# Autonomic Nervous System

- Drugs affecting the autonomic nervous system are divided into two groups according to the type of neuron involved in their mechanism of action.
  Cholinergic System – Acetylcholine
  Adrenergic System- Adrenaline
- The cholinergic drugs act on receptors that are activated by acetylcholine.
- The second group the adrenergic drugs act on receptors that are stimulated by norepinephrine or epinephrine.
- Cholinergic and adrenergic drugs both act by either stimulating or blocking receptors of the autonomic nervous system.

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# Cholinergic system

**Cholinergic Transmission**
Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic, somatic as well as central sites.

**Synthesis, Storage and destruction of acetylcholine**
1. Synthesis of acetylcholine
2. Storage of acetylcholine in vesicles
3. Release of acetylcholine
4. Binding to the receptor
6. Recycling of choline

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# Cholinergic system

**Cholinergic Transmission**
Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic, somatic as well as central sites.

**Synthesis, Storage and destruction of acetylcholine**
**1. Synthesis of acetylcholine**
Acetylcholine is synthesized by choline acetyltransferase that catalyzes the transfer of an acetyl group from acetylcoenzyme A to choline.

**2. Storage of acetylcholine in vesicles**
Acetylcholine is stored into the small presynaptic vesicles by an active transport process

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**3. Release of acetylcholine**
Upon the arrival of an action potential in the cholinergic neuron terminal, voltage- sensitive calcium channels open and ACh stores are released by exocytosis to trigger a postsynaptic physiological response. The release of acetylcholine can be blocked by **botulinum toxin**

**4. Binding to the receptor**
Acetylcholine released from the synaptic vesicles diffuses across the synaptic space, and it binds to either of two postsynaptic receptors (muscarinic and nicotinic receptor) on the target cell or to presynaptic receptors in the membrane of the neuron that released the acetylcholine.

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**5. Degradation of acetylcholine**

Acetylcholine is rapidly hydrolyzed into choline and acetic acid, a reaction catalyzed by the enzyme **acetylcholinesterase** in the synaptic cleft.

**6. Recycling of choline**

Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron.

**Cholinergic Receptor**

Two classes of receptors for Ach

- ✓ Muscarinic (G protein coupled receptor) and
- ✓ Nicotinic (ligand gated cation channel)

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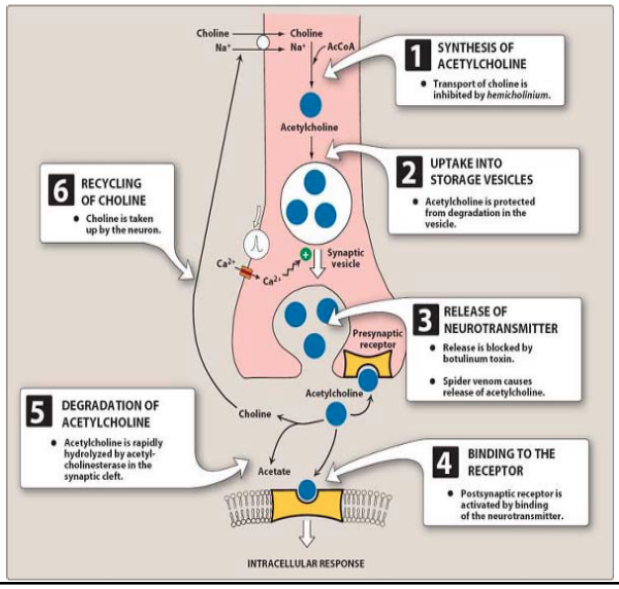
## Synthesis, Storage and destruction of acetylcholine

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## Cholinergic Receptor

Two classes of receptors for Ach

- Muscarinic (G protein coupled receptor) and
- Nicotinic (ligand gated cation channel)

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## Muscarinic Receptor

- These receptors are selectively stimulated by muscarine and blocked by atropine.
- They are located primarily on autonomic effector cells in **heart, blood vessels, eye, smooth muscles and glands of gastrointestinal, respiratory and urinary tracts, sweat glands, etc. and in the CNS.**
- 5 subtypes (M1, M2, M3, M4 and M5) have been identified but only M1, M2 and M3, receptors have been functionally characterized.

