INDIRECT CHOLINOMIMETICS

Prof. Hanan Hagar **Dr. Ali Alhoshani**

Pharmacology Unit

Medical College

Indirect acting cholinomimetic drugs

What students should know:

- ***Classification of indirect acting cholinomimetics***
- ***Mechanism of action, kinetics, dynamics and uses of anticholinesterases***
- ***Adverse effects & contraindications of anticholinesterases***
- ***Symptoms and treatment of organophosphates toxicity.***

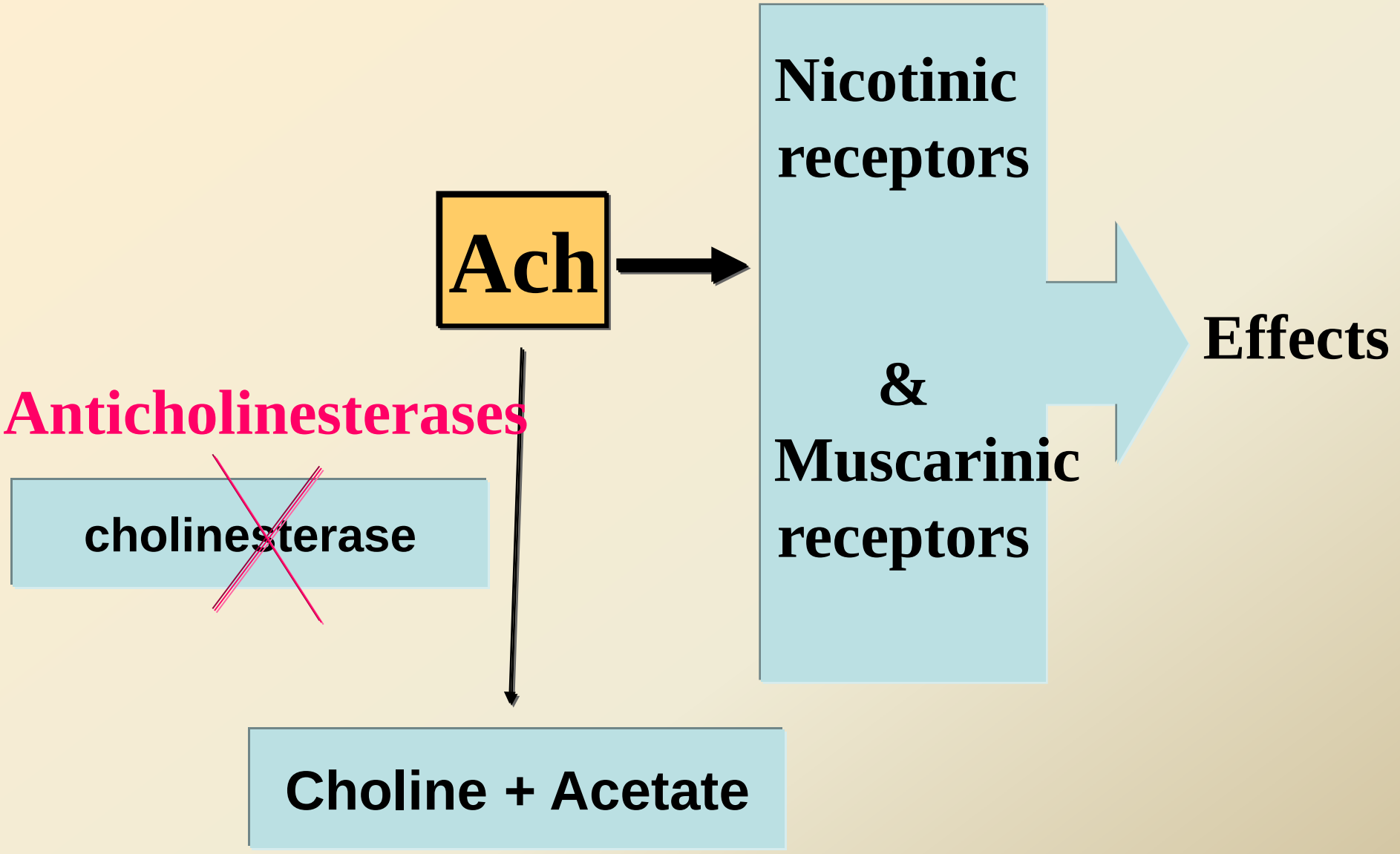
Indirect cholinomimetics

(also called anticholinesterases)

Mechanism of action:

