2- carbachol

- **Potent** agonist activity.
- direct act : Nonselective (Muscarinic / Nicotinic)
- Also acts indirectly by promoting ACh release and anticholinesterase (weak) activity.
**USES:**

1. Topically for glaucoma;
2. intraocular for miosis in surgery.
3. expel gases
4. stimulate intestinal motility.
5. relive urinary retention

**Side Effects:** Corneal edema; decreased vision.
3- bethanechol

- **Action:**
  - Potent muscarinic agonist (directly stimulate Muscarinic receptors)
  - Orally effective, also administered by subcutaneous injection.
  - Increased hydrolytic stability
• **Therapeutic applications:**
  - For the relief of post-surgical urinary retention and abdominal distention and stimulate atonic bladder
  - (Stimulant of GI tract smooth muscle and urinary bladder).

• **Adverse effects**
  - Low toxicity, no serious side effects.
  - Should be used with caution in asthmatic patients.
4-Methacholine -----  
More stable than acetylcholine.  
* More selective action (muscarinic > nicotinic).

B- Natural alkaloid :  
* muscarine, arecolin, pilocarpine
5- Pilocarpine

- Natural product. Isolated from the leaves of *Pilocarpus jaborandi*.

**Actions:**
- Decrease in IOP, miosis
- Stimulator of secretions.
- Available as ophthalmic solution, gel, tablet.
- **Systemic effects:** include copious sweating, salivation and gastric secretion.
- **Uses:**
  - lowering of IOP therefore Used in the treatment of glaucoma
  - treatment of xerostomia (dry mouth)
- **Adverse effects:**
  - 1-blurred vision
  - 2- lacrimation
  - 3- sever sweating
  - 4-bronchospsm
Glaucoma

disease characterized by increase of intraocular pressure, atrophy of optic disc, loss in the field of vision.

**Glaucoma**: divided into 2 types
1- open wide angle Glaucoma (chronic)
2- narrow closed angle Glaucoma (acute)
Parasympathomimetic drug:

1- Direct acting cholinergic agent (Natural and choline esterase)

2- Indirect acting cholinergic agent: Divided into reversible & irreversible
2- Indirect acting cholinergic agent: Divided into reversible & irreversible
Acetylcholinesterase Inhibitors (AChEI) (cholinesterase enzyme inhibitors (ChEI))

- Inhibition of acetylcholinesterase (AChE) lead to increases the concentration of acetylcholine (ACh) in the synapse.
- This results in prolonging the action of ACh, producing both muscarinic and nicotinic responses.
There are two types of cholinesterases in humans:

- Acetylcholinesterase (AChE) and Butyrylcholinesterase (BuChE).
- Differs in their location in the body and substrate specificity.
Acetylcholinesterase is an enzyme that cleaves Ach to acetate and choline. Drugs that inhibit this enzyme provide cholinergic action.
AGENTS AFFECTING CHOLINERGIC TRANSMISSION

- Hemicholinium
- Latrotoxin
- Vesamicol
- Botulinus toxin
- Calcium
- Physostigmine
- Atropine
- d-Tubocurarine

Diagram:

- choline
  - + acetyl CoA
  - choline acetyltransferase
  - acetylcholine
  - \(\rightarrow\) choline
  - \(\rightarrow\) Ach
  - \(\rightarrow\) Ach
  - \(\rightarrow\) calcium
  - \(\rightarrow\) Ach
  - \(\rightarrow\) Ach
  - \(\rightarrow\) Ach

- Ach \(\rightarrow\) AchE \(\rightarrow\) choline + acetic acid

- A.P.
1- physostigmine

Actions:
- Stimulate Muscarinic & Nicotinic sites.
- Stimulate Nicotinic receptors of neuromuscular junctions.
- Duration of action about 2-4 hr.
- Stimulate CNS
Natural product, isolated from the seeds of *Physostigma venenosum*

- Phystostigmine: Sensitive to heat, light, moisture etc.
- Diffuses into the CNS
- Antidote for atropine poisoning
- Topical application in the treatment of glaucoma
physostigmine

Therapeutics uses:

- Topically in eye.
- **Anti dote for atropine** *(treat over dose of anticholinergic drugs.)*
- Treatment of myasthenia gravies.
- Increase intestinal & bladder motility
- Terminate the effect of tubocurarine.
physostigmine

Adverse effects:
- convulsions
- Bradycardia
- paralysis of skeletal muscles
2- neostigmine

- Chemically more stable than physostigmine
- Longer duration of action (2-4 hr)
- Neostigmine administered orally or iv

*adverse effects:
generalized cholinergic stimulation.
**Therapeutics uses:**

1- stimulate bladder & GIT.
2- antidote of tubocurarine.
3- treat of myasthenia gravis.
4- The most frequent use of neostigmine is to prevent atony of the intestinal, skeletal, and bladder musculature.
5- Also used as urinary stimulant.
Myasthenia gravis

Autoimmune disease
Ab against Ach receptors at neuromuscular junction
Weakness of skeletal muscles
Edrophonium used for diagnosis
Neostigmine, pyridostigmine used for treatment
3-pyridostigmine

** treatment of myasthenia gravis
** duration of action 3-6hr.

- **Pyridostigmine** is the most widely used for the treatment of myasthenia gravis
4-Edrophonium

- Administered parenterally
- Rapid onset
- **short duration of action** 10-20 min (short acting)
- Also exhibits direct cholinomimetic effect on skeletal muscle
- Used in the Diagnosis of myasthenia gravis.
- Overdose cause cholinergic crisis
- **Atropine is the antidote**
Irreversible cholinesterase inhibitors

1- organophosphorus (malathion & parathion): used in insecticide

2- Tabun & Sarin: nerve gas (chemical war agent)
- Irreversible Inhibitors
  - Compounds containing phosphoryl or phosphonic group that can react with ChE to form ChE-phosphate complexes stable to hydrolytic cleavage.
  - Mainly used as agricultural insecticides and nerve gas agents.
Mechanism of action

- Combined of o.p.c with choline esterase enzyme irreversible & formation anew compound
- O.p.c + chE -------------- o.p—chE
- O.p.c highly lipid soluble
Adverse effects of organophosphate compounds:

- Miosis, Rhinorrhea
- Frontal headache, Bronchoconstriction
- Laryngospasm, Salivation
- GIT disturbances, Bradycardia
- Sweating, Lacrimation
- Involuntary micturition, Muscle weakness
- Ataxia, confusion
- Death
treatment

- 1- stop exposure
- 2-wash skin
- 3-oxygen supply
- 4 replace fluid
- 5-atropine
- 6- 2-PAM(Pralidoxime)
Reactivation of acetylcholinesterase

- **Pralidoxime**: synthetic compound that can reactivate the acetylcholinesterase if it is given before aging of the enzyme ((aging mean: loss of an alkyl gp from the structure of enzyme)).

**Pralidoxime** : Effective antidote for poisoning by parathion and related pesticides

- Most effective by intramuscular, intravenous, or subcutaneous administration
- Treatment is effective if initiated within few hours
Neostigmine

Indirect parasympathomimetics

$\text{OC}_2\text{H}_5$

Paraoxon (E 600)

Acetylcholine + AChE → Acetyl + Choline

Deacetylation

Neostigmine + AChE → Carbaminoyl

Decarbaminoylation

Hours to days

Paraoxon + AChE → Phosphoryl

Dephosphorylation impossible