DIRECT CHOLINOMIMETICS

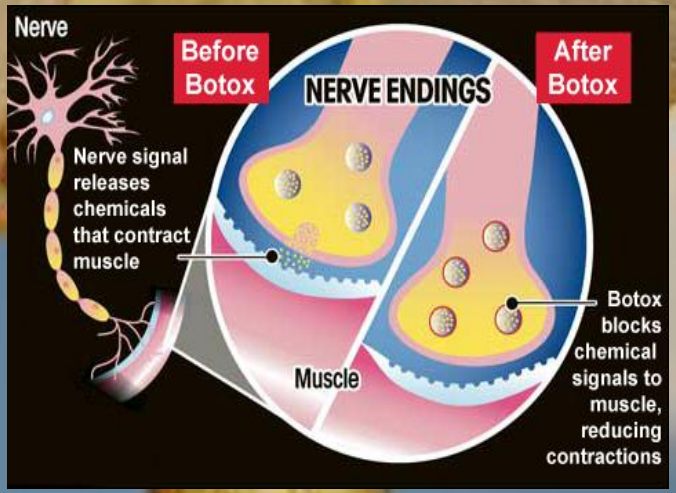
Amanita muscaria

Muscarine

What is botox?

Botulinum toxin

A toxin produced by *Clostridium botulinum*



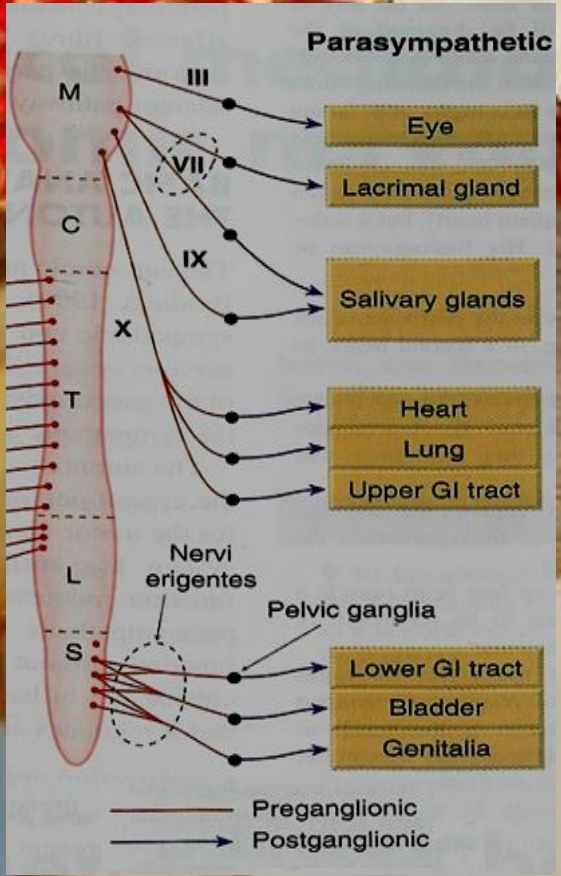
DIRECT CHOLINOMIMETICS

ILOS

To identify the mechanism of action of direct acting acetylcholine receptor stimulants

