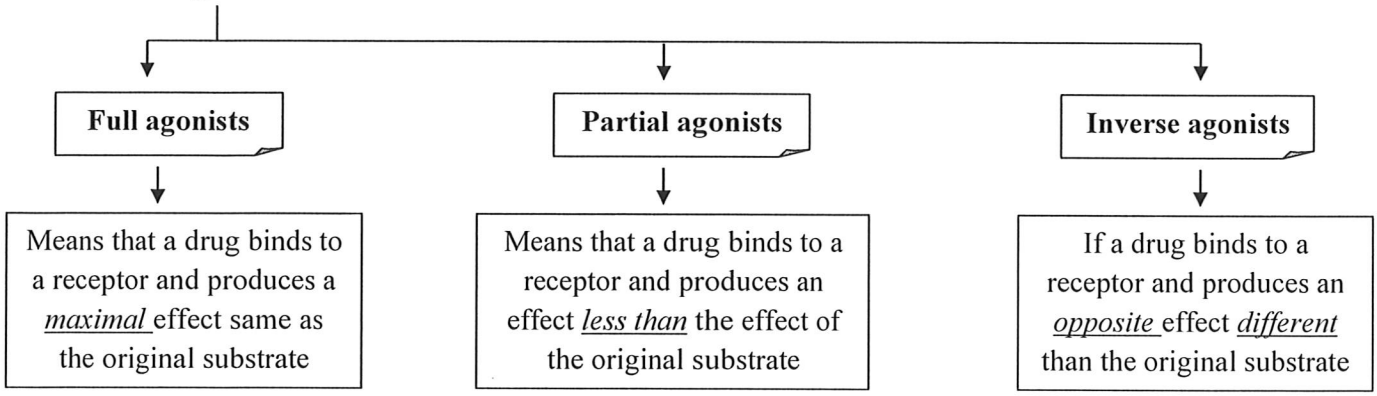
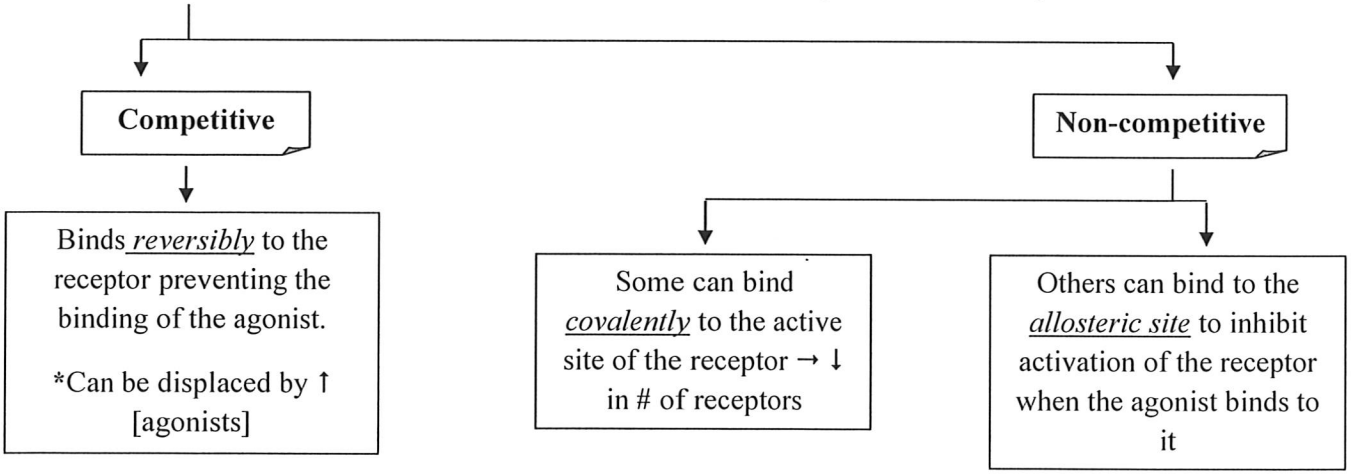
- Agonists:



- Antagonists: are substances or molecules that bind to the receptor and prevent agonists from binding to it. Therefore, it will inhibit the action of agonists on the receptor.



