CHOLINERGIC AGONISTS

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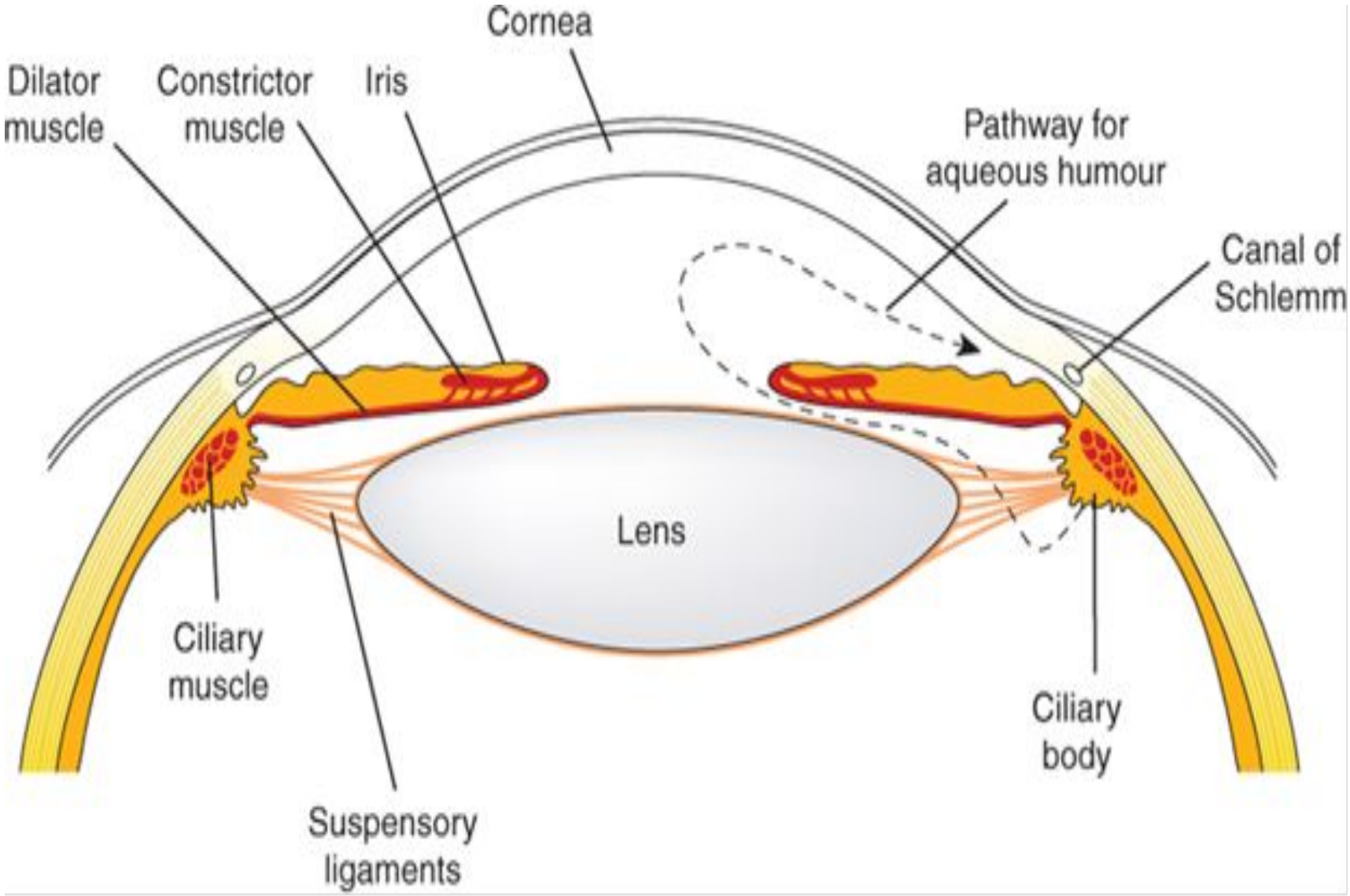
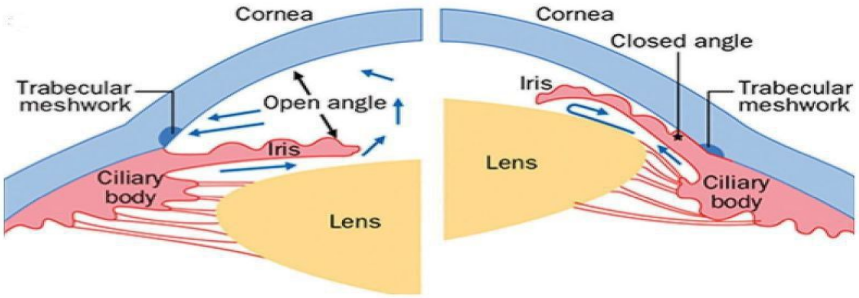
- **Alkaloids :**
- ***Muscarine* :** is toxic and used as experimental tool only.
- ***Pilocarpine:***
- **It is tertiary amine** (can **cross the BBB** at therapeutic doses), **stable to hydrolysis** by acetylcholinesterase. It is **less potent** than ACh
- It has **muscarinic activity** and used primarily in ophthalmology.
- **Pharmacological effects:**
- ***On the eye:***
- - rapid **miosis** (contraction of the circular muscle of the iris)
- - contraction of ciliary muscles (**accommodation for near vision**).
- This will results in opening the trabecular meshwork around Schlemm's canal, causing an immediate drop in intraocular pressure ***(IOP)*** as a result of the increased drainage of aqueous humor. This effect lasts up to 8 hours.