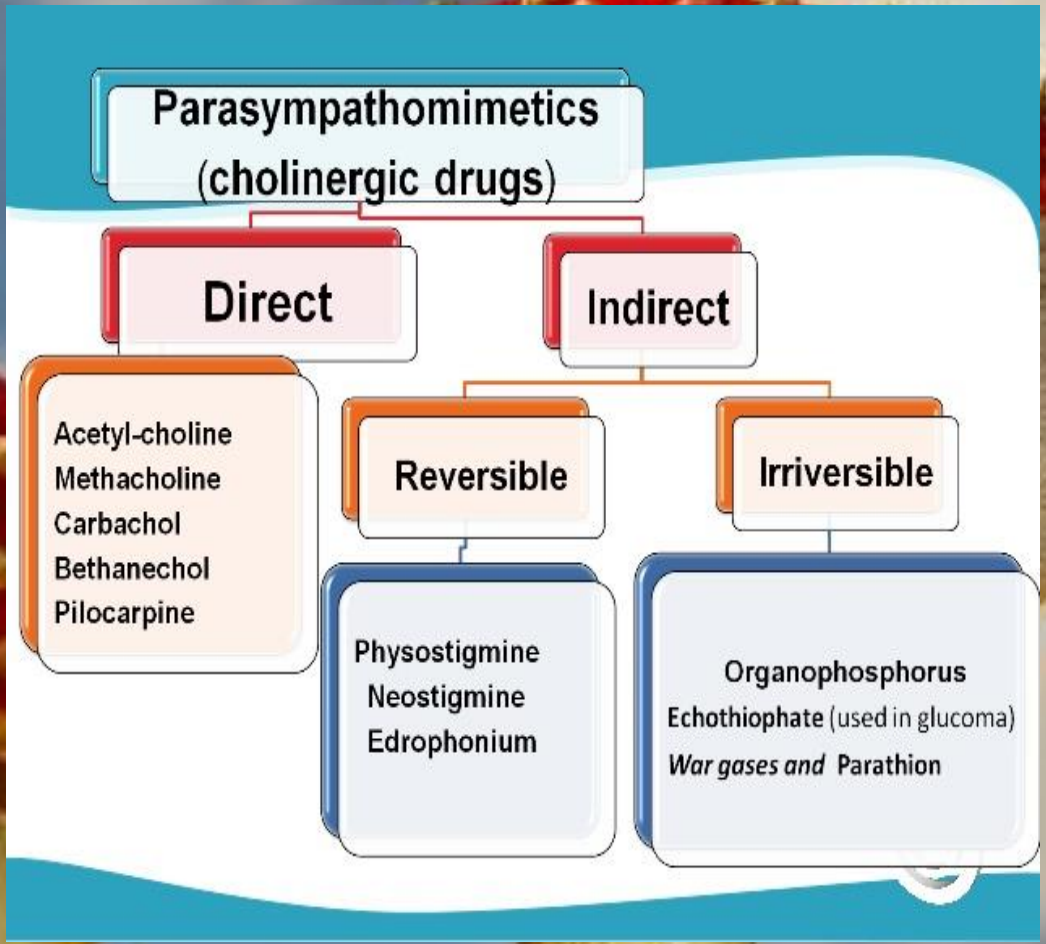
To discuss the pharmacokinetic aspects and pharmacodynamic effects of direct cholinomimetics

To outline the therapeutic uses and toxicity of direct cholinergic agonists



DIRECT CHOLINERGIC AGONISTS

Classification of cholinergic agonists



DIRECT CHOLINERGIC AGONISTS

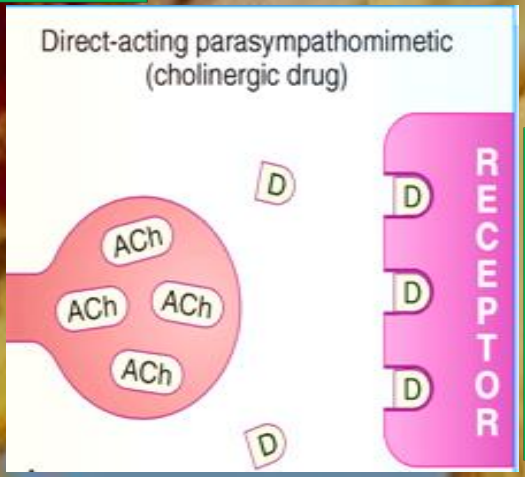
Produce primarily effect by activation of **muscarinic or nicotinic** receptors

Classification according to chemical structure

Tertiary cholinomimetics

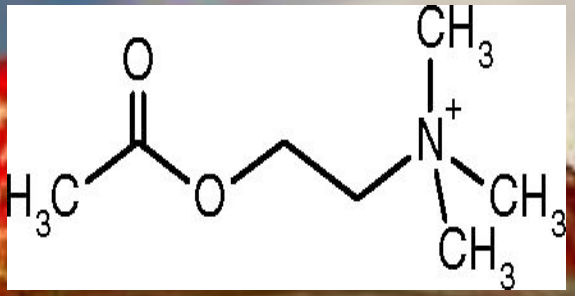
pilocarpine, nicotine , lobeline

Quaternary group



acetylcholine , methacholine, carbachol, bethanechol

PHARMACOKINETICS



Acetylcholine low lipid- solubility

Poorly absorbed poorly distributed in the CNS

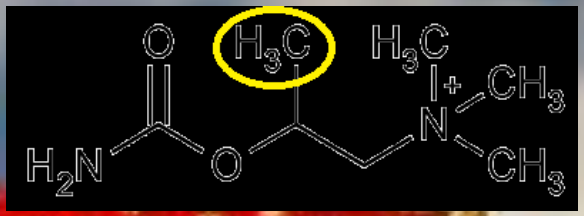
Hydrolyzed in the GIT , not active by the oral route

Ach is very sensitive to hydrolysis by cholinesterases

Methacholine is 3 times more **resistant** to hydrolysis

Carbachol & bethanechol are completely resistant to hydrolysis

PHARMACOKINETICS



Presence of a methyl group on **bethanechol** reduces its potency at **nicotinic** junction.

Tertiary cholinomimetics are well absorbed from most sites of administration

Nicotine, lipid –soluble, absorbed across the skin.

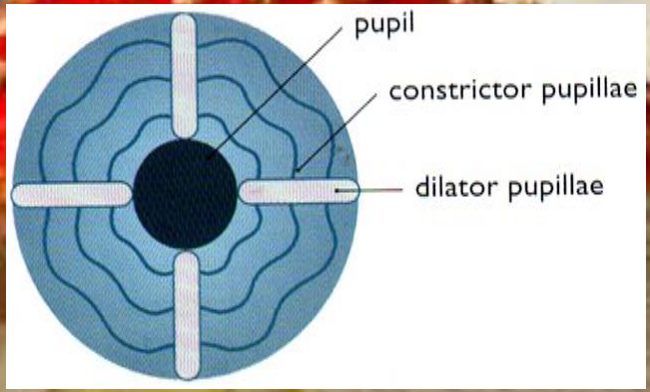
- **Muscarinic quaternary amines** , less completely absorbed from the GIT but still toxic when ingested in **mushroom.**

- Excretion by **kidney**, clearance of tertiary amines can be enhanced by **acidification of urine**

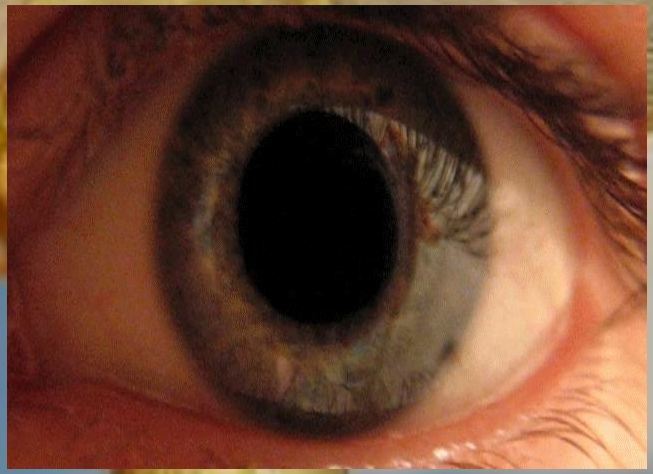
PHARMACODYNAMIC EFFECTS

1-Eye

The parasympathetic innervates the **constrictor pupillae** , runs cirumferentially in the **iris**



Constrictor pupillae is important for adjusting the pupil in response to change in **light intensity** & regulating the **intraocular pressure**

