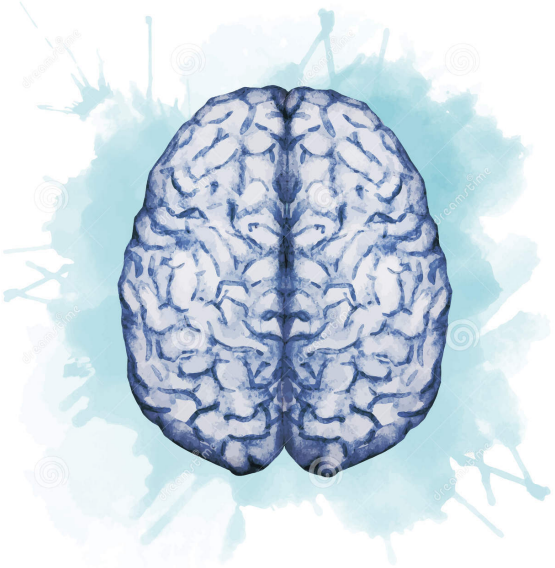
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



Pharmacology of central neurotransmitter

Objectives:

- To understand the role of neurotransmitters in the etiology and treatment of CNS diseases.
- To define neurotransmitters.
- To understand neuronal circuits system for neurotransmitters.
- To compare the location, receptor subtypes, effect of release, and general physiological and pharmacological roles of the neurotransmitter systems and the dysregulation of their level .
- Basic classes of neurotransmitters: Cholinergic (Ach),Biogenic amines (norepinephrine, epinephrine, dopamine, glutamate, and serotonin) , Inhibitory amino acids (GABA, glycine) , Opioid peptides.

color index:

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

Check out the mnemonics file :
https://docs.google.com/presentation/d/1Z0Vf9oEOJSXo4JIA0mTCk5jB-OU9LP5TFCwz8iBgNac/edit?usp=sharing

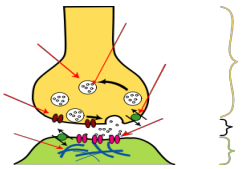
Kindly check the editing file before studying this document
https://docs.google.com/presentation/d/1_-g1vol4eBWPet5xVCkuTGFvvnhFF3PJmU0tWtEEw_o/edit?usp=sharing

Introduction

What are Neurotransmitters?

Endogenous chemicals or chemical messengers that transmit signals from a neuron to a target cell across a synapse.

- They're 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 postsynaptic 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. One way to treat depression :

MAO enzyme responsible for degradation of serotonin and dopamine if you inhibit this enzyme serotonin and dopamine levels will go high that will lead to antidepressant effect.

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

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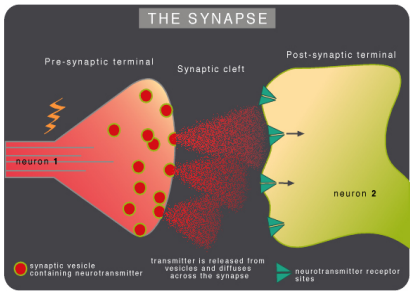
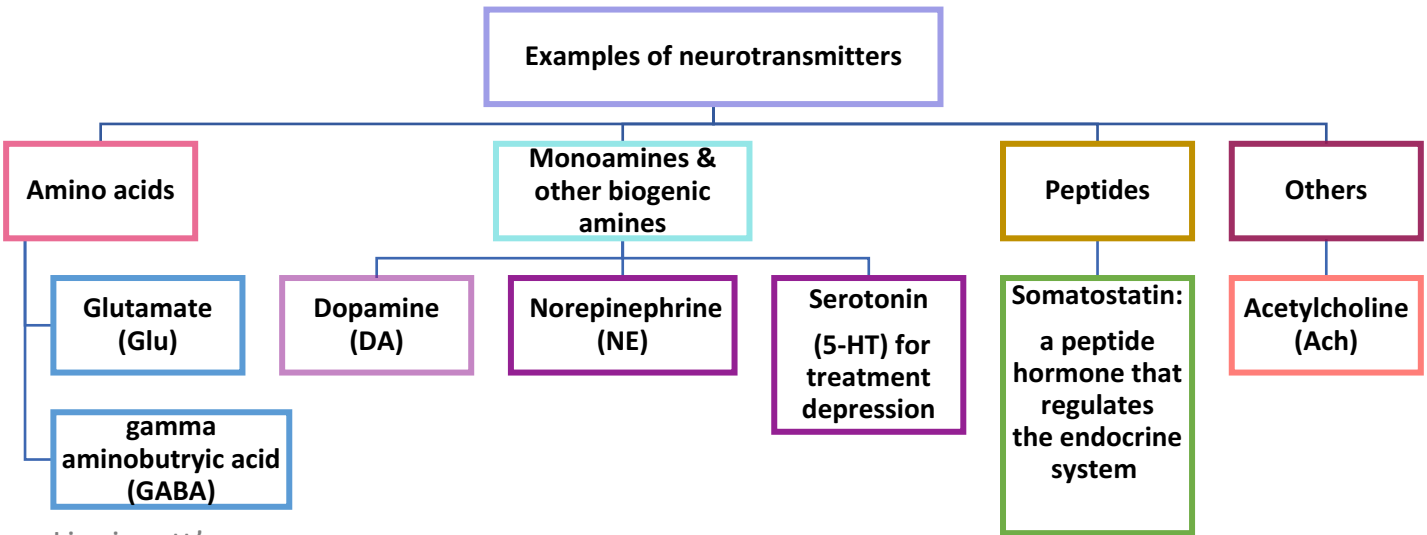


