#4

Pharmacology of central neurotransmitter

Objectives:

- Understand the role of neurotransmitters in the etiology and treatment of CNS diseases

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

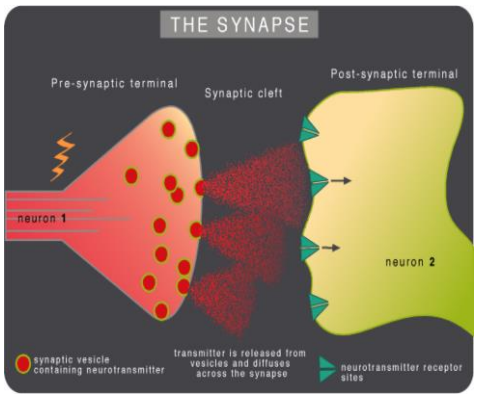
Neurotransmitters

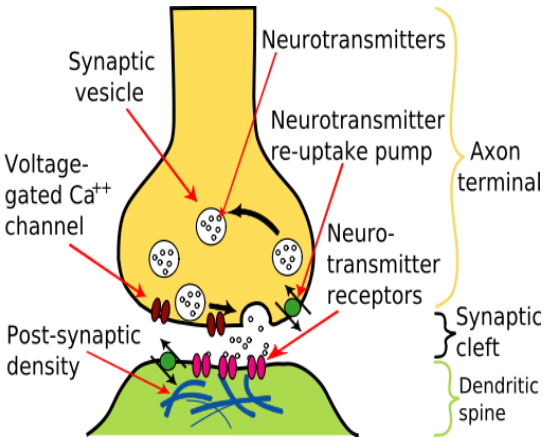
What are they?

Endogenous chemicals that 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 postsynaptic side.





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.

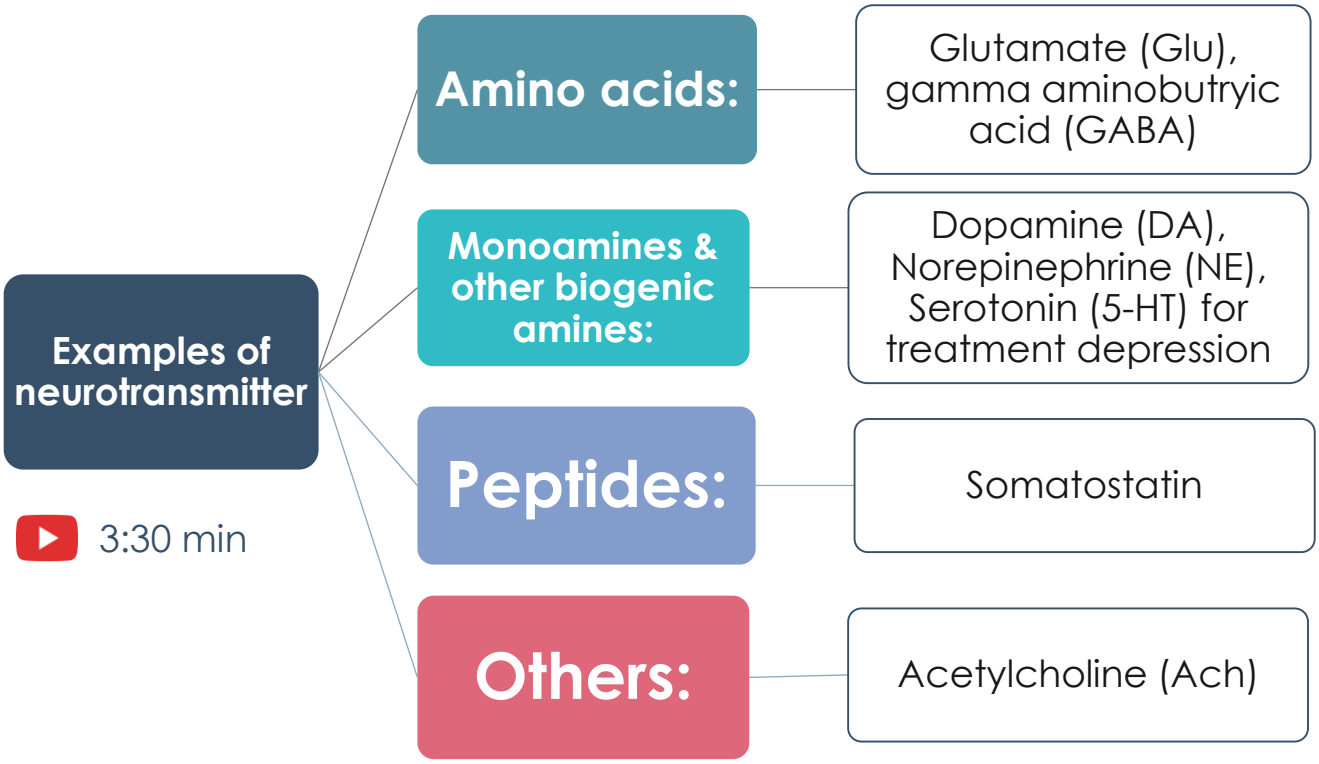
- The neurotransmitter-receptor interaction must be terminated quickly to allow rapid, repeated activation of receptors. **One of the following can happen to neurotransmitters that have interacted with receptors**:

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.



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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.

Importance of understanding neurotransmitters

1. To understand the etiology of diseases.
2. To suggest the best drugs to be used.
3. To understand the other clinical uses of any particular drug.

1- Norepinephrine (NE)

- Pathway:

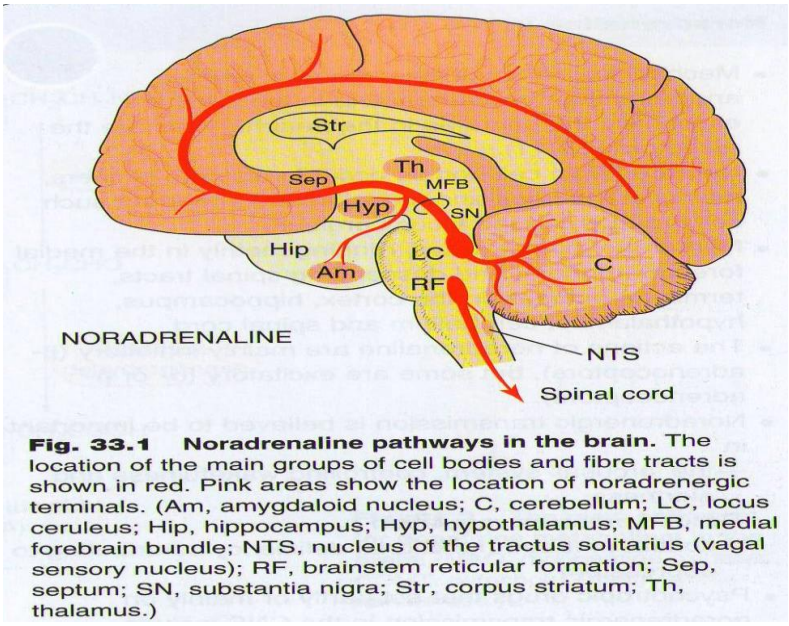


Fig. 33.1 Noradrenaline pathways in the brain. The location of the main groups of cell bodies and fibre tracts is shown in red. Pink areas show the location of noradrenergic terminals. (Am, amygdaloid nucleus; C, cerebellum; LC, locus ceruleus; Hip, hippocampus; Hyp, hypothalamus; MFB, medial forebrain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

- Mood disorders and NE:

			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. Opposite of depression, الهوس

2- Serotonin (5-HT)

- Pathway:

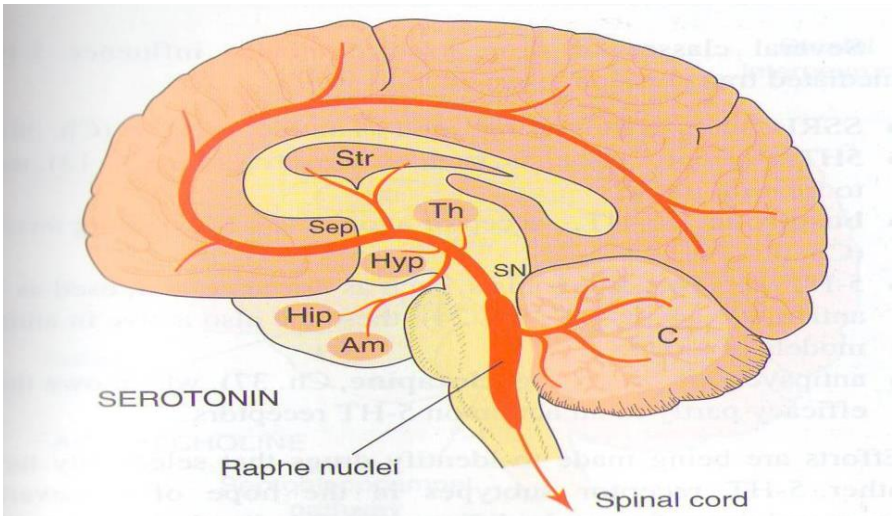


Fig. 33.5 5-Hydroxytryptamine (serotonergic) pathways in the brain. (Abbreviations and drawn as in Fig. 33.1.)

- Facts:

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

Diseases that are influenced by changes in serotonin brain content:

Depression → w\ low serotonin

Social phobia

Schizophrenia → w\ dopamine & ACh

Vomiting→ bc its receptors are found in GIT & vomiting center of the medulla. ($5\text{-}HT_3$)

Obsessive compulsive disorders*

Generalized anxiety

* الوسواس القهري

3- Dopamine:

- Pathway:

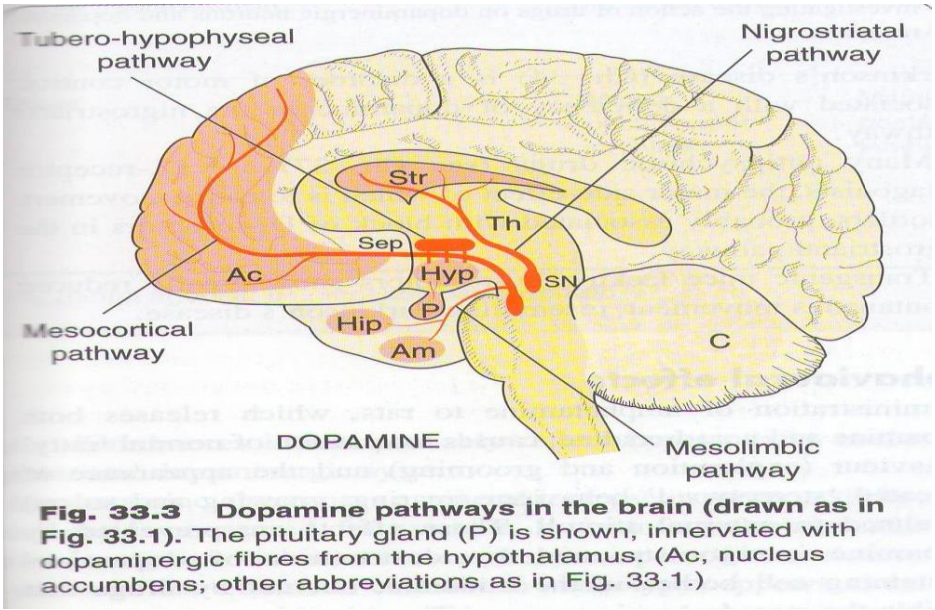


Fig. 33.3 Dopamine pathways in the brain (drawn as in Fig. 33.1). The pituitary gland (P) is shown, innervated with dopaminergic fibres from the hypothalamus. (Ac, nucleus accumbens; other abbreviations as in Fig. 33.1.)