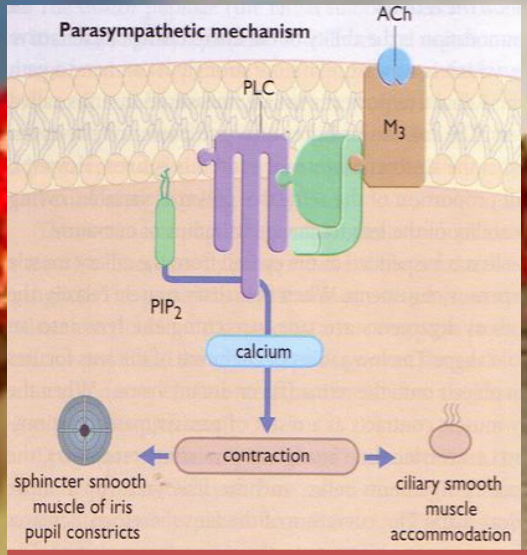


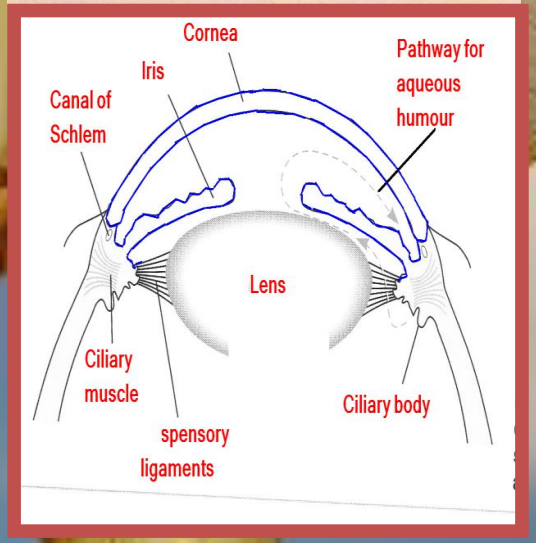
PHARMACODYNAMIC EFFECTS

1-Eye

Parasympathetic activation contracts the ciliary muscle

Contraction of ciliary muscle pulls the ciliary body **forward & inward** , relaxing the tension on the **suspensory** ligaments of the lens

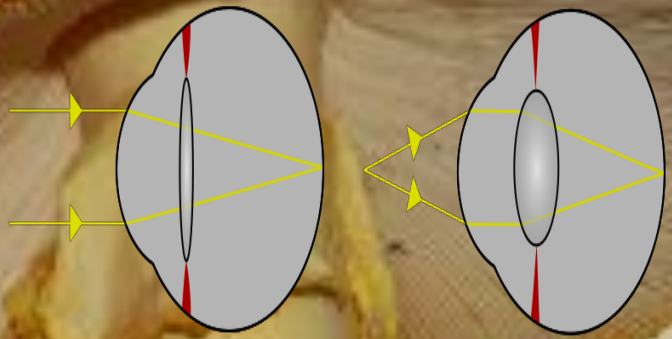




PHARMACODYNAMIC EFFECTS

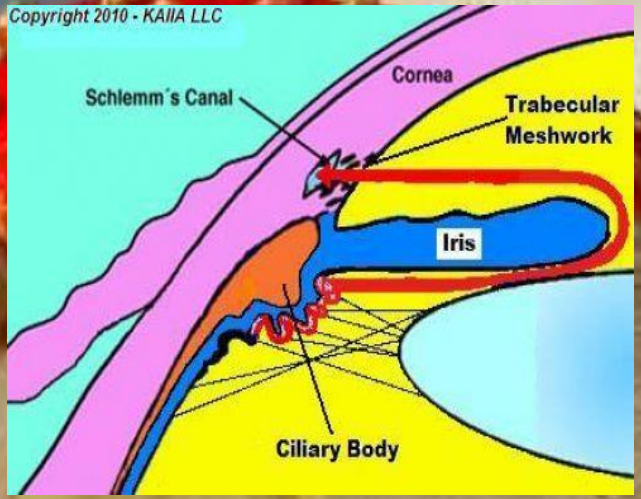
1-Eye

When the ciliary muscle contracts, the lens **bulg**e more →↓**focal length**, this parasympathetic reflex is essential to **accommodate for near vision**

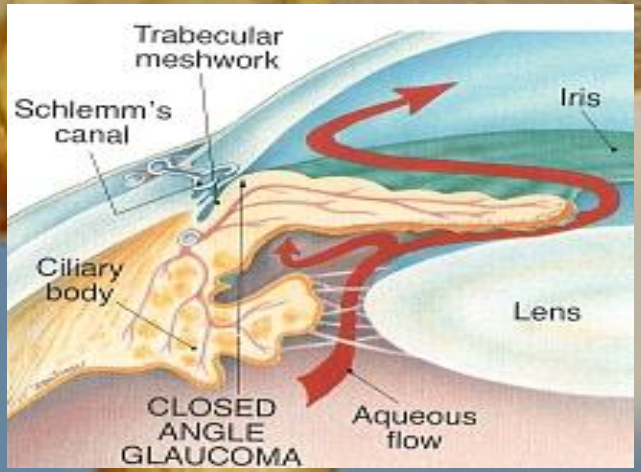


PHARMACODYNAMIC EFFECTS

Aqueous humour secreted by the cells of the epithelium covering the **ciliary body** , is removed continuously by drainage into the **canal of Schlemm**



In some people drainage of aqueous humour is impeded when the **iris is dilated** → folding of the iris tissue occludes the drainage angle →↑**intraocular pressure**

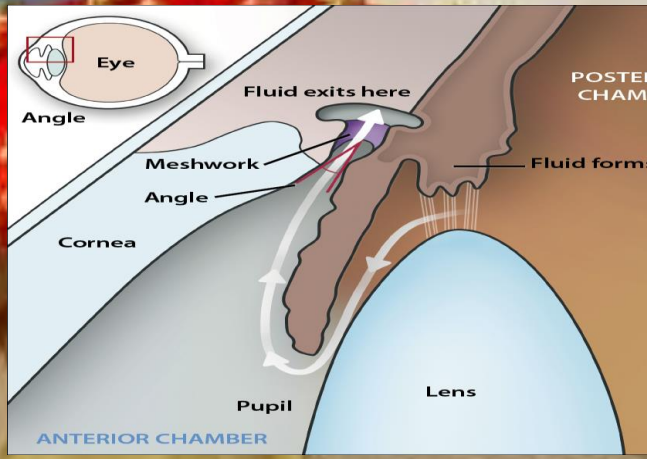


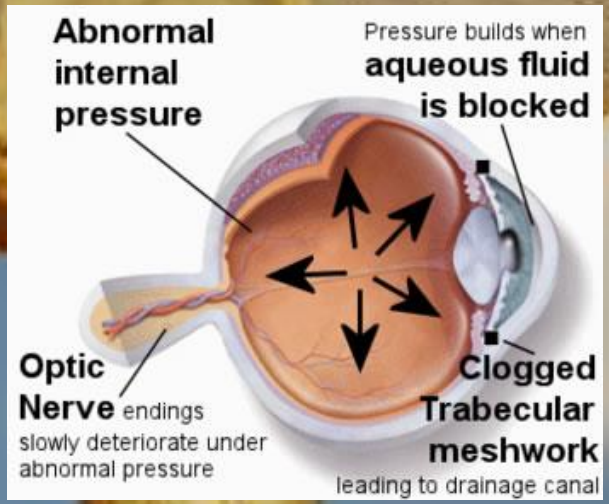
PHARMACODYNAMIC EFFECTS

Activation of constrictor pupillae →↓ intraocular pressure in these individuals

Also ↑**tension** in the ciliary body allow drainage

Normal **intraocular pressure** is 10-15mmHg above **atmospheric pressure** .
Abnormally raised pressure →**retinal detachment**