Cornea
Dilator muscle
Constrictor muscle
Iris
Pathway for aqueous humour
Canal of Schlemm
Lens
Ciliary muscle
Ciliary body
Suspensory ligaments

- **Other effects:** Pilocarpine is one of the most potent **stimulators of secretions** such as sweat, tears, and saliva.
- **Therapeutic uses:**
- ***Glaucoma:*** pilocarpine is the drug of choice in the emergency lowering of ***IOP*** of both narrow-angle (closed-angle) and wide-angle (open-angle) glaucoma. It is used topically (eye drops) for this purpose.
- ***Xerostomia*** (dryness of mouth)**:** pilocarpine is used orally in patients with xerostomia resulting from irradiation of the head and neck tumors or sjögren's syndrome.
- **Adverse effects:**
- **CNS disturbances, profuse sweating, salivation and lacrimation**
- ***Cevimeline :*** New cholinergic agonist drug that used for the treatment of xerostomia.



- **Cholinesterase inhibitors (Anticholinesterases)**
- **They Inhibit** the action of ***AChE* enzyme**, resulting in **accumulation of ACh** at muscarinic and nicotinic sites and this will lead to **intensifying ACh effects**.
- According to their **binding** to the enzyme the inhibition could be **reversible or irreversible**.
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- **Cholinesterase Enzymes:**
- There are two distinct types of cholinesterase:

1. ***Acetylcholinesterase*** (found in *neural tissue & RBC*)
2. ***Butyrylcholinesterase*** or ***pseudocholinesterase*** (found in plasma, liver, skin, brain and GIT)

- Anticholinesterases **inhibit both forms** of the enzyme
- - Measurement of **RBC or plasma cholinesterase** activity is important in the **diagnosis of organophosphorous poisoning**.

- **Reversible Anticholinesterases :**
- The **binding** with the enzyme is **reversible.** The **duration of binding** will determine the **duration of drug action**. **After dissociation** the enzyme will not destroyed and **can hydrolyze ACh again.**
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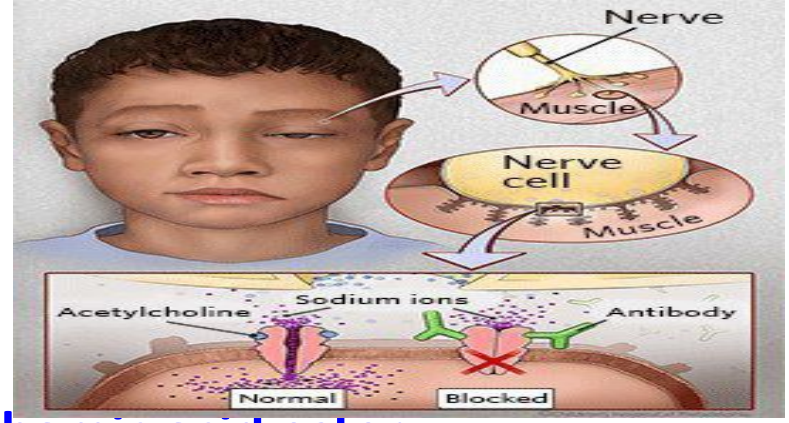
- ***Physostigmine :***
- **Natural alkaloid tertiary amine** derived from ***Physostigma Veneosum* plant.**
- It is **carbamic acid ester** Inhibit cholinesterase enzymes reversibly by forming **stable carbamylated intermediate** with the enzyme.
- This will **delay the hydrolysis of ACh until the AChE became free**. The result is **potentiation of cholinergic activity throughout the body**.
- **Muscarinic** and **nicotinic** effects (wide effects in the body)
- **CNS effects** because it cross the BBB.