The difference between these two types of antagonists is:

1. The competitive ↓ the agonist potency
2. The non-competitive ↓ the agonist efficacy

Physiological/Functional antagonism: initiates effects that are functionally opposite those of the agonist.

Chemical antagonist: prevents the action of an agonist by modifying the agonist so it is unable to bind to its receptor and activate it.

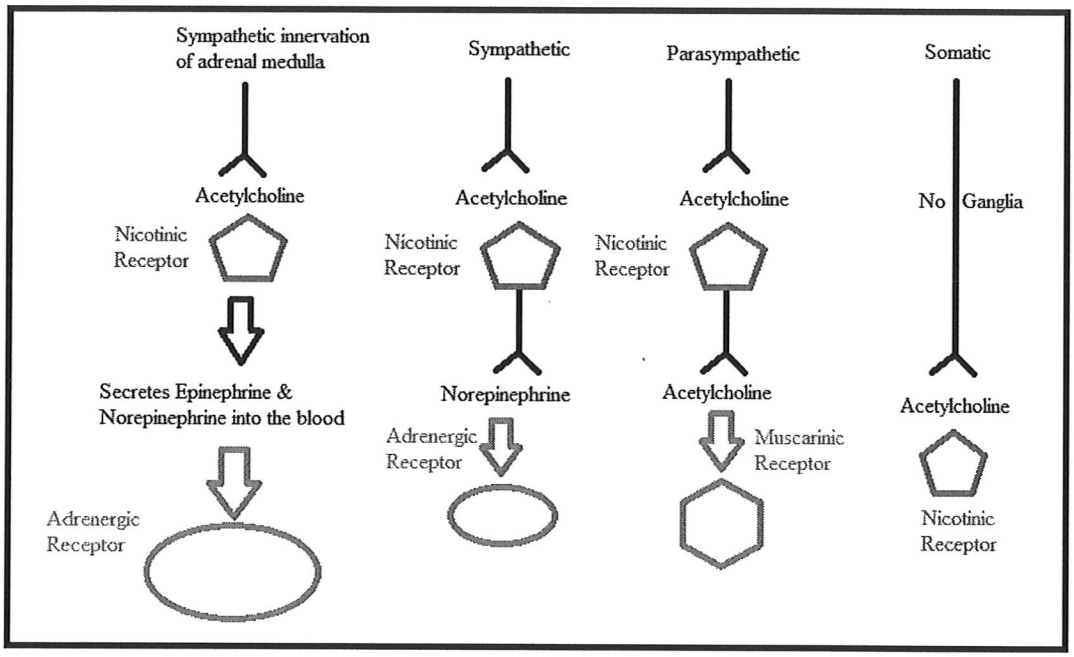
Done by: Aysha Khalid

Pharmacokinetic antagonism: a situation in which antagonism reduces the active [drug].

And this can occur when: the absorption ↓s, or when the metabolism and renal excretion ↑s.

Introduction to Cholinergic & Adrenergic Fibers

- **Cholinergic fibers** are those that secret Acetylcholine
- **Adrenergic fibers** are those that secret Norepinephrine