PHARMACODYNAMIC EFFECTS

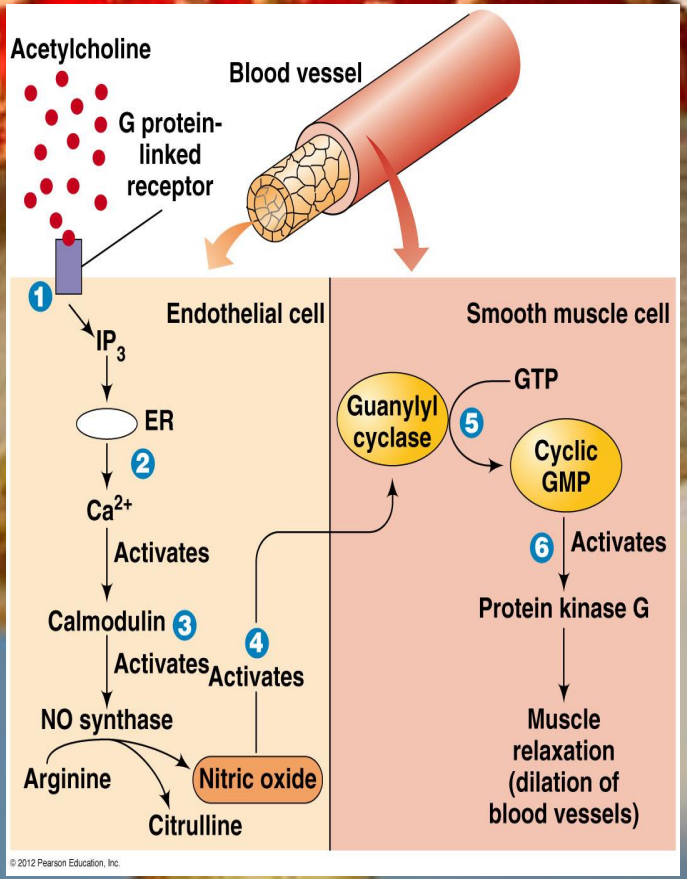
2-Cardiovascular effect

Ventricle has sparse **parasympathetic** innervations

Cardiac **slowing , ↓CO→↓force** of contraction of the atrium

Vasodilation occurs , effect not associted with muscarinic innervations

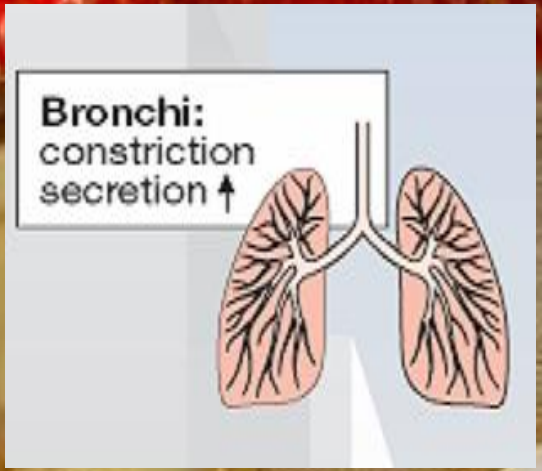
BP: Hypotension is opposed by **reflex sympathetic** discharge



PHARMACODYNAMIC EFFECTS

3-Respiratory system

Muscarinic stimulants contract smooth muscles of **bronchial tree**



↑**Glandular secretion**, may cause symptoms in individuals with **asthma**

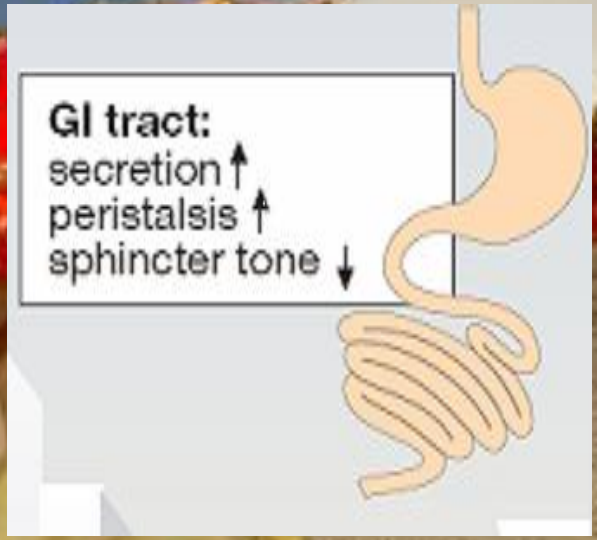
PHARMACODYNAMIC EFFECTS

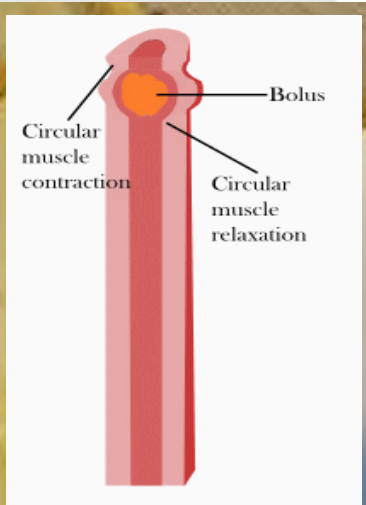
4-GIT:-

↑Secretion of **gastric glands**

↑**Peristaltic movement**

Sphincters relaxed.