A membrane action potential arriving at the terminal opens axonal Ca channels; Ca inflow releases neurotransmitter molecules from many vesicles by fusing the vesicle membranes to the nerve terminal membrane. Membrane fusion generates an opening through which the molecules are expelled into the synaptic cleft via exocytosis.



Lippincott's corner

Although over fifty signal molecules in the nervous system have been identified, six signal compounds, including norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and γ-aminobutyric acid (GABA), are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and nor- epinephrine are the primary chemical signals in the ANS, whereas a wide variety of neurotransmitters function in the CNS.

Central Neurotransmitter

Neuropsychopharmacological science seeks to:

Understand how drugs can affect the CNS **selectively** to relieve pain, improve attention, induce sleep, reduce appetite, suppress disordered movements .... etc

To provide the means to develop **appropriate drugs** to correct pathophysiological events in the abnormal CNS.

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

Doctor note :
Diseases related to ↑ or ↓ neurotransmitters : e.g.
- schizophrenia ↑ dopamine which we will give medication to close the receptor
- depression we give medication to elevate NE and E .

1- Norepinephrine (NE)

Pathway :

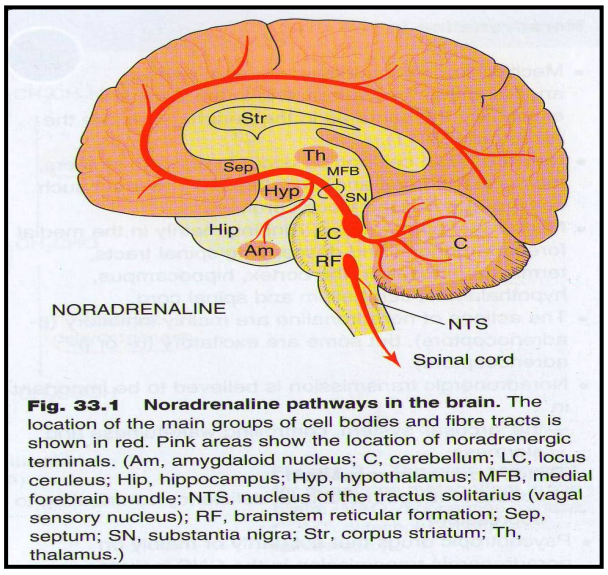


Fig. 33.1 Noradrenaline pathways in the brain. The location of the main groups of cell bodies and fibre tracts is shown in red. Pink areas show the location of noradrenergic terminals. (Am, amygdaloid nucleus; C, cerebellum; LC, locus ceruleus; Hip, hippocampus; Hyp, hypothalamus; MFB, medial forebrain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

So, used in treatment of depression patients.

Fight and flight.