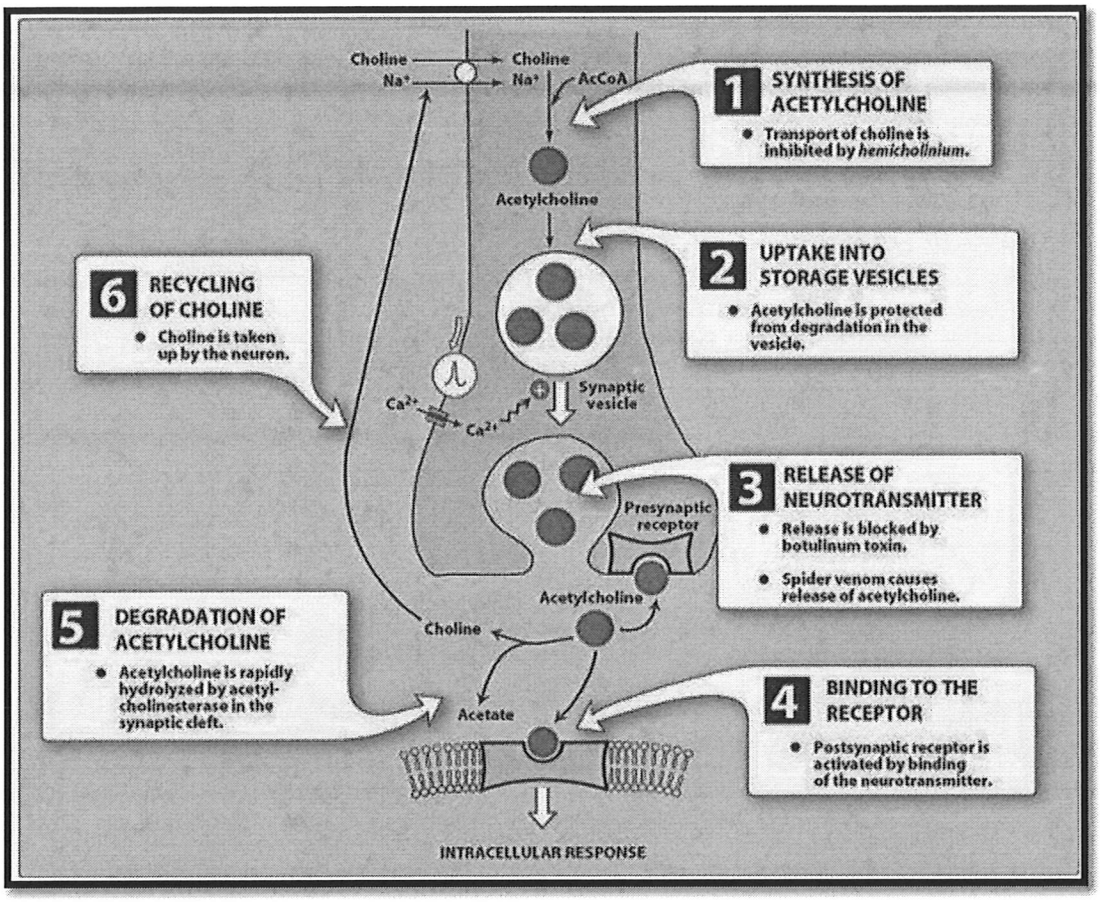


I. Cholinergic Neurons:

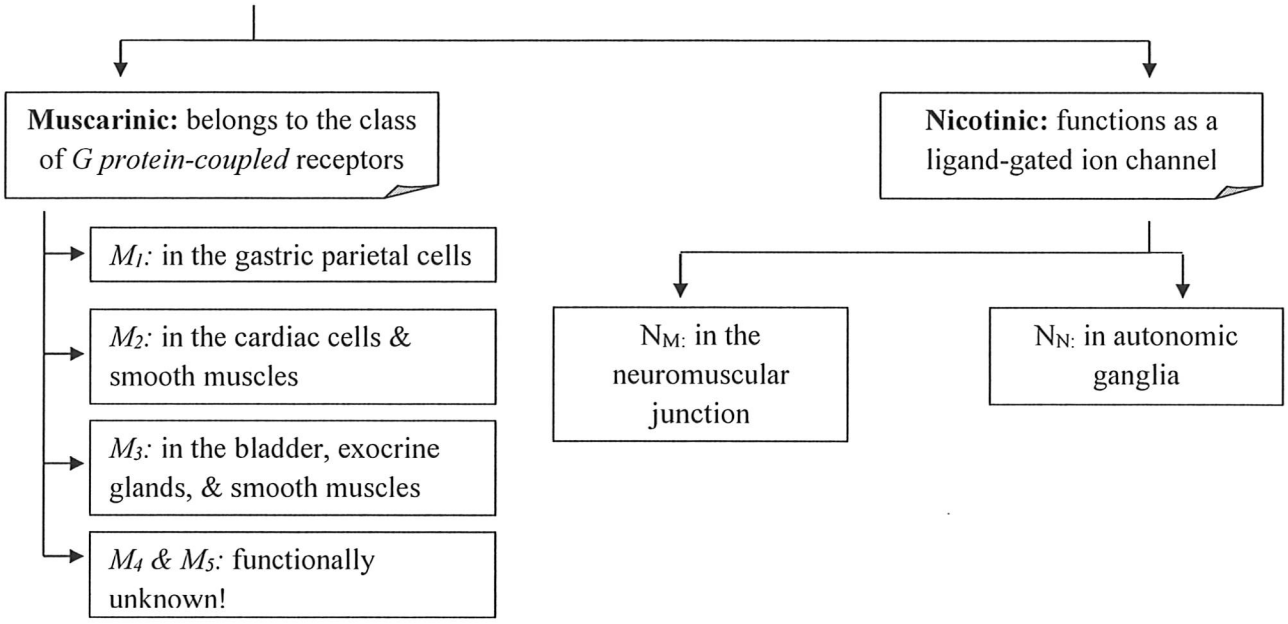
- **Neurotransmission at cholinergic neurons:**
  Involves 6 steps: "the picture below sums them all up"
  1. Synthesis of Acetylcholine (ACh): ***The uptake of choline** is the rate-limiting step*
  2. Storage of ACh.
  3. Release of ACh.
  4. Binding of ACh to its receptor
  5. Degradation of ACh