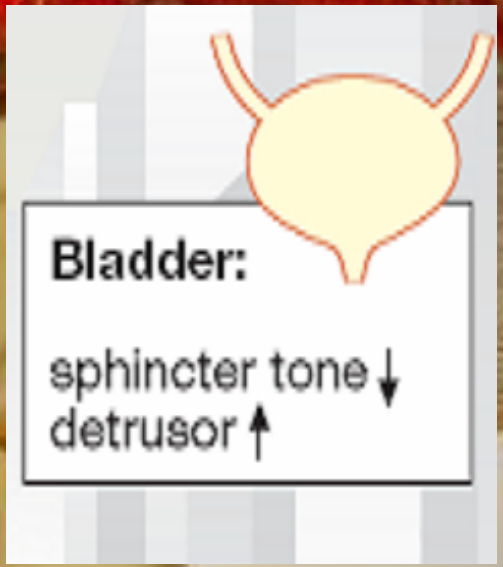




PHARMACODYNAMIC EFFECTS

5-Genitourinary tract:-

Stimulate muscles of **bladder & relax sphincters** promoting voiding



Human uterus is **not sensitive** to muscarinic agonists

6-Miscellaneous secretory glands:-

Stimulate secretion of **sweat , lacrimal, nasopharyngeal glands**

PHARMACODYNAMIC EFFECTS

7-CNS:-

Both muscarinic & nicotinic receptors are found in the CNS

Nicotine & lobeline
- **alerting action**

High level of nicotine
- **convulsions & coma**

CLINICAL USES

1-The Eye

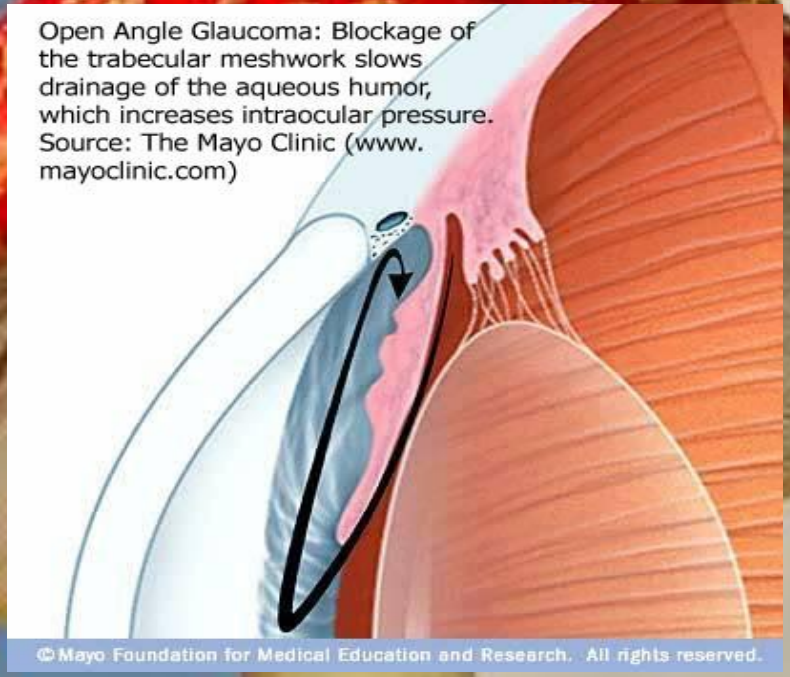
Glaucoma

1- Primary

A- Angle closure

B- Open angle

2- Secondary



caused by trauma, inflammation, surgical procedures

CLINICAL USES

Acute angle closure

Medical emergency , initially treated by drugs

Surgery for permanent correction **[irridectomy]**

Muscarinic stimulants ↓intraocular pressure by:-

1-facilitating **outflow** of aqueous humor

2-↓rate of its **secretion**

e.g. Direct stimulants

Methacholine, carbachol, pilocarpine

CLINICAL USES

2-GIT & Urinary tract

A-Postoperative ileus **"atony** or paralysis of the stomach following surgery

B-Postoperative **urinary retention**

Bethanechol

C-Xerostomia ⟶ Pilocarpine

Sjogren's Syndrome

Sjogren's Syndrome is an autoimmune disease.
characterized by the abnormal production of antibodies directed to the lacrimal and salivary glands→ eye and mouth dryness.

Cevimeline is a direct muscarinic agonist with particular effect on M3 receptors.

By activating the M3 receptors cevimeline stimulates secretion by the salivary & lacrimal glands thereby alleviating dry mouth & dry eye

Rapidly absorbed after oral administration and excreted unchanged in urine

TOXICITY

DUMBELS

A-Directly- acting muscarinic stimulants:-
nausea, vomiting ,diarrhoea, salivation, cutaneous vasodilatation, bronchial constriction

B-Directly- acting nicotinic stimulants:-

I] Acute toxicity

- **1- CNS stimulant action**, convulsions , coma , respiratory arrest
- **2-Skeletal muscle endplate depolarization**
→depolarization block & respiratory paralysis
- **3-Hypertension & cardiac arrhythmias**

TOXICITY

- Treatment of **symptoms:-**

Muscarinic excess→ **atropine**

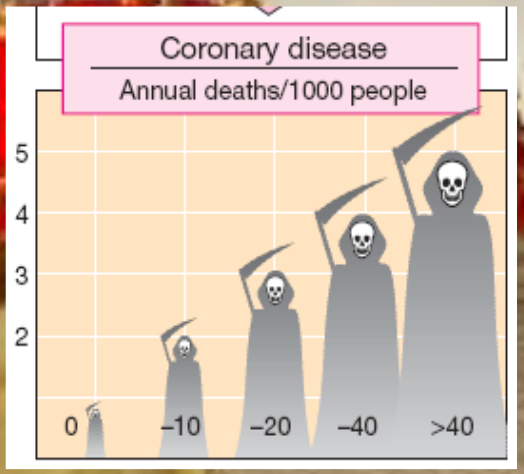
CNS stimulation → central anticonvulsants e.g. **diazepam**