➢ A variety of medically important drugs work by altering the actions of NE e.g., for treatment of CV problems (vasoconstriction, ↑ BP) and some of psychiatric conditions

➢(e.g. depression)

Mood disorders and NE:

*Very important

			Treatment
Affective disorders	↑NE	**Mania***	Drugs that ↓NE
	↓NE	**Depression**	Drugs that ↑NE

* Mania is characterized by: enthusiasm, rapid thought and speech patterns, extreme self-confidence, and impaired judgment. الهوس

2- Serotonin (5-HT)

Pathway:

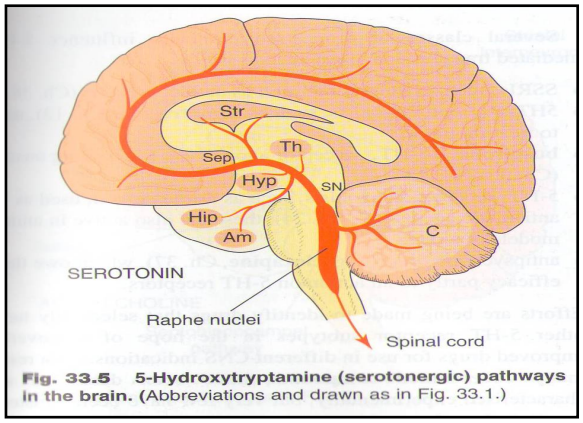
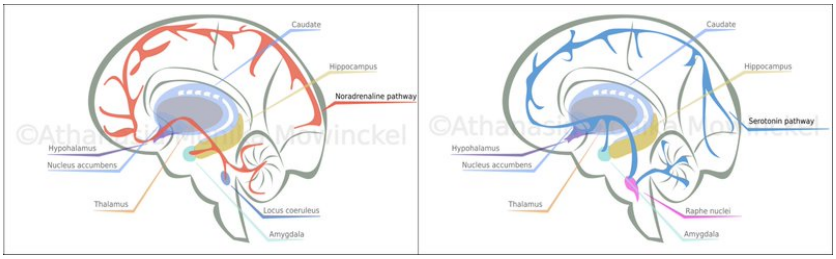


Fig. 33.5 5-Hydroxytryptamine (serotonergic) pathways in the brain. (Abbreviations and drawn as in Fig. 33.1.)

extra



Facts:

1. 5-hydroxytryptamine (5-HT) is a monoamine.
2. Primarily found in the **CNS , GIT, platelets.**
3. serotonin is responsible for feeling of ***well-being*** & ***happiness***.
   E.g.: dark chocolate contain large amount of serotonin that's why it bring happiness
4. It plays an important role : in **regulation of Mood, sleep, appetite** and **pain perception**. and some cognitive functions, including **memory and learning.** (memory and learning mostly with acetylcholine but serotonin may have a little role here)
5. Modulation of serotonin at synapses is a major action of several classes of antidepressants e.g. selective serotonin re-uptake inhibitors (SSRIs).(will lead to ↑ serotonin in post synaptic)

Diseases that are influenced by changes in serotonin brain content:

***Very important**

Vomiting → because its receptors are found in GIT & vomiting center of the medulla. (5-HT3) give Serotonin antagonism

Generalized anxiety
All the time, unknown reason

Obsessive compulsive disorders*OCD

Social phobia
(e.g.: talking in front of people)

Depression → low serotonin

Schizophrenia → dopamine & Ach

*الوسواس القهري : مثال الهوس بالنظافة بشكل مبالغ فيه و خارج عن الإرادة

3- Dopamine

↑Dopamine = ↓ Ach

Pathway:

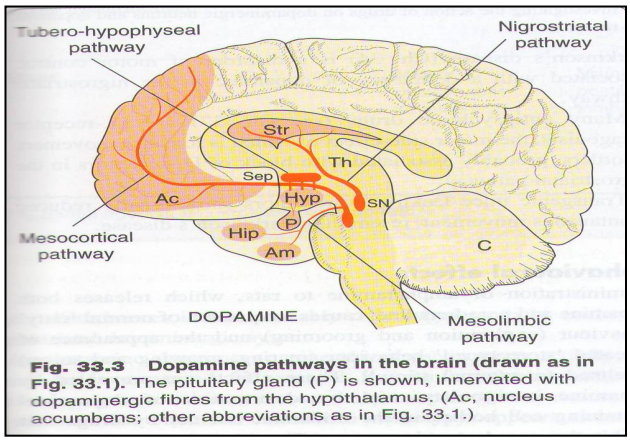
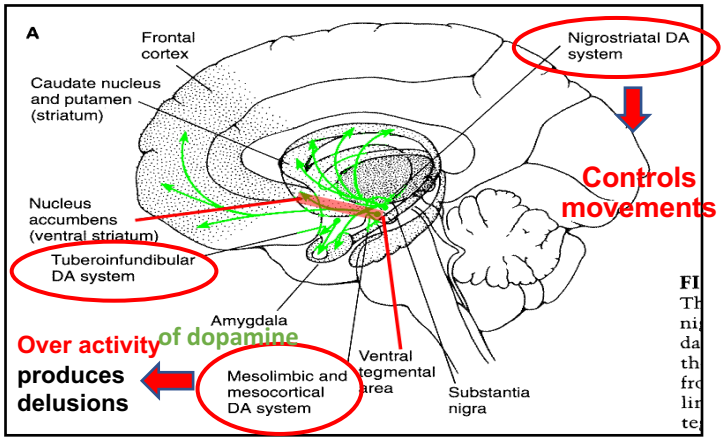
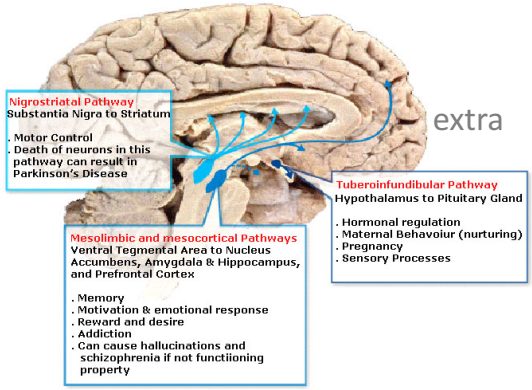


Fig. 33.3 Dopamine pathways in the brain (drawn as in Fig. 33.1). The pituitary gland (P) is shown, innervated with dopaminergic fibres from the hypothalamus. (Ac, nucleus accumbens; other abbreviations as in Fig. 33.1.)



Effects on dopaminergic synapses:

Dopamine has 4 pathway to synapse in :-



extra

1- In chemoreceptor trigger zone (**CTZ**)

↓

Antiemetic effect (low dose)

2- In **mesolimbic system**

(reward pathway)

↓

Ameliorate schizophrenia (psychiatric effect)

(↑dopamin → schizophrenia)

Blockade of postsynaptic dopamine receptors

3-In **tuberoinfundibular pathway** (hypothalamus – ant.-pituitary)

↓

↑Release of prolactin→hyperprolactinemia (endocrinal effect)

4- In **nigrostriatal system** (**basal ganglia**)

↓

Predispose to parkinsonism symptoms (neurologic)

The same pharmacodynamics action may have distinct psychiatric "neurologic" and endocrine effects

Diseases that are influenced by dopamine level:

Caused by ↑Dopamine

Treatment: Drugs that ↓Dopamine

Parkinson's disease

↓Dopamine= ↑ Ach

Drug addiction

(NE,dopamin,5-HT)

Depression

↓ Dopamine

Treatment: Drugs that ↑Dopamine

Schizophrenia

Attention deficit hyperactivity disorder*

ADHD

* فرط الحركة

4-Acetylcholine

Pathway:

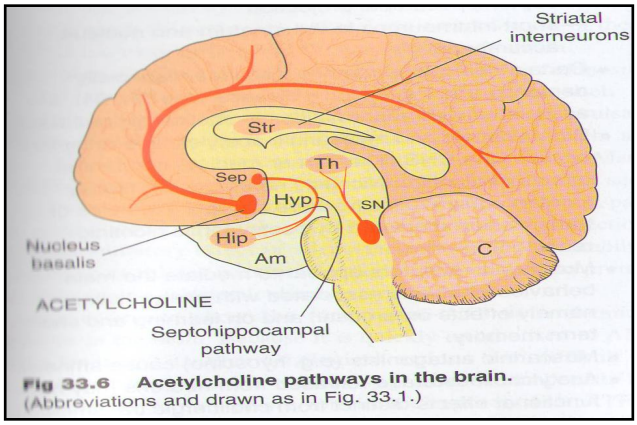


Fig 33.6 Acetylcholine pathways in the brain. (Abbreviations and drawn as in Fig. 33.1.)

