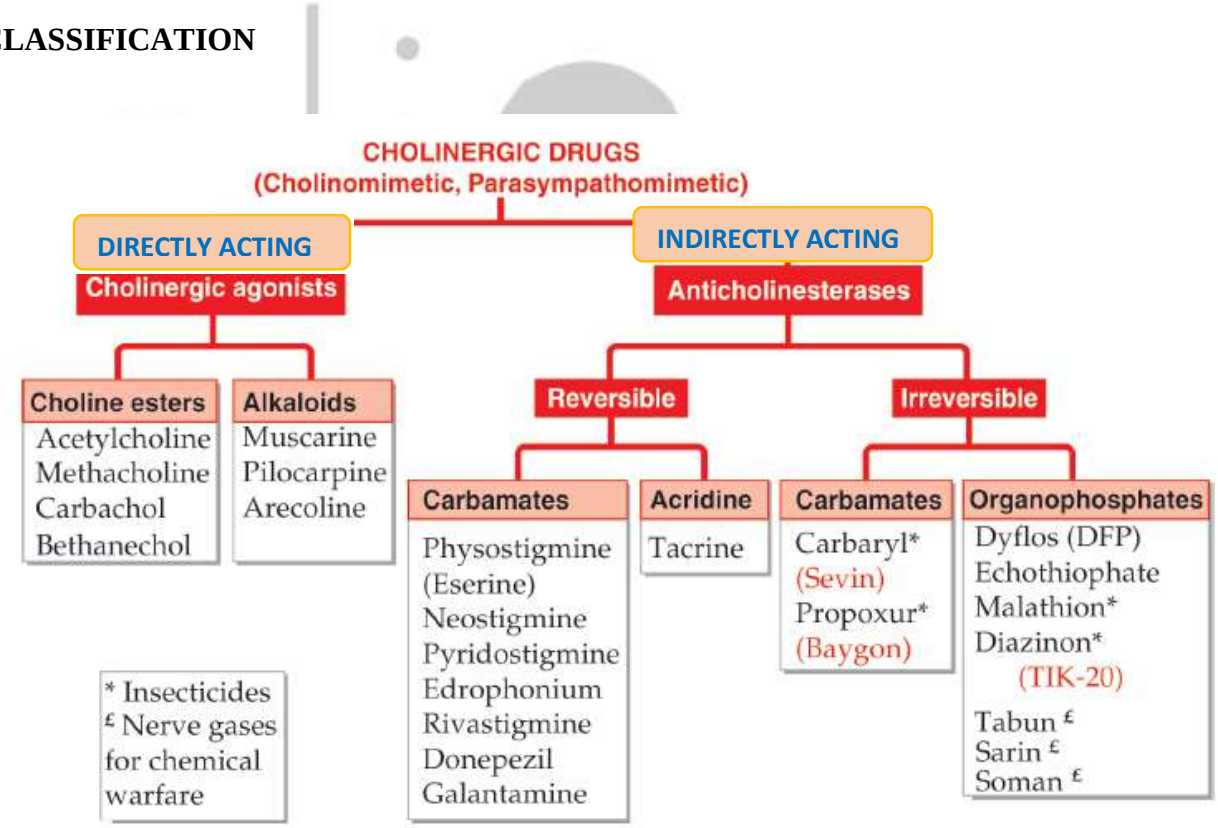
# PARASYMPATHOMIMETICS/CHOLINERGICS/CHOLINERGIC AGONISTS

Cholinergic agonists/Parasympathomimetics are drugs that mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic).

**OR**

Drugs which produce actions similar to that of ACh either by directly interacting with cholinergic receptors (cholinergic agonists) or by increasing availability of Ach (anticholinesterases) at these sites.

**CLASSIFICATION**




**DIRECTLY ACTING CHOLINERGIC AGONISTS**

**Choline esters**

Acetyl choline

Quaternary ammonium compound

Rapidly hydrolyzed by Cholinesterases

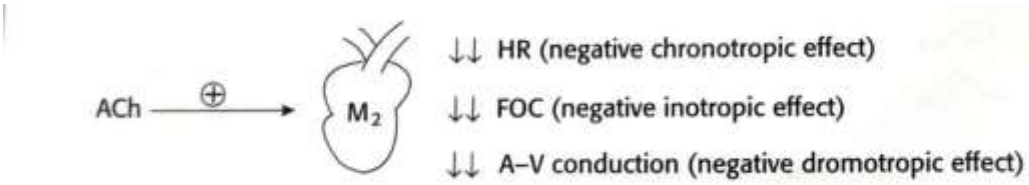
Mechanism of action

Pharmacological actions:

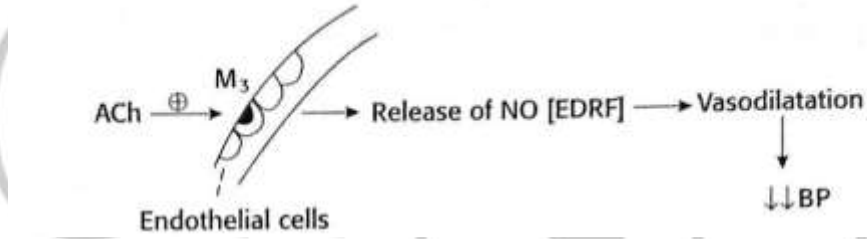
**MUSCARINIC ACTIONS:**

1. **Cardiovascular system**

   **Heart :**

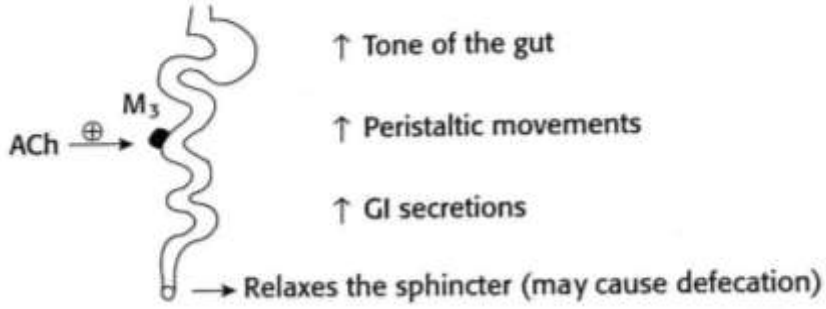



   **Blood vessels:**

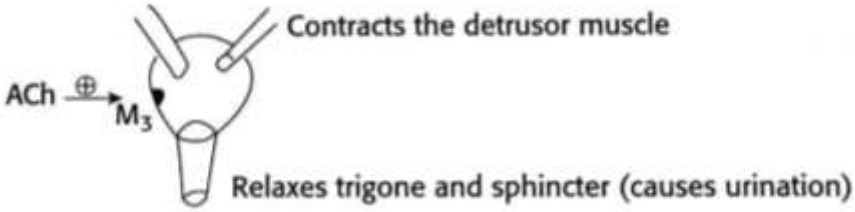



2. **Smooth muscles**

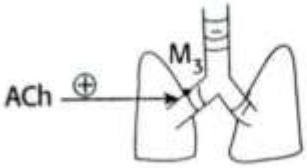
   a. **Gastrointestinal tract**




   b. **Urinary bladder**




**c. Bronchi**




Contracts the bronchial smooth muscle (bronchospasm)
Increases tracheobronchial secretion – therefore, cholinergic drugs are contraindicated in asthmatics

3. **Exocrine glands**
   Increase in salivary, lacrimal, sweat, bronchial, gastric and other gastrointestinal secretions

4. **Eye :**
   Contract ciliary muscle- spasm of acconnodation, near vision
   Contract sphincter pupillae – **miosis (pupillary constriction)**

**<u>NICOTINIC ACTIONS:</u>**

1. **Autonomic ganglia:** Depolarization- postganglionic impulse
2. **Adrenal medulla:** Catecholamine release
3. **Skeletal muscles:** contraction

- Ach has no therapeutic application

## Methacholine, Carbachol, Bethanechol

- Effective orally
- Methacholine is resistant to pseudocholinesterase but rarely used

- Carbachol and bethanechol are resistant to both cholinesterases and have longer duration of action
- Carbachol is used in glaucoma
- Bethanechol is used in :

✓ Hypotonia of bladder
✓ Hypotonia of GI smooth muscles
✓ Urinary retention and neurogenic bladder
✓ Xerostomia

**ADR:**

- Diarrhoea
- Flushing
- Salivation
- Bradycardia
- Hypotension
- Bronchospasm

**CHOLINOMIMETIC ALKALOIDS**

**Pilocarpine**

- Obtained from *Pilocarpus microphyllus*
- Muscarinic actions are prominent
- Tertiary amine
- Crosses BBB and cause CNS effects
- Most potent stimulators of secretions such as sweat, tears, and saliva,
- Exhibits muscarinic activity and is used primarily in ophthalmology
- lack of selectivity

**Actions:**

- Miosis
- Contraction of ciliary muscles- Spasm of accommodation
- Fall in intraocular tension

- Increase sweat(diaphoretic)
- Sialogogue (increase salivary secretions)