***NOTE:** **the enzyme Butyrylcholinesterase,** (known also as **pseudo cholinesterase**, is found in the plasma but does not play a significant role in the termination of ACh's effect in the synapse.

  6. Recycling of Choline


Choline
Na+
Choline
Na+
AcCoA
1 SYNTHESIS OF ACETYLCHOLINE
Transport of choline is inhibited by hemicholinium.
Acetylcholine
2 UPTAKE INTO STORAGE VESICLES
Acetylcholine is protected from degradation in the vesicle.
6 RECYCLING OF CHOLINE
Choline is taken up by the neuron.
Ca2+
Ca2+
Synaptic vesicle
3 RELEASE OF NEUROTRANSMITTER
Release is blocked by botulinum toxin.
Spider venom causes release of acetylcholine.
Presynaptic receptor
Acetylcholine
5 DEGRADATION OF ACETYLCHOLINE
Acetylcholine is rapidly hydrolyzed by acetyl-cholinesterase in the synaptic cleft.
Choline
Acetate
4 BINDING TO THE RECEPTOR
Postsynaptic receptor is activated by binding of the neurotransmitter.
INTRACELLULAR RESPONSE

- **Cholinergic receptors (Cholinoceptors):**



A. Muscarinic Receptors:

- It can recognize ACh and Muscarine (an alkaloid present in poisonous mushrooms).
- If M_1 or M_3 are activated:

They will interact will the G-protein (G_q) → + Phospholipase C → activate → DAG: +PKC to +P on other enzymes; IP_3: ↑ $[Ca^{2+}]$ intracellular

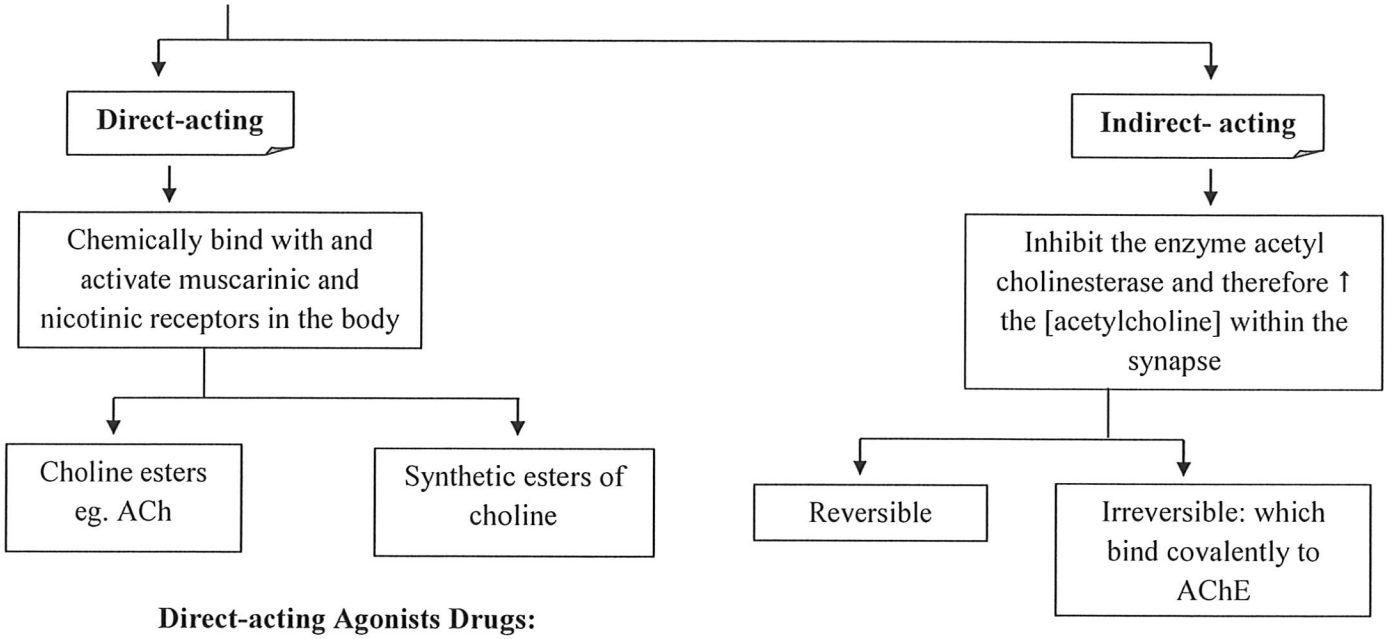
- If M_2 is activated:

It will interact with G-protein (G_i) → - cAMP & ↑ K+ conductance → ↓ rate/force of ♥ contractility

B. Nicotinic Receptors:

- Binding of two ACh molecules elicits a conformational change that allows the entry of Na+, resulting in depolarization of the effector cell.
- These receptors are located in the CNS, adrenal medulla, autonomic ganglia, and neuromuscular junction.

- **Cholinergic Agonists Drugs: (aka parasympathomimmetics):**



Direct-acting Agonists Drugs:

- Have longer durations than ACh
- Show little specificity in their actions, which limits their clinical usefulness.

1. **ACETYLCHOLINE:** (same as parasympathetic effects: on many organs)

★ Check Pharmacology Recall, 2nd edition, pages 36-37 ★

2. **CARBACHOL:**

★ Check Pharmacology Recall, 2nd edition, page 37 ★

3. **PILOCARPINE:** This drug can enter the brain and cause CNS disturbances along with **DUMBELS**.

★ Check Pharmacology Recall, 2nd edition, page 38 ★

	Receptor(s) it activates	Adverse Effects
Acetylcholine	Both muscarinic & nicotinic	Excessive generalized cholinergic stimulation: **DUMBELS** **D**iarrhea & **D**ecreased BP **U**rination **M**iosis **B**ronchoconstriction & **B**radycardia **E**xcitation of skeletal muscles **L**acrimation **S**alivation & **S**weating
Carbachol	Both muscarinic & nicotinic and it can also release epinephrine & norepinephrine from the adrenal medulla	
Pilocarpine	Muscatinic receptors	

Indirect- acting Agonists Drugs:

4. **NEOSTIGMINE:** reversible.

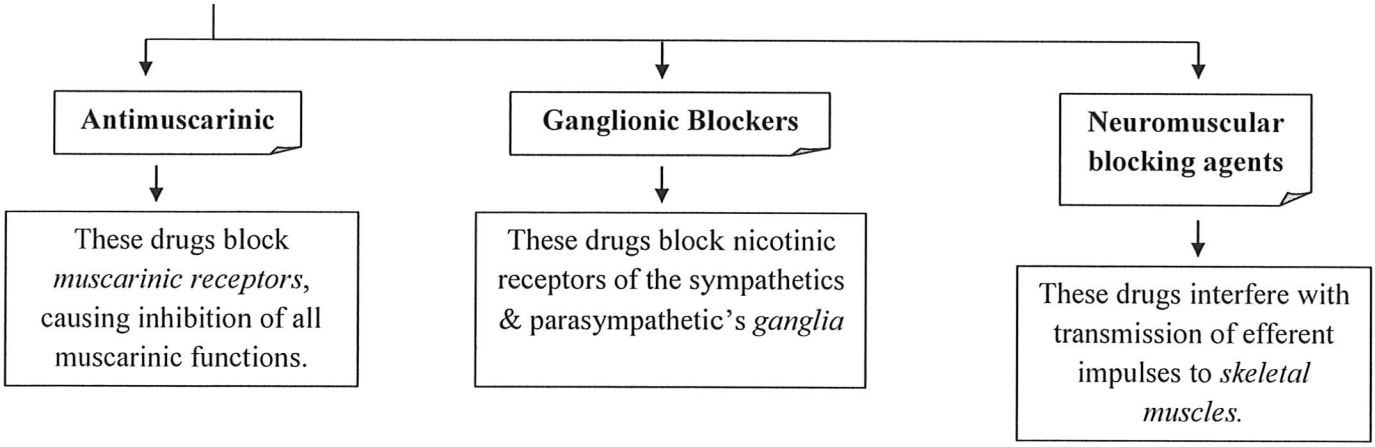
★ Check Pharmacology Recall, 2nd edition, pages 40-42 ★