- Effects on **dopaminergic synapses**:

In chemoreceptor trigger zone (**CTZ**)

↓

Antiemetic effect (low dose)

In **mesolimbic system**

(reward pathway)

↓

Ameliorate schizophrenia (psychiatric effect)

Blockade of postsynaptic dopamine receptors

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

↓

↑ Release of prolactin (endocrinal effect)

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

↓

Predispose to parkinsonism symptoms (neurologic)

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

Diseases that are influenced by **dopamine** level:

Parkinson's disease	Schizophrenia	Drug addiction	Depression	Attention deficit hyperactivity disorder*

* فرط الحركة

4- Acetylcholine

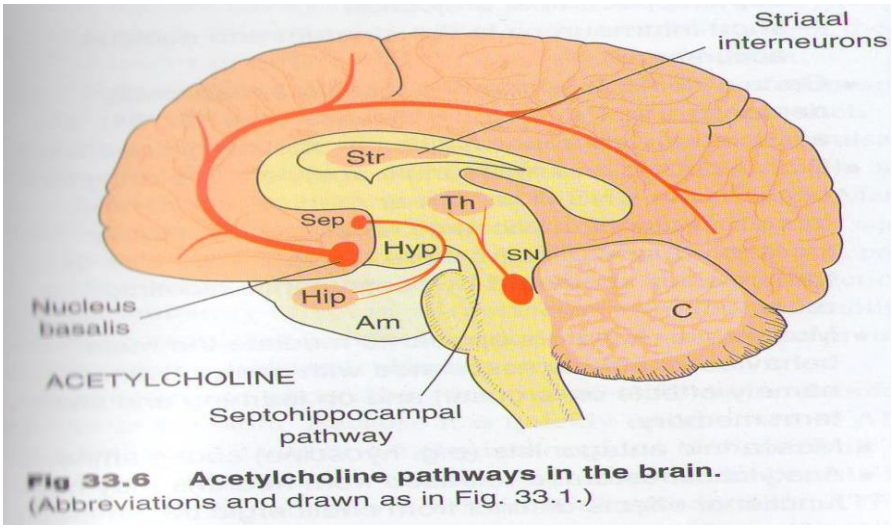


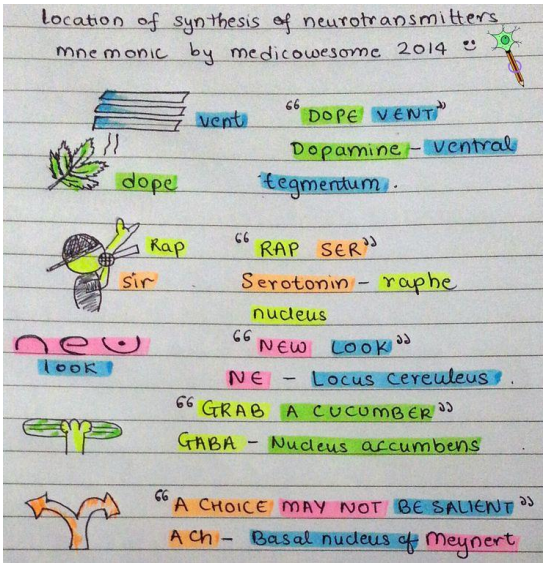
Fig 33.6 Acetylcholine pathways in the brain.
(Abbreviations and drawn as in Fig. 33.1.)

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.

Extra, to help you remember the site of NTs production ☺



Acetylecholine

Overview

Acetylcholine is the first neurotransmitter discovered.

Inside the brain Ach functions as a neuro-modulator, which is 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?
Ach is both excitatory and inhibitory.

Role of Acetylcholine in the CNS

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

- Memory
- Arousal ** الإثارة
- Attention انتباه

***Cognitive functions** can be defined as cerebral activities that lead to knowledge, including reasoning, memory , attention, and language.
** Arousal is the physiological and psychological state of being awoken or of sense organs stimulated to a point of perception.

What are the CNS diseases linked to ACH derangement?

- **Damage to cholinergic (muscarinic) receptors** is associated with **memory deficits** as in Alzheimer's disease.
- **Muscarinic antagonists** as **hyoscine** cause amnesia (deficit in memory).
- **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.**

* Dopamine & Ach work with each other → when you take a dopamine antagonist = Ach will take the upper hand → that's why the increased level of Ach may be predispose to Parkinson's disease.