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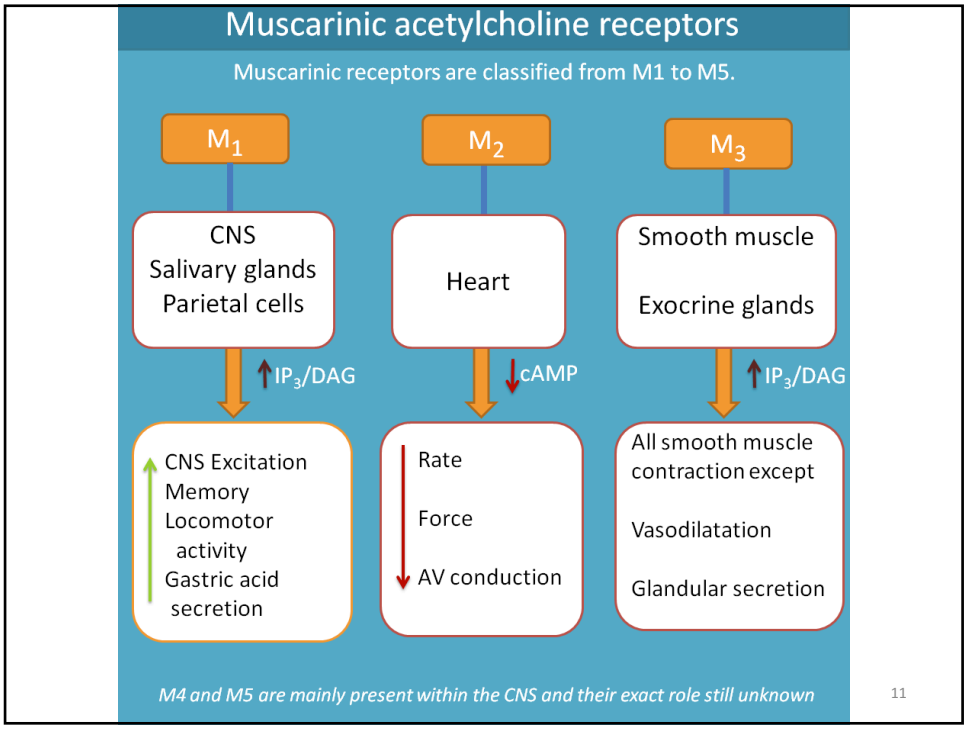


# Nicotinic Receptor

- These receptors are selectively activated by nicotine and blocked by tubocurarine or hexamethonium.
- Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction.
- Two subtypes $N_M$ and $N_N$ (previously labelled N1 and N2) are recognized.

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# Cholinergic drugs

- Also known as Cholinomimetic or Parasympathomimetic
- These are drugs, which produce actions similar to that of ACh, either by-
  - ✓ directly interacting with cholinergic receptors (cholinergic agonists) or
  - ✓ by increasing availability of ACh at these sites (anticholinesterases).

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# Classification

**1. Directly acting cholinergic drugs (cholinergic agonist)**: Acetylcholine, Pilocarpine, Carbechol, Bethanechol, Methacholine

**2. Indirectly acting cholinergic drugs (Anticholinestarases)**

*Reversible*- Neostigmine, Physiostigmine, Pyridostigmine, Rivastigmine, Donepezil, Edrophonium, Tacrine

*Irreversible*- Isoflurophate, parathion, malathion

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## Acetylcholine: Pharmacological action

**A. Muscuranic**

*Heart*: rate of impulse generation is reduced- bradycardia or even cardiac arrest may occur.

*Blood vessels*: All blood vessels are dilated- Fall in BP and flushing occurs.

*Smooth muscle*: contraction

*Glands*: Secretion is increased- sweating, salivation, lacrimation.

*Eye*: Constriction of pupil - miosis.

**B. Nicotinic**

*Skeletal Muscle*: contraction

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## Bethanechol

- Structurally similar to acetylcholine
- not hydrolyzed by cholinesterase → long duration of action.

**Action**

- increased intestinal motility and tone.

**Uses**

- In urologic treatment: used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.
- Bethanechol may also be used to treat neurogenic atony as well as megacolon.