5. **PARATHION:** irreversible.

★ Check Pharmacology Recall, 2nd edition, pages 39-40 ★

***NOTE: PRALIDOXIME:** is a drug that reactivates acetyl cholinesterase.

- **Cholinergic Antagonist Drugs:** (aka as cholinergic blockers, smpatholytics, and anticholinergic drugs)



A. Antimuscarinic Agents:

1. **ATROPINE: (Antimuscarinic):** "causes sympathetic responses"

It causes reversible, nonselective blockade of muscarinic receptors (to prevent ACh from binding).

★ Check Pharmacology Recall, 2nd edition, pages 43-45 ★

2. **TROPICAMIDE** (short acting atropine):

★ Check Pharmacology Recall, 2nd edition, page 46 ★

B. Ganglionic Blockers:

These drugs block the entire output of the autonomic nervous system at the nicotinic receptor.

C. Neuromuscular-blocking Drugs:

These are clinically useful during surgery for producing complete muscle relaxation, orthopedic surgery, and tracheal intubation.

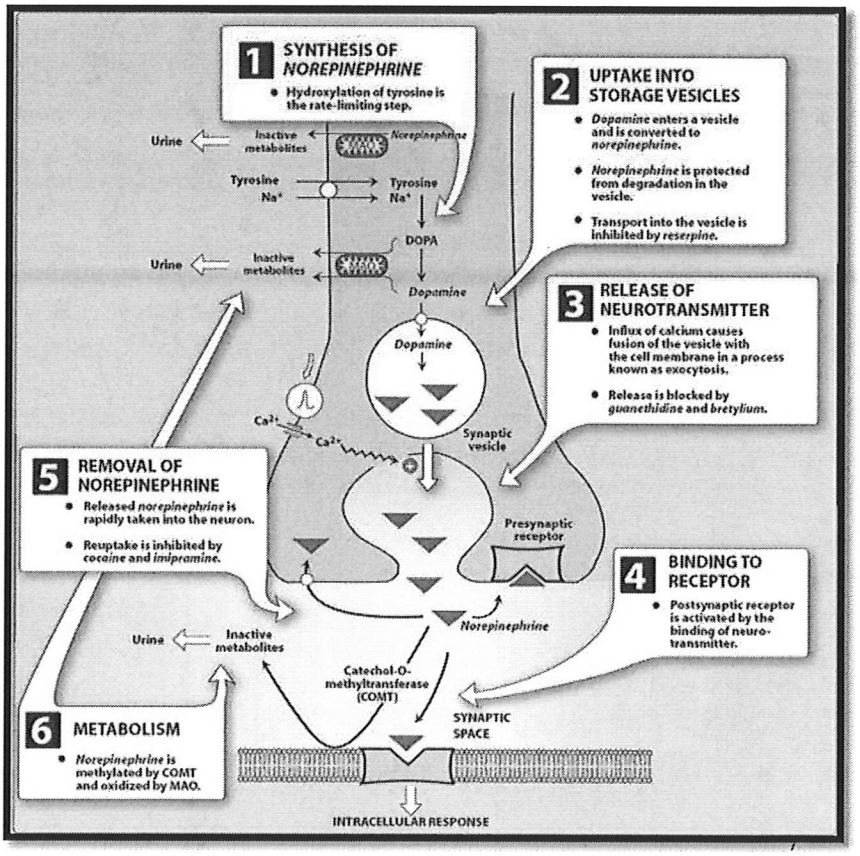
II. Adrenergic Neurons:

- **Neurotransmission at adrenergic neurons:**
  Involves 5 steps: "refer to the picture below"

1. Synthesis of norepinephrine (NE):

This is the rate-limiting step in the formation of norepinephrine.