❖ Duration of action is 2 - 4 hr.

- **Clinical uses:**
- Used topically in the treatment of **glaucoma** (pilocarpine is preferred)
- Postoperatively to **stimulate GIT & bladder**
- Treatment of **atropine poisoning**, because both agents enter the CNS. It is also used in the treatment of overdose with other centrally anticholinergic drugs.
- Effective in improving cognitive function in **Alzheimer** type of dementia {other anticholinesterases like ***Rivastigmine*** and ***Tacrine*** are preferred (less S.E.) and used now in the treatment of Alzheimer disease}

- **Adverse effects:**
- ***CNS:*** The effects on the CNS may lead to **convulsions** when high doses are used.
- ***Muscarinic:*** Bradycardia, fall in cardiac output and other muscarinic effects may also occur.
- ***Nicotinic:*** Inhibition of AchE at the skeletal ***NMJ*** causes the accumulation of Ach, results in paralysis of skeletal muscle.
- Because of its CNS effects (S.E.), physostigmine is not used in the treatment of *Myasthenia Gravis*, other carbamates are used like (neostigmine and pyridostigmine)

- ***Neostigmine :***



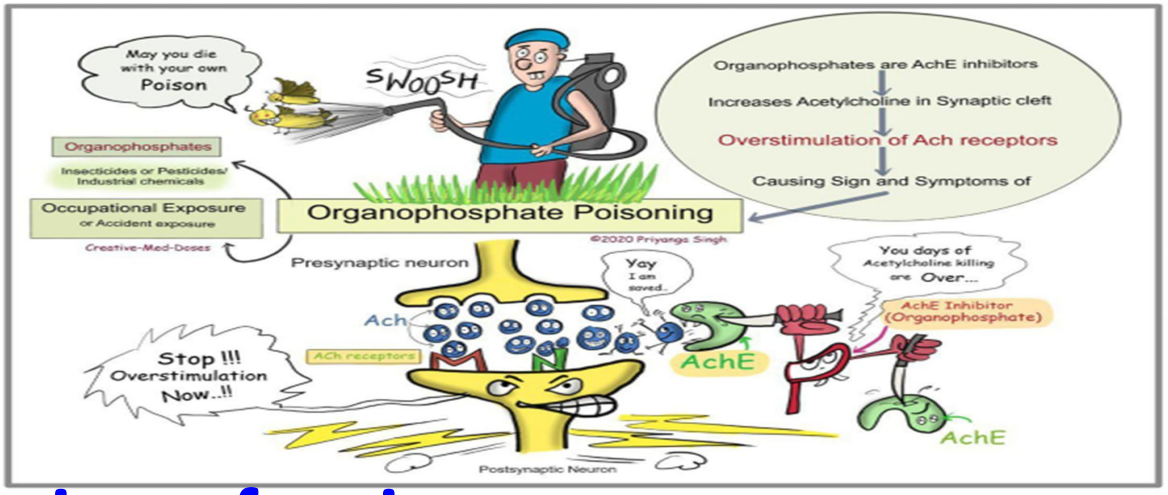
- **Synthetic** compound that is also a **carbamic acid ester**
- **Quaternary amine**, hence, it is more polar (water soluble) and **not enter the CNS**. It has **shorter duration of action** (1-2 hr.)
- **Indications:**
  - Treatment of **Myasthenia Gravis (nicotinic action)**.
  - ***Myasthenia Gravis*** is **autoimmune disease** in which there are antibodies against ***NMJ*** results in decrease in the No. of **nAChRs** and in the No. of ACh vesicles in the nerve terminal. The disease is characterized by **muscle weakness** started in the face & neck and in progressive stage involves limbs and intercostal muscles.
  - Termination of action of ***Curare*** and other non-depolarizing blockers of ***NMJ*** (muscle relaxants) during **general anesthesia (nicotinic action)**.
  - Also used for its **muscarinic action** in (**atony of bladder & GIT**)