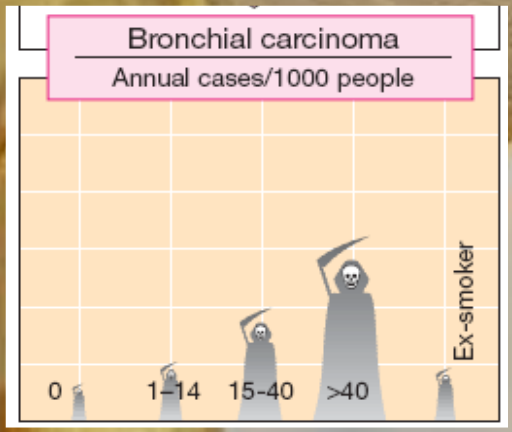
Neuromuscular block → **mechanical** respiration

ii-Chronic nicotinic toxicity

30% of deaths due to cancer & coronary heart disease are due to smoking

Nicotine contributes to ↑risk of vascular diseases, sudden coronary death, ↑ulcer





No. cigarettes / day

Muscarinic receptors

Receptor	Locations	Pharmacological actions
M1 Excitatory	CNS gastric parietal cells	CNS excitation Gastric acid secretion
M2 Inhibitory	Heart	Cardiac inhibition (Bradycardia)
M3 Excitatory	Exocrine glands Smooth muscles (GIT, urinary tract, bronchial muscles) Vascular endothelium	• Secretion of glands • Smooth muscle contraction • Vasodilatation (via nitric oxide)
M4 & M5	CNS	memory, arousal, attention and analgesia

Cholinergic or parasympathetic receptors

Nicotinic receptors Central cholinoceptors	Muscarinic receptors Peripheral cholinoceptors
Almost excitatory	Excitatory or inhibitory
Autonomic ganglia Nn sympathetic & parasympathetic stimulation	On all peripheral organs innervated by postganglionic parasympathetic fibers
Adrenal medulla Nn release of catecholamines (adrenaline & noradrenaline)	Heart (bradycardia, M2) exocrine glands (secretion, M3)
Skeletal muscles Nm contraction	Smooth muscles (contraction, M3) (GIT, urinary tract, bronchial muscles, uterus)

Muscarinic actions of Ach

Organs	Cholinergic actions
Eye	Contraction of circular muscle of iris (miosis)(M3) Contraction of ciliary muscles for near vision (M3) Decrease in intraocular pressure (IOP)
Heart endothelium	bradycardia (decrease in heart rate) (M2) Release of NO (EDRF)
Lung	Constriction of bronchial smooth muscles Increase in bronchial secretion M3
GIT	Increase in motility (peristalsis) Increase in secretion Relaxation of sphincter –defecation M3
Urinary bladder	Contraction of muscles Relaxation of sphincter M3 Urination
Exocrine glands	Increase of secretions of exocrine glands sweat, saliva, lacrimal, bronchial, intestinal secretions M3

	ACh	Carbachol	Bethanechol	Pilocarpine
Chemistry	Quaternary Polar	Quaternary Polar	Quaternary Polar	Tertiary non polar
Absorption	NOT	better absorbed than Ach	better absorbed than Ach	Complete
Metabolism by cholinesterase	metabolized by cholinesterase	NOT metabolized by cholinesterase		
Duration	Very short	Longer (++)	Longer (++)	Longer (++)
administration	I.V. eye drops	Oral, eye drops S.C.	Oral S.C.	oral, eye drops

direct Cholinomimetic

	ACh M, N	Carbachol M,N	Bethanechol M	Pilocarpine	Cevimeline M
Receptors	Muscarinic Nicotinic	Muscarinic Nicotinic	Muscarinic	Muscarinic	Muscarinic
Muscarinic	+++	+++	+++	+++	+++
Selectivity	NOT	Eye, GIT Urinary bladder	GIT, Urinary bladder	More on eye, exocrine glands	Exocrine glands
Nicotinic	+++	+++	NO	NO	NO
Uses	NO	Glaucoma	Paralytic ileus Urinary retention	Glaucoma Xerostomia	Sjogren's syndrome