2. Storage of NE in vesicles.
3. Release of NE.
4. Binding to receptors.
5. Removal of epinephrine:
   By: - diffusing out of the synaptic space & enter the general circulation
   - being metabolized by Catechol-O-MethylTransferase (COMT)
   -be recaptured by an uptake system (which involves a Na+ or K+-activated ATPase) which will pump NE back into the neuron.
6. Fates of recaptured NE: it can be oxidized by monoamine oxidase (MAO) present in the neuronal mitochondria.



Done by: Aysha Khalid

- **Adrenergic Receptors (Adrenoceptors):**

α-receptors

- **α_1:** present on the postsynaptic membrane of the effector organs and it mediates the *constriction of the smooth muscles*
- **α_2:** present on the presynaptic nerve endings and on the β cells of the pancreas and some vascular smooth muscle cells.

β-receptors

- **β_1:** have equal affinities for E & NE
- **B_2:** ↑ affinity for E than NE
- **B_3:** involved in lipolysis

- **<u>Activation of α_1 receptors results in:</u>**

They will activate the G-protein → + Phospholipase C → activate →
- DAG: +PKC to +P on other enzymes
- IP_3: ↑ $[Ca^{2+}]$ intracellular

- **<u>The α_2 receptors act as:</u>**

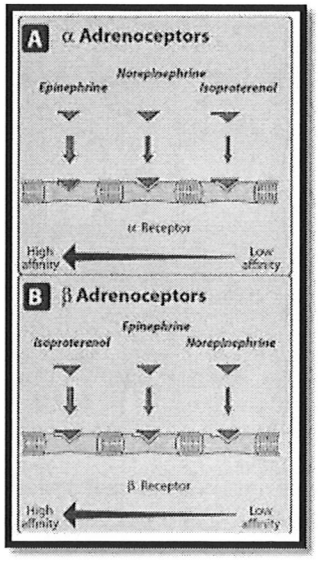
***Inhibitory Auto receptors:** when norepinephrine is released from the synaptic vesicle, part of it binds to α_1 receptors and part of it bind to α_2 which are found on the neuronal membrane to inhibit the ongoing release of norepinephrine.

***Inhibitory Heteroreceptors:** sometimes norepinephrine can diffuse to and interact with these receptors to inhibit the release of Acetylcholine.

- **Activation of any one of the three β receptors:** will activate adenylyl cyclase, and therefore, ↑ [cAMP].

-Major Effects mediated by α & β adrenoceptors:

α_1	α_2	β_1	β_2
-Vasoconstriction -↑ peripheral resistance -↑BP -Mydriasis -↑ closure of internal sphincter of bladder	-↓ of NE release -↓ of ACh release -↓ of insulin release	-Tachycardia -↑lipolysis -↑ myocardial contractility -↑ release of renin	-Vasodilation -↓ peripheral resistance -Bronchodilation -↑ glycogenolysis -↑ release of glucagon -Relaxed uterine smooth muscle



Done by: Aysha Khalid

-Desensitization of receptors:

Prolonged exposure to the catecholamine ↓ the responsiveness of these receptors (Desensitization): and this can be explained by:

1. Sequestration of the receptors so they are not available for interaction
2. Down-regulation (disappearance of the receptors by destruction or ↓ synthesis)
3. Inability to couple to G- protein because it has been "+P"

-Characteristics of adrenergic agonists:

Most of the adrenergic drugs are derivates of β-phenylethylamine `

Important structural features of these drugs are:

1. The # and location of OH molecules on the benzene ring
2. The nature of the molecule on the amino nitrogen.

A. **Catecholamines:** are sympathomimetic amines that contain 3,4-dihydroxybenzene (eg. Epinephrine, norepinephrine, dopamine, and isoproternol).