- **Adverse effects:**
- Generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. (**muscarinic S.E**)
- When nicotinic effect of the drug is wanted (as in the 1st & 2nd indications) muscarinic side effects can be blocked by **atropine** (antimuscarinic drug)
- ***Pyridostigmine:***
- Used in the **chronic management of myasthenia gravis.**
- Durations of action is intermediate (3 - 6 hours), but longer than that of neostigmine. Adverse effects are similar to those of neostigmine.

- ***Edrophonium***
- Similar to neostigmine, except that it is more rapidly absorbed and has **very short duration of action** of (10 to 20 minutes).
- **Indications:**
- **Diagnosis of myasthenia gravis** (i.v. injection leads to a rapid increase in muscle strength).
- **Differentiation** between ***Myasthenic Crisis*** **&** ***Cholinergic Crisis***
- *Myasthenic Crisis* is sudden worsening of myasthenic pt. (severe muscle weakness),
- *Cholinergic crisis* due to drug overdose that is also characterized by sever muscle weakness because accumulation of ACh at NMJ results in persistent depolarization which cause weakness or paralysis.
- For differentiation we give **edrophonium i.v.** ;
- If the pt. get better *Myasthenic Crisis*
  - If the pt. get worse *Cholinergic Crisis*

- ***Irreversible Anticholinesterases :***

- **Organophosphorous compounds** bind covalently to ***AChE*** to produce phosphorylated enzyme.
- The result is a long-lasting accumulation of ACh at all sites.
- Many of these agents are **extremely toxic** and were developed as **nerve agents**.{ ***Tabun*** (GA), ***Sarin*** (GB) and ***Soman*** (GD) are gases
- Compounds, such as ***parathion*** & ***malathion*** are employed as organophosphorous insecticides used to control insects in agricultural practice.
- Very few compounds are used as **drugs** like ***Ecothiophate*** that is used topically in the treatment of glaucoma (**never used systemically**)
- Other organophosphorous compounds are used as **drugs**:
- **Isoflurophate** → **Glaucoma**
- **Malathion** → **Scabies**
- **Metrifonate** → **Bilharziasis**



- **Mechanism of action:**
- Covalently binds via its **phosphate group** to the active site of ***AChE***. Once this occurs, the enzyme is **permanently inactivated**, and restoration of ***AChE*** activity requires the **synthesis of new enzyme** molecules.
- Following covalent modification of ***AChE***, the **phosphorylated enzyme slowly releases one of its ethyl groups**. The loss of an alkyl group, which is called **aging**, makes it impossible for chemical reactivators, such as ***pralidoxime***, to break the bond between the remaining agent and the enzyme.

- **Manifestations of toxicity :**
- **Muscarinic:** **(DUMBLES)** diarrhea, urination, miosis, bronchospasm, bradycardia, lacrimation, emesis, salivation and sweating.
- **Nicotinic:** muscle fatigue and weakness, twitching, fasciculation, tremors, muscle paralysis.
- **CNS:** ataxia, confusion, convulsions, depressed respiration and cardiovascular function.
- in sever acute exposure **death co**

- **Treatment of poisoning :**

❖ ***Initial treatment: (a,b,c,d)***

1. Maintaining **airways**
2. Suction of **bronchial secretions**.
3. Control **convulsions**.
4. Rapid **decontamination**

- Skin and eyes

❖ *Antidotes:*

- Antidotes are (atropine) and (pralidoxime)
- **Atropine (antimuscarinic drug):** reverse muscarinic manifestations only and the treatment should be continued with Pralidoxime to reactivate the enzyme.

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- **Pralidoxime :(specific antidote)**, should be given early (1st 16 hours of exposure) and after 24 hrs there will be aging and permanent inactivation of the enzyme. Nicotinic will be improved after Pralidoxime administration.