**Adverse Effects**

Eye drops: Burning sensation, painful spasm of accommodation

Long term use cause retinal detachment

**USES**

In glaucoma

Used to counter the dryness of mouth

**INDIRECTLY ACTING CHOLINERGIC DRUGS**

- Anticholinesterases
- Inhibit the enzyme cholinesterase and nicotinic receptors of the ANS as well as at NMJs and in the brain
- Anticholinesterases are either Esters of carbamic acids (carbamates) or Derivatives of phosphoric acid( organophosphates)
- ACh Esterase is an enzyme that hydrolyses ACh to acetate and choline and terminates its actions.
- It is located in both pre- and postsynaptic nerve terminals.
- Anticholinesterases inhibit enzyme AchE reversibly/irreversibly
- Thus, ACh is not metabolized, gets accumulated at muscarinic and nicotinic sites and produce cholinergic effects

**REVERSIBLE ANTICHOLINESTERASES**

Physostigmine

Neostigmine

Pyridostigmine

Rivastigmine

Edrophonium

Galantamine

Donepezil

- Reversible anticholinesterases inhibit both true and pseudocholinesterases reversibly

**MECHANISM OF ACTION:**

- ACh is rapidly hydrolysed by both true and pseudocholinesterases
- ACh binds to anionic and esteratic sites of cholinesterase
- Acetylated enzyme undergoes rapid hydrolysis

- Carbamates bind to both anionic and esteratic sites of cholinesterase. So, Ach can't bind the enzyme

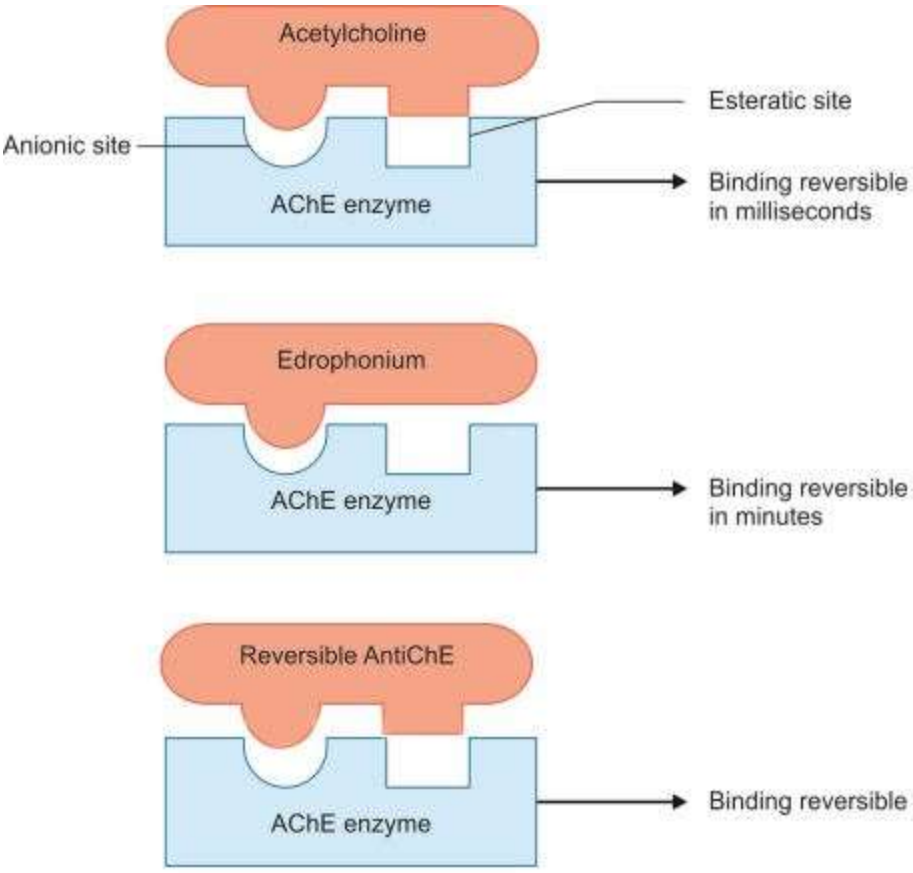
- Carbamoylated enzyme undergoes slow hydrolysis to release the enzyme