These have the following properties:

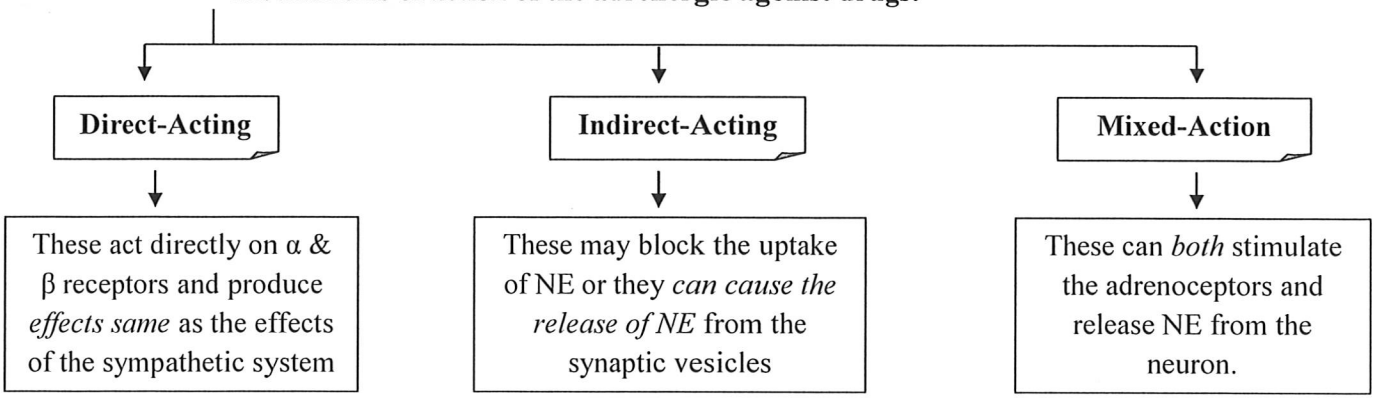
a. High potency: in directly activating α & β receptors.
b. Rapid interaction: due to the fact that they get metabolized by the enzymes MAO & COMT
c. Poor penetration into the CNS: because they are polar

B. **Noncatecholamines**: are compounds that lack the catechol hydroxyl groups (eg. Phenylephrine, ephedrine, and amphetamine)

These have a longer half-lives because they are not inactivated by COMT

They may penetrate the CNS because they have an increased lipid solubility (due to the lack of polar OH groups)

- **Mechanisms of action of the adrenergic agonist drugs:**



-Direct- Acting Adrenergic Agonists:

1. EPINEPHRINE:

★ Check Pharmacology Recall, 2nd edition, pages 57-58 ★

Pharmacokinetics:

Has a rapid onset but a brief duration of action so its better to give it intramuscularly.

2. NOREPINEPHRINE:

★ Check Pharmacology Recall, 2nd edition, pages 58-59 ★

Pharmacokinetics:

It may be given IV for rapid onset

Indirect-Acting Adrenergic Agonists:

3. AMPHETAMINE:

★ Check Pharmacology Recall, 2nd edition, page 60 ★

Mixed-Actions Adrenergic Agonists:

4. EPHEDRINE:

★ Check Pharmacology Recall, 2nd edition, page 61 ★

- **Adrenergic Antagonist Drugs:** (aka blockers or sympatholytic agents): bind to adrenoceptors but do not make the usual receptor-mediated intracellular effects.

These are also <u>further classified</u> into reverible and irreversible antagonists.

A. α-adrenergic blocking agents:

These affect the blood pressure the most because they ↓ the sympathetic tone of the blood vessels, that will result in ↓ periphral vascular resistance.

5. PRAZOSIN: selective competitive blocker

Its useful in treating hypertensive patients

★ Check Pharmacology Recall, 2nd edition, page 63 ★

B. β-adrenergic blocking agents: (competitive agonsits)

<u>Non-selective blockers</u> → work on both β_1 & β_2 receptors

<u>Cardioselective β antagonists</u> primarily block β_1 receptors.

The <u>names</u> of these types of drugs end in "-olol"

6. PROPRANOLOL:

<u>Pharmacokinetics:</u>

After oral administration, this drug is totally absorbed because its highly lipophilic.

It can cross the blood-brain barrier

★ Check Pharmacology Recall, 2nd edition, pages 66-67 ★