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# Bethanechol

**Adverse effect**

- Sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

**Dose**: 10-40 mg oral, 2.5-5 mg s.c.

**Contraindication**

- contraindicated in patients with asthma, coronary insufficiency, peptic ulcers, intestinal obstruction.

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# Carbachol

- Carbachol has both muscarinic as well as nicotinic actions.
- Carbachol a poor substrate for acetylcholinesterase

**Therapeutic uses**

- used in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.

**Adverse effects**

At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine).

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# Pilocarpine

Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

**Action**:

- Applied topically to the cornea, pilocarpine produces a rapid miosis and contraction of the ciliary muscle.

**Uses**: glaucoma

**Dose**: 1%, 2%, 4% eye drops

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# Cholinergic drugs

**Bethanachol**- Post op and neurogenic ileus and urinary retention

**Carbachol**- Glaucoma, Pupillary contraction and relief of IOP, also for post op urinary retention.

**Methacholine**- induces bronchospasm; used in Asthma challenge test

**Pilocarpine**- cystic fibrosis sweat test, glaucoma

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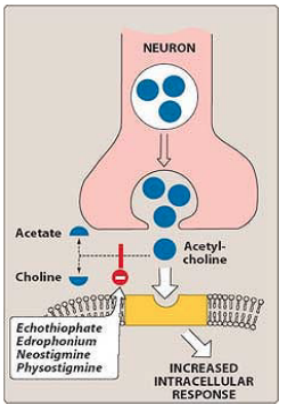
# Anticholinesterases (Indirectly acting cholinergic drugs)

- Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its actions.
- Anticholinesterases (anti-ChEs) are agents which inhibit Cholinesterases (ChE), protect ACh from hydrolysis- potentiate the action of Ach.

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# Reversible Anticholinesterases

**Edophonium**: diagnosis of MG

**Neostigmine/ pyridostigmine**

- used as an antidote for tubocurarine and other competitive neuromuscular blocking agents.
- used in symptomatic treatment of myasthenia gravis.
- Urinary retention

**Physostigmine**
Atropine overdose
Glaucoma

**Tacrine, donepezil, rivastigmine and galantamine**
Used in the alzheimer's disease

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## Irreversible anticholinesterase (Parathion, Malathion)

- A number of synthetic organophosphate compounds have the capacity to bind covalently to acetylcholinesterase.
- The result is a long-lasting increase in acetylcholine at all sites where it is released.
- *Organophosphate poisoning- PAM (pralidoxime) / atropine*

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## Anticholinergic Drugs

- Also called cholinergic antagonists or cholinergic blockers or parasympatholytics.
- Conventionally, anticholinergic drugs are those, which block actions of Ach on autonomic effectors.

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# Classification

1. **Antimuscarinic agents**: Atropine, Ipratopium, Scopolamine, Tropicamide, Hyoscine butyl bromide

2. **Ganglionic blockers:** Nicotine, Mecamylamine

3. **Neuromuscular blockers**: Tubocurarine, vecuronium, succinylcholine

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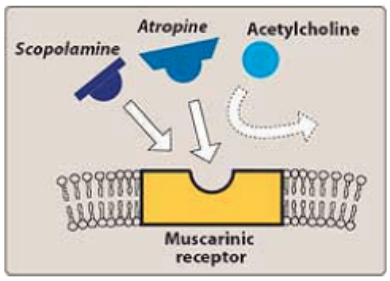
# Antimuscarinic agents

- Commonly known as antimuscarinics.
- These agents block muscarinic receptors causing inhibition of all muscarinic functions.
- They do not block nicotinic receptors, have little or no action at skeletal neuromuscular junctions or autonomic ganglia.
- Atropine, the prototype drug of this class.