There are two constellations of cholinergic neurons:

1. **The basal forebrain constellation** is located in the telencephalon, medial and ventral to the basal ganglia. It includes **the basal nucleus of Meynert (nucleus basalis)**, which provides cholinergic innervation to the entire neocortex, amygdala (Am), hippocampus (Hip), and thalamus (Th). **The medial septal nuclei (Sep)** provide cholinergic innervation to the cerebral cortex, hippocampus (Hip), and amygdala (Am).

2. **The second** constellation includes cholinergic neurons located in the dorsolateral tegmentum of the pons that project to the basal ganglia, thalamus, hypothalamus, medullary reticular formation, and deep cerebellar nuclei.

Pathway:

*First two points are not important(physiology)

- Acetylcholine is 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
- Ach is both excitatory (as in skeletal muscles) and inhibitory (as in heart muscle->bradycardia) neurotransmitter

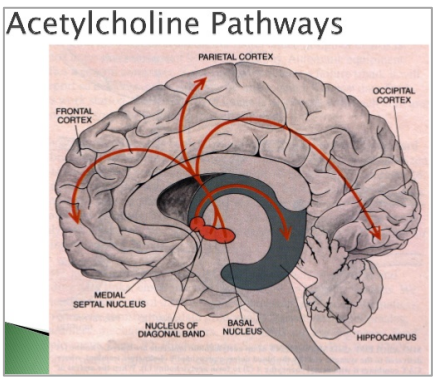
Role of Acetylcholine in the CNS :

*Very important

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

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

Extra:



CNS diseases linked to ACH derangement:

*Very important

Ach=Alzheimer's

- Damage to **cholinergic receptors** (muscarinic) is associated with memory deficits as in Alzheimer's disease. (↓Ach)
- **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).
- Schizophrenia may be due to **imbalance** between **Ach & dopamine** brain levels.
- Depression may be a manifestation of a central **cholinergic predominance**.

Just a theory, not important point.

5-Glutamic acid + GABA

Glutamic acid	Gamma amino butyric acid "GABA"
• It's an excitatory neurotransmitter. • An **increase** in its level predispose to epilepsy.	• **GABA** is the main **inhibitory** neurotransmitter in the brain. • Present throughout the brain; there is very little in peripheral tissues. *Glycine is the main inhibitory neurotransmitter in the spinal cord.
Potential therapeutic effect of glutamate antagonists **Very important!!!**	**Pathophysiological role of GABA**
Reduction of brain damage following : • **strokes & head injury** • **Treatment of epilepsy** • **Drug dependence** • **Schizophrenia**	Decrease GABA brain content is associated with : **Epilepsy** which is an over activity so that's why we use GABA which inhibit the excess secretion of neurotransmitter. **Anxiety** **Convulsions** **Insomnia** Benzodiazepine (diazepam) enhances GABA function and used in treatment of above diseases. (it give sedate affect)

Conclusion

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

Glutamate:

Glutamate is an important neurotransmitter in the brain it's a precursor to GABA and its very abundant in quantity.

But an increase in glutamate levels in the brain can lead to multiple brain damages and injuries epilepsy being one of them, due to its excitatory functions (over exciting neurons). Due to that we use glutamate antagonists to help decrease levels of glutamate and treat such cases.

مفيد و وجوده مهم بس الشي اذا زاد عن حده يتقلب ضده لذلك يبدأ يأذي الخلايا

GABA:

GABA on the other hand is inhibitory in function meaning it regulates neuronal activity, if neurons are over exited they will cause disease like anxiety, stress , insomnia etc.

So a decrease in GABA levels will cause these diseases.

