomiting.
- Infertility.

- ↑ of **dopamine** levels in brain has a role in the development of Schizophrenia.

  •Rx of Schizophrenia: By blocking Dopamine receptors with the use of Neuroleptic drugs.

- ↓ of **dopamine** levels is a contributing factor to Parkinson's disease.

  •Rx of Parkinson's disease: By increasing the amount of Dopamine in the patient. (↑ Dopamine).

Note: Dopamine generally exerts a slow inhibitory action on CNS neurons.

Dopamine Pathways / Areas:

1- Mesocortical and mesolimbic pathways : these two areas are responsible for the behavior
2- Basil ganglia (nigrostriatal system) : responsible for the neurological activity (movement)
3- Tuberoinfundibular pathway: transmits dopamine from the hypothalamus to the pituitary gland by dopaminergic fibers. This pathway influences the secretion of certain hormones, and inhibits the secretion of prolactin.
4- Chemoreceptor in the medulla: has emetic effect.

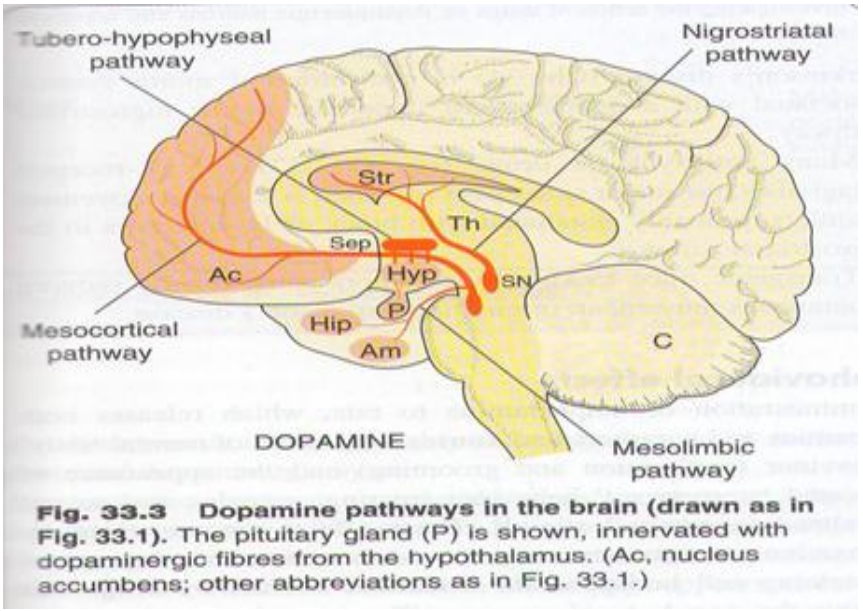
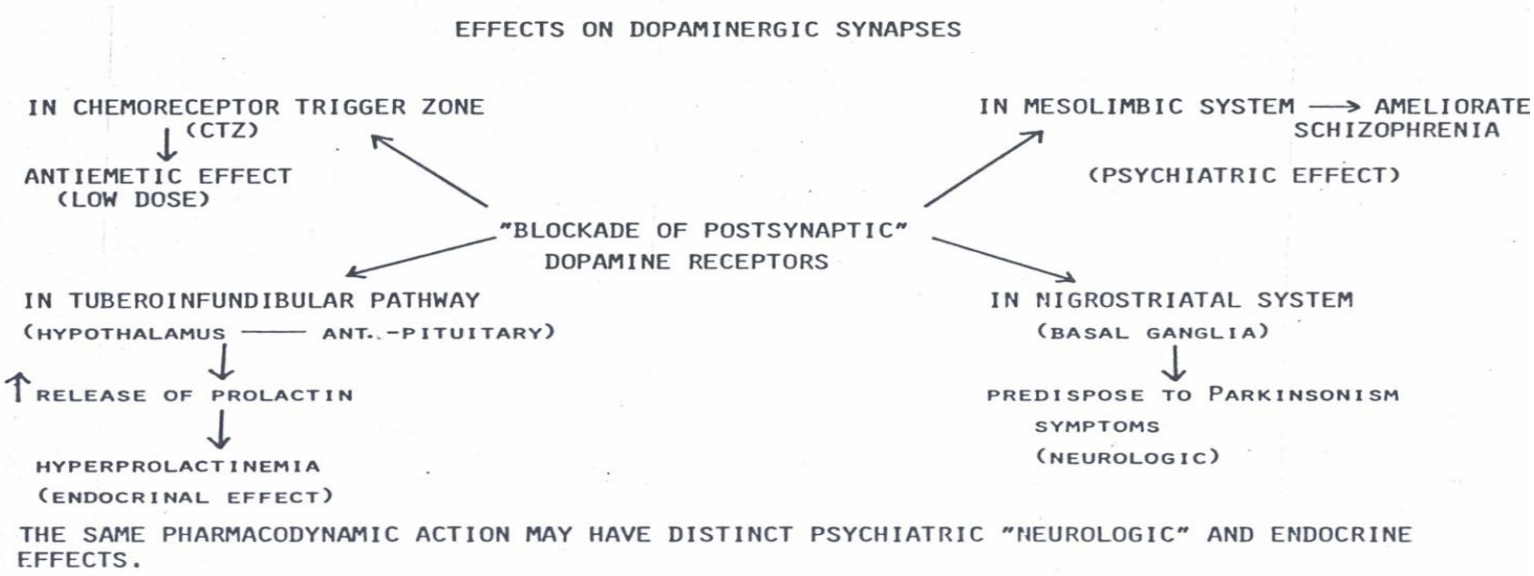


Fig. 33.3 Dopamine pathways in the brain (drawn as in Fig. 33.1). The pituitary gland (P) is shown, innervated with dopaminergic fibres from the hypothalamus. (Ac, nucleus accumbens; other abbreviations as in Fig. 33.1.)

Blocking Dopamine receptors (important)



Note: the positive effects of blocking dopamine receptors are the ones above, the negative effects are the ones below.

Note: Hyperprolactinemia causes infertility in women. (It's treated by dopamine agonists such as levodopa)

4-Acetylcholine (Ach):

- Acetylcholine is both an Excitatory and Inhibitory neurotransmitter.

- Acetylcholine slows the heart rate when functioning as an inhibitory neurotransmitter. However, Acetylcholine also behaves as an excitatory neurotransmitter at neuromuscular junctions.

- It is also thought that Ach is involved in cognitive functions such as: (**M**emory, **A**rousal and **A**ttention).

CNS Diseases which are linked to Ach derangement:

- Damage to cholinergic receptors (muscarinic) is associated with memory deficits as in Alzheimer's disease
- ↑ **Ach** in the brain predisposes patients to Parkinson's Disease.
- Muscarinic antagonists as **hyoscine** cause amnesia.

Note: Alzheimer's disease is usually treated by **cholinesterase inhibitors such as donepezil (increases Ach)**. Patients with severe damage in their muscarinic receptors, however, would not respond to the treatment since there are no receptors available to bind with **Ach.**

5- Glutamic Acid:

- Glutamic Acid is an Excitatory neurotransmitter.
- ↑ in Glutamic acid level predisposes patients to Epilepsy.

Potential therapeutic effect of glutamate antagonists

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

6- GABA (*gamma*-Aminobutyric acid):

- **GABA** is an Inhibitory neurotransmitter.
- Present throughout the brain; there is very little in peripheral tissues
- ↓ in **GABA** level is associated with Epilepsy.

Pathophysiological role of GABA

Decrease **GABA** brain content is associated with:

- Epilepsy
- Anxiety
- Convulsions
- Insomnia

Conclusion:

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