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**1. Natural alkaloids:** Atropine, Hyoscine (Scopolamine).
**2. Semisynthetic derivatives**: Homatropine, Atropine methonitrate, *Hyoscine butyl bromide, Ipratropium bromide, Tiotropium bromide.*
**3. Synthetic compounds**
*(a) Mydriatics:* Cyclopentolate, Tropicamide.
*(b) Antisecretory-antispasmodics:*
(i) Quaternary compounds: Propantheline, Oxyphenonium, Clidinium, Pipenzolate methyl bromide, Isopropamide, Glycopyrrolate.
(ii) Tertiary amines: Dicyclomine, Valethamate, Pirenzepine.
*(c) Vasicoselective:* Oxybutynin, Flavoxate, Tolterodine.
*(d) Antiparkinsonian:* Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

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# Actions

**Eye:** dilation of pupil (mydriasis), unresponsiveness to light, and cycloplegia (inability to focus for near vision)

**Heart:** Tachycardia

**Smooth muscles**: relaxation; constipation may occur, spasm may be relieved

**Lungs**: Atropine causes bronchodilatation and reduces airway resistance, especially in COPD and asthma patients

**Glands:** marked decreases sweat, salivary, lacrimal secretion

**Local Anaesthetic**: Atropine has a mild anaesthetic action on the cornea

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**Indications:**

- ✓ *Opthalmic*: mydriatic
- ✓ *Antispasmodic*: Atropine is used as an antispasmodic agent to relax the GI tract and bladder
- ✓ *Antidote for cholinergic agonist*
- ✓ *Antisecretory*: to block secretion in URT and LRT prior to surgery.

**Adverse effect:**

- ✓ May cause dry mouth, blurred vision, tachycardia, and constipation
- ✓ CNS effect: restlessness, confusion, hallucinations, and delirium, collapse of the circulatory and respiratory systems, and death.
- ✓ atropine toxicity: cholinesterase inhibitors

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**Ipratopium bromide:** Asthma and COPD

**Scopolamine**: motion sickness.

**Hyoscine butyl bromide**: used for esophageal and gastrointestinal spastic conditions.

**Dicyclomine**: antispasmodic and antiemetic action (morning sickness and motion sickness)

**Trihexyphenidyl/ Biperiden**: Use for parkinson's disease and EPS

**Glycopyrrolate:** *Preanesthetic medication*; to reduce salivary, tracheobronchial & pharyngeal secretions, to reduce gastric secretion and to block cardiac vagal inhibitory reflexes

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# Adrenergic system

**Adrenergic Transmission**

- Adrenergic transmission is restricted to the sympathetic division of the ANS.
- There are three closely related endogenous catecholamines (CAs); *Noradrenaline, Adrenaline and Dopamine*.

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# Synthesis and release of catecholamines

**1. Synthesis of Norepinephrine:** Norephinephrine are synthesized from the amino acid tyrosine. Tyrosine is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme dopa decarboxylase to form dopamine in the cytoplasm of the presynaptic neuron.

**2. Storage of norepinephrine in vesicles:** Dopamine is then trans-ported into synaptic vesicles by an amine transporter system that is also involved in the reuptake of preformed norepinephrine. This carrier system is blocked by reserpine. Dopamine is hydroxylated to form norepinephrine by the enzyme, dopamine β hydroxylase.

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## Synthesis and release of catecholamines

**3. Release of Norepinephrine**: The nerve impulse coupled release of CA takes place by exocytosis.

**4. Binding to a receptor:** Norepinephrine released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending.

**5. Removal of norepinephrine**: Norepinephrine may i) diffuse out of the synaptic space and enter the general circulation, ii) be metabolized by catechol O-methyltransferase (COMT) & Monoamine oxidase (MAO) in the synaptic space, or iii) be recaptured by an uptake system that pumps the norepinephrine back into the neuron.

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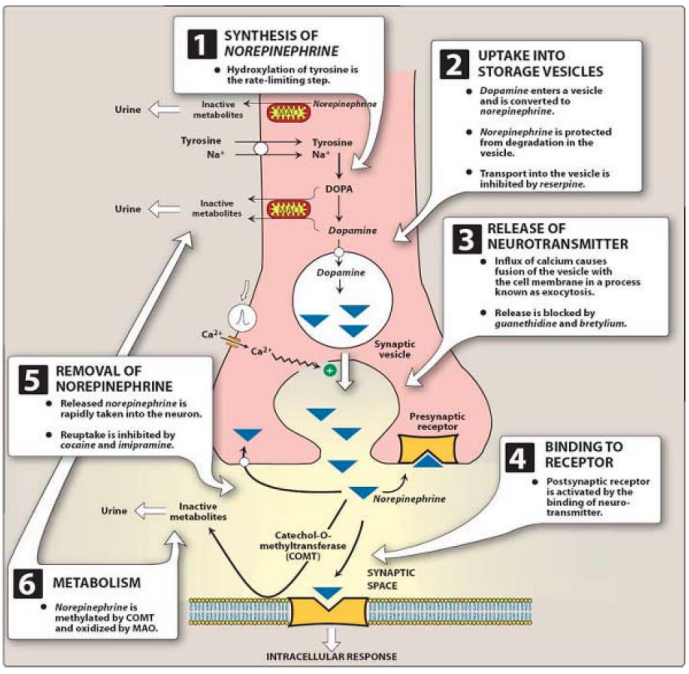
## Synthesis and release of catecholamines

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# Adrenergic receptors

- Adrenergic receptors are membrane bound G protein coupled receptors.
- Adrenergic receptors are classified into two types-
  i. Alpha receptor- $\alpha_1$ and $\alpha_2$
  ii. Beta receptor- $\beta_1$, $\beta_2$ and $\beta_3$

| | $\alpha_1$ | $\alpha_2$ |
|---|---|---|
| Location | Postjunctional on effector organs | Prejunctional on nerve ending ($\alpha_{2A}$), also postjunctional in brain, pancreatic β cells and extrajunctional in certain blood vessels, platelets |

| | $\beta_1$ | $\beta_2$ | $\beta_3$ |
|---|---|---|---|
| Location | Heart, JG cells in kidney | Bronchi, blood vessels, uterus, liver, g.i.t., urinary tract, eye | Adipose tissue |

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| | α | β |
|---|---|---|
| Rank order of potency of agonists | Adr ≥ NA > Iso | Iso > Adr > NA |

Adr: $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak $\beta_3$ action
NA: $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no $\beta_2$ action
Iso: $\beta_1 + \beta_2 + \beta_3$ but no α action

**Alpha Activity**
norepinephrine = epinephrine > dopamine > phenylephrine

Strongest ⟷ Weakest

**Beta Activity**
epinephrine > dopamine > norepinephrine

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# Adrenergic Drugs (Sympathomimetics)

- These drugs have similar action to that of norepinephrine or epinephrine or sympathetic stimulation.

**Classification**

1. **Directly acting agonists**- Adr, NA, isoprenaline (Iso), phenylephrine, clonidine, xylometazoline, salbutamol
2. **Indirectly acting agonists**- tyramine, amphetamine.
3. **Mixed acting agonists**- ephedrine, psuedoephedrine

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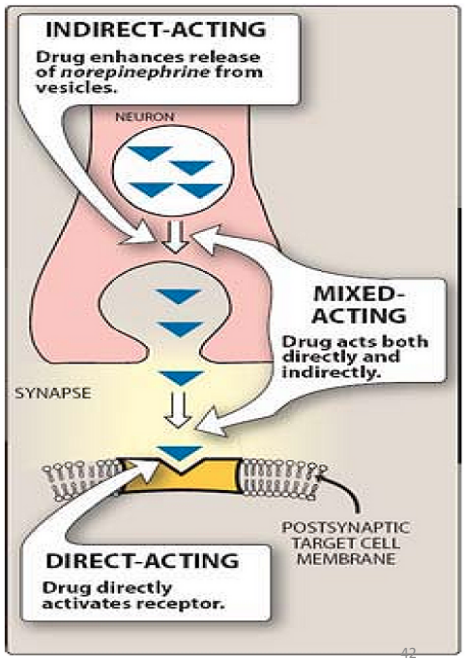
1 **Directly acting agonists**- They act directly as agonists on α and/ or β receptors
2 **Indirectly acting agonists**- They act on adrenergic neurone to release NA, which then acts on the adrenoceptors
3 **Mixed acting agonists**- They act directly as well as indirectly

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# Epinephrine

- Epinephrine is synthesized from tyrosine in the adrenal medulla.
- interact with both α and β receptor

**Action**

***CVS***: Increase HR and force of contraction.

***Blood vessel***: Both vasoconstriction (α) and vasodilatation (β) can occur depending on the drug and its dose (high dose- vasocontriction; low dose- vasodilatation).

***Eye***: cause mydriasis.

***Liver***: cause glycogenolysis→ hyperglycaemia.

***Adipose tissue***: Lipolysis→ rise in plasma FFA

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## Uses

- ***Bronchospasm***
- ***Glaucoma***
- ***Anaphylactic shock***
- ***Cardiac arrest***
- ***Anesthetics***

**Adverse effects**

- Restlessness, palpitation, anxiety, tremor, pallor, fear, tension
- Cardiac arrhythmias
- Pulmonary edema

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**Dopamine (**alpha and beta receptors**) –** heart failure, cardiogenic shock

**Dobutamine (**beta 1 receptors)**-** heart failure, cardiogenic shock

**Clonidine**- alpha 2 agonist; used hypertension

**Salbutamol**- short-acting beta 2 agonists; used as bronchodilators.

**Salmeterol** are long-acting beta 2 adrenergic agonist.

**Oxymetazoline-**stimulates both alpha-1 and Beta-2 adrenergic receptors; used as Nasal decongestant

**Phenylephrine-** binds to alpha receptors; Used as Nasal decongestant

**Psuedoephedrine-** nasal and sinus congestion or congestion

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# Indirect-acting adrenergic agonists

- cause norepinephrine release from presynaptic terminals or inhibit the uptake of norepinephrine.

**Amphetamine**

- synthetic compounds having a pharmacological profile similar to ephedrine
- Drug of abuse and is capable of producing psychological or physical dependence.
- The central effects include alertness, increased concentration and attention span, euphoria, talkativeness, increased work capacity.
- It is one of the drugs included in the 'dope test' for athletes

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**THERAPEUTIC CLASSIFICATION OF ADRENERGIC DRUGS**

I. *Pressor agents*
- Noradrenaline
- Ephedrine
- Dopamine
- Phenylephrine
- Methoxamine
- Mephentermine

II. *Cardiac stimulants*
- Adrenaline
- Isoprenaline
- Dobutamine

III. *Bronchodilators*
- Isoprenaline
- Salbutamol (Albuterol)
- Terbutaline
- Salmeterol
- Formoterol
- Bambuterol

IV. *Nasal decongestants*
- Phenylephrine
- Xylometazoline
- Oxymetazoline
- Naphazoline
- Pseudoephedrine
- Phenyl propanolamine

V. *CNS stimulants*
- Amphetamine
- Dexamphetamine
- Methamphetamine

VI. *Anorectics*
- Fenfluramine
- Dexfenfluramine
- Sibutramine

VII. *Uterine relaxant and vasodilators*
- Ritodrine
- Isoxsuprine
- Salbutamol
- Terbutaline

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# Anti adrenergic Drugs

- The adrenergic antagonists (also called adrenergic blockers or adrenergic antagonists or sympatholytic agents)
- Act by either reversibly or irreversibly binding to the receptor, thus preventing its activation by endogenous catecholamines.

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**Classification of adrenergic antagonist**

**1. Alpha adrenergic blockers**

a. Non equilibrium type- phenoxybenzamine

b. Equllibrium type/ competitive alpha blocker

i. Non selective- Ergotamine, phentolamine, chlorpromazine,

ii. Alpha 1 selective- prazosin, terazosin

iii. Alpha 2 selective- yohimbine

**2. Beta adrenergic blockers**

a. Beta1 selective (cardioselective)- atenolol, metoprolol, esmolol, bisoprolol

b. Non selective (beta 1 and beta 2)

i. *Without intrinsic sympathomimetic activity*- Propranolol, Sotalol, Timolol.

ii. *With intrinsic sympathomimetic activity*- Pindolol

iii. *With additional α blocking property*- Labetalol, Carvedilol

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**Labetelol**: used in treatment of hypertension of pheochromocytoma, in pregnant women and hypertensive emergencies.

**Carvedilol**: CHF

**Prazosin**: Used in HTN, refractory CHF, Benign prostatic hypertrophy (BPH)

**Phentolamine-** Pheochromocytoma

**Phenoxybenzamine**- Pheochromocytoma

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