يعني هو زي الأم اللي تهدي اطفالها اذا راحت انهبلوا

Summary

Trans-mitter	Function	Diseases that are influenced
Acetylcholine	Ach is thought to be involved in cognitive functions such as : ➢ **Memory** ➢ **Arousal** ➢ **Attention**	• 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) • Schizophrenia may be due to **imbalance** between **Ach & dopamine** brain levels. • Depression may be a manifestation of a central **cholinergic predominance**.
dopamine		**Parkinson's disease** **Schizophrenia** **Drug addiction** **Depression** **Attention deficit hyperactivity disorder***
Norepinephrine	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.	**Mania** high NE **Depression** low NE
Serotonin (5- hydroxy-tryptamine)	5-hydroxytryptamine (5-HT) is a monoamine Primarily found in the **CNS**, **GIT**, **platelets.** It is a popular thought that serotonin is responsible for feeling of **well-being** & **happiness**. It plays an important role : in **regulation of Mood**, **sleep**, **appetite** and **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).	**Vomiting** **Generalized anxiety** **Obsessive compulsive disorders** **Depression** **Social phobia** **Schizophrenia**
GABA	• **GABA** is the main **inhibitory** neurotransmitter in the brain • Present throughout the brain; there is very little in peripheral tissues	Decrease GABA brain content is associated with **Epilepsy , Anxiety , Convulsions , Insomnia** Benzodiazepine (diazepam) enhances GABA function and used in treatment of above diseases
Glutamate	• is an An **increase** in its level predispose to epilepsy • excitatory neurotransmitter	• Reduction of brain damage following : • **strokes & head injury** • **Treatment of epilepsy** • **Drug dependence** • **Schizophrenia**

Self reading

To understand !

Trans-mitter	Anatomic distribution	Receptor subtype	Receptor mechanism
Acetylcholine	Cell bodies at all levels, short and long axons	- M1: blocked by pirenzepine and atropine	Excitatory : decrease K conductance & increase IP3 & DAG
		- M2: blocked by atropine	Inhibitory : increase K conductance & decrease cAMP
	Motoneurons – renshew cells synapse	Nicotinic, N	Excitatory: increase cation conductance
dopamine	Cell bodies at all levels, short, medium and long axons	D1: blocked by phenothiazine	Inhibitory: increase cAMP
		D2: blocked by phenothiazine & haloperidol	Inhibitory (presynaptic): decrease ca conductance - Inhibitory (postsynaptic) : increase K conductance, decrease cAMP
Norepinephrine	Cell bodies in pons and brainstem project to all levels.	Alpha1: blocked by prazosin	Excitatory : decrease K conductance & increase IP3 & DAG
		Alpha2: activated by clonidine	Inhibitory (presynaptic): decrease ca conductance - Inhibitory (postsynaptic) : increase K conductance, decrease cAMP
		Beta1 : blocked by propranolol	Excitatory : decrease K conductance & increase cAMP
		Beta2 :blocked by propranolol	Inhibitory: increase in electrogenic sodium pumps & increase cAMP
Serotonin (5- hydroxy-tryptamine)	Cell bodies in pons and midbrain project to all levels.	5-HT1A: buspirone is a partial agonist	Inhibitory: increase K conductance, decrease cAMP
		5-HT2A: blocked by clozapine , resperidone & olanzapine	Excitatory : decrease K conductance & increase IP3 & DAG
		5-HT3: blocked by ondansetron	Excitatory: increase cation conductance
		5-HT4	Excitatory : decrease K conductance

Self reading

To understand !

Trans-mitter	Anatomic distribution	Receptor subtype	Receptor mechanism
GABA	Supraspinal interneurons: spinal interneurons involved in presynaptic inhibition	GABAa: facilitated by benzodiazepine and zolpidem	Inhibitory: increase CL conductance
		GABAb: activated by baclofen	- Inhibitory (presynaptic): decrease ca conductance - Inhibitory (postsynaptic) : increase K conductance
Glutamate	Relay neurons at all levels	-Four subtypes: NMDA subtype blocked by phencyclidine. - Metabotropic subtype.	- Excitatory: increase Ca or cation conductance - inhibitory (presynaptic): decrease ca conductance & decrease cAMP -Excitatory (postsynaptic): decrease K conductance & increase IP3 & DAG
Glycine	Interneurons in spinal cord and brain stem	Single subtype: blocked by strychnine	Inhibitory: increase CL conductance
opioid peptide	Cell body at all levels	Three major subtypes: mu, delta & kappa.	Inhibitory (presynaptic): decrease ca conductance & decrease cAMP
			Inhibitory (postsynaptic) : increase K conductance & decrease cAMP

إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

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