4:25 min

Glutamic acid & GABA

Glutamic acid

- An **excitatory** neurotransmitter
- Increased levels predispose to Epilepsy

Glutamate **anta**gonist effects:

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

Schizophrenia: is a brain disorder that affects how people think, feel, and perceive.
Drug dependence is the body's physical need, or addiction, to a specific agent.

GABA

- It is the main **inhibitory** transmitter in the brain (in spinal cord = Glycin)
- It's present throughout the brain; there is very little in peripheral tissue.

- Decreased GABA brain content is associated with:

- **Epilepsy**
- **Anxiety**
- **Convulsions**
- **Insomnia**

Extra, to help you remember the site of NTs production ☺

To understand better-1

ملاحظة: الدكاترة قرؤوا هذا الجدول واللي بعده على السريع، وركزوا على النيوروترانزمترز اللي معنا في المحاضرة.

Trans-mitter	Anatomic distribution	Receptor subtype	Receptor mechanism
Acetylcholine	Cell bodies at all levels, short and long axons	- M1: blocked by pirenzepine and atropine - M2: blocked by atropine	Excitatory : decrease K conductance & increase IP3 & DAG
	Motoneurons – renshew cells synapse	Nicotinic, N	Inhibitory : increase K conductance & decrease cAMP
			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 trptamin)	Cell bodies in pons and midbrain project to all levels, GIT & platelets	5-HT_{1A}: buspirone is a partial agonist	Inhibitory: increase K conductance, decrease cAMP
		5-HT_{2A}: blocked by clozapine , resperidone & olanzapine	Excitatory : decrease K conductance & increase IP3 & DAG
		5-HT_{3}: blocked by ondansetron	Excitatory: increase cation conductance
		5-HT_{4}	Excitatory : decrease K conductance

To understand better-2

Trans-mitter	Anatomic distribution	Receptor subtype	Receptor mechanism
GABA	Supraspinal ▪ interneurons: spinal interneurons involved in presynaptic inhibition & very little in peripheral tissues	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

Summary of the lecture

Trans-mitter	Function	Diseases that are influenced
Acetylcholine	• Inside the brain Ach functions as a neuromodulator • Ach is thought to be involved in cognitive functions: 1. Memory 2. Arousal 3. Attention	• **Alzheimer's disease** → Damage to muscarinic receptors. • **Amnesia** → Muscarinic antagonist. • **Parkinson's disease** → increased Ach level in CNS is predispose to Parkinsonism. • **Schizophrenia** → ~ imbalance between Ach & dopamine. • **Depression**
Dopamine	—	• Parkinson's disease • attention deficit • hyperactivity disorder, • schizophrenia, • depression • drug addiction
Norepinephrine	—	• Mania → **high** NE • Depression → **Low** NE
Serotonin (5- HT)	• Primarily found in the CNS, GIT, platelets • Responsible for feeling of well-being & happiness. • Plays an important role in regulation of ; Mood, sleep, appetite and pain perception	• Depression • Social phobia • Obsessive Compulsive Disorders • Generalized Anxiety • Schizophrenia • Vomiting
GABA	• The main **inhibitory** transmitter in the brain.	- With **low** levels of GABA: • Epilepsy • Anxiety • Convulsions • Insomnia
Glutamate	• An **excitatory** neurotransmitter.	- Therapeutic effect of glutamate antagonists: • Strokes • Head injury • Schizophrenia • Treatment of epilepsy

Flash Cards | MCQs | Editing File

Thank you for checking our team!

Pharmacology 435

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أثير النشوان

أسرار باطرفي
العنود العمير
آية غانم
حصه المزيني
دلال الحزيمي
رغدة قاسم
ريم العقيل
سارا الحسين
ساره الخليفة
لمى الزامل
لولوه الصغيّر
لينا إسماعيل
ملاك اليحيا
نورة البصيص

خالد أبوراس

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محمد ابونيان
محمد السحيباني
يوسف الصامل

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5- Basic & Clinical Pharmacology by Katzung. Chapter 21, 12th edition

Revised by
هشام الغفيلي & خولة العماري