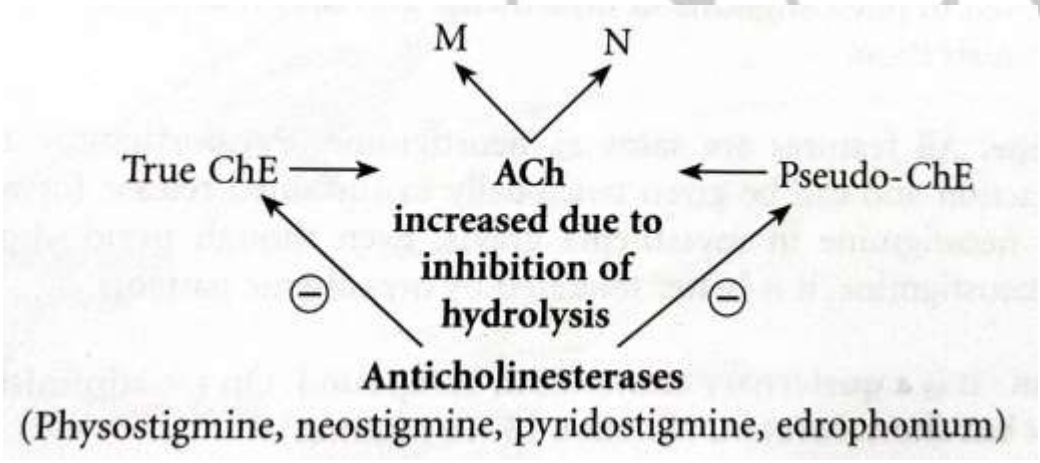
- Edrophonium binds only to anionic site of ChE

- It forms a weak hydrogen bond with the enzyme

- It diffuses away from the enzyme

- Duration of action is 8-10minutes




**PHYSOSTIGMINE (ESERINE)**

- Alkaloid obtained from Physostigma venenosum
- Tertiary amine

**Actions:**

- Stimulates not only the muscarinic and nicotinic sites of the ANS, but also the nicotinic receptors of the NMJ
- Muscarinic stimulation can cause contraction of gastrointestinal smooth muscles, miosis, bradycardia, and hypotension
  **(Explain cholinergic effects)**
- Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses).
- Its duration of action is about 30 minutes to 2 hours

**Therapeutic uses:**

1. Glaucoma: physostigmine reduces intraocular Pressure by producing miosis, thus facilitates drainage of aqueous humour.
On chronic use – accelerates cataract formation,so rarely used in glaucoma
2. Atropine poisoning: Intravenous administration

**Adverse effects: (**rarely seen with therapeutic doses)

- well absorbed orally and it enters the CNS cause CNS side effects
- High doses of *physostigmine* may lead to convulsions.
- Bradycardia and a fall in cardiac output may also occur.
- Accumulation of Ach at the NMJ causes continuous depolarization, results in paralysis of skeletal muscle.

**NEOSTIGMINE**

- Synthetic compound
- It reversibly inhibits ache
- Neostigmine has a quaternary nitrogen. Hence, more polar, is absorbed poorly from the GI tract
- Does not cross BBB and has no central side effects

**Actions**:

- Pronounced action on NMJ, GIT and urinary bladder
- Increases Ach concentration at NMJ by inhibiting anticholinesterases
- Due to structural similarity with Ach, directly stimulates $N_M$ receptors
- Thus improves muscle power in myasthenia gravis

**Therapeutic uses:**

- Used to stimulate the bladder and GI tract
- Antidote for competitive neuromuscular- blocking agents.
- Used to manage symptoms of myasthenia gravis
- to overcome toxicity of central-acting antimuscarinic agents such as atropine

**Adverse effects:**

- Salivation
- Flushing
- Decreased blood pressure
- Nausea
- Abdominal pain
- Diarrhea
- Bronchospasm
- Contraindicated when intestinal Or urinary bladder obstruction is present

| | *Physostigmine* | *Neostigmine* |
|---|---|---|
| 1. Source | Natural alkaloid from *Physostigma venenosum* (Calabar bean) | Synthetic |
| 2. Chemistry | Tertiary amine derivative | Quaternary ammonium compound |
| 3. Oral absorption | Good | Poor |
| 4. CNS actions | Present | Absent |
| 5. Applied to eye | Penetrates cornea | Poor penetration |
| 6. Direct action on $N_M$ cholinoceptors | Absent | Present |
| 7. Prominent effect on | Autonomic effectors | Skeletal muscles |
| 8. Important use | Miotic (glaucoma) | Myasthenia gravis |
| 9. Dose | 0.5–1 mg oral/parenteral<br>0.1–1.0% eye drops | 0.5–2.5 mg i.m./s.c.<br>15–30 mg orally |
| 10. Duration of action | Systemic 4–6 hrs<br>In eye 6 to 24 hrs | 3–4 hrs. |

**PYRIDOSTIGMINE**

- Same as neostigmine
- Longer duration of action
- Preferred to neostigmine in myasthenia gravis

**EDROPHONIUM**

- Short acting (8-10min)

**Uses:**

- Diagnosis of myasthenia gravis
- Used to differentiate myasthenic crisis from cholinergic crisis
- In curare poisoning

**Adverse effects of anticholinesterases**

- Sweating
- Salivation
- Nausea
- Vomiting
- Bradycardia
- Hypotension