Cholinergic Antagonists

:Muscarinic Antagonists

.A- Selective

.B- Non selectives

:Nicotinic Antagonists

.A- neuromuscular blockers

.B- ganglionic blockers

• MUSCARINIC ANTAGONISTS

- ***(Antimuscarinic Drugs) or (Parasympatholytic drugs)***

- ***Anticholinergic*** ≈ ***Antimuscarinic*** ??
- **Competitive antagonists** that block the muscarinic receptors and prevent ACh from binding to and activation of these receptors.
- The blocking effects are **overcomed** by **increasing the concentration of Ach** or by **using a muscarinic agonist**.
- **muscarinic antagonists are *selective*** (e.g. $\mathbf{M_1}$ blockers) or ***nonselective*** (block all subtypes) ***natural*** or ***synthetic***.
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- **Natural alkaloids :**
- The deadly nightshade (***Atropa Belladonna***) contains mainly ***atropine.***
- The thorn apple (***Datura Stramonium***) contains mainly ***scopolamine.***
- They are **tertiary amines** that are sufficiently **lipid-soluble** to be **readily absorbed** and **penetrate the BBB**.

- **Pharmacological effects of muscarinic antagonists**
- ***Atropine*** **(the prototype drug) :**
- **Inhibition of secretions:**
- **Salivary, lacrimal, bronchial** and **sweat** glands are **inhibited** by very **low doses** of atropine
- **Gastric secretion** is **reduced**.
- **Effects on heart rate:**
- Atropine causes ***tachycardia*** through block of cardiac mAChRs (**M_2**).
- The tachycardia is modest, (**up to 80-90 beats/min**). This is because there is **no effect on the sympathetic system**, but **only inhibition of the existing parasympathetic tone.**

- **Effects on the eye:**
- The **pupil** is dilated (***mydriasis***) by atropine administration, and becomes unresponsive to light (**-ve light reflex**).
- Relaxation of the **ciliary muscle** causes paralysis of accommodation (***cycloplegia***), so that near vision is impaired (**blurred vision**).
- Intraocular pressure (***IOP***) may **rise**; although this is unimportant in normal individuals, it can be dangerous in patients suffering from **narrow-angle glaucoma**.
- **Effects on the gastrointestinal tract:**
- **Gastrointestinal motility** is **inhibited** (**requires larger doses and is not complete**). This is because other transmitters (other than ACh) are important in GI motility.
- Atropine is used in **pathological conditions** in which there is **increased gastrointestinal motility**.

- **Effects on other smooth muscle:**
- ***Bronchial smooth muscles*** are **relaxed** by atropine. **Reflex bronchoconstriction** (e.g. during **anesthesia**) is **prevented by atropine**.
- ***urinary tract smooth muscles*** are also **relaxed** by atropine. Antimuscarinic drugs commonly precipitate **urinary retention** in **elderly men with *BPH***.
- **Effects on the CNS: SAD**
- Atropine produces sedation, amnesia
- **higher doses** cause ***excitatory effects*** **agitation and disorientation.**
- In **atropine poisoning**, (mostly in young children who eat deadly nightshade) CNS effects are:
- **marked excitement**
- **irritability**
- **hyperactivity**
- **Hyperpyrexia**, (which is aggravated by the loss of sweating).
- These central effects are the result of **blocking mAChRs in the brain**, and they are opposed by anticholinesterase drugs such as ***physostigmine***, which is an effective antidote to atropine poisoning.

- ***Scopolamine*** in low doses causes marked ***sedation***, but has **excitatory effects in high dosage**. Scopolamine also has a useful **antiemetic effect** and is used in treating **motion sickness.**
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- ***Atropine***
- **non-selective, readily absorbed from the GIT, partially metabolized and 60% excreted unchanged in urine. Cross BBB and cause CNS stimulation.**
- **The half-life is about 2 hours (but the effect of atropine on the eye may last from three days to one week).**

- ***Main Indications:***
- **As adjunct for anesthesia** (reduce secretions, bronchodilatation)
- **Anticholinesterase poisoning**
- **Treatment of Bradycardia**
- **Gastrointestinal hypermotility** (antispasmodic, antidiarrheal)
- ***Main side effects:***
- **Urinary retention, dry mouth, blurred vision, constipation, tachycardia, CNS disturbance (excitation, restlessness, agitation, hallucination).**
- ***Contraindications:***
- **Glaucoma** (especially closed-angle)
- **Benign prostatic hypertrophy** (BPH),
  Used with caution in infants with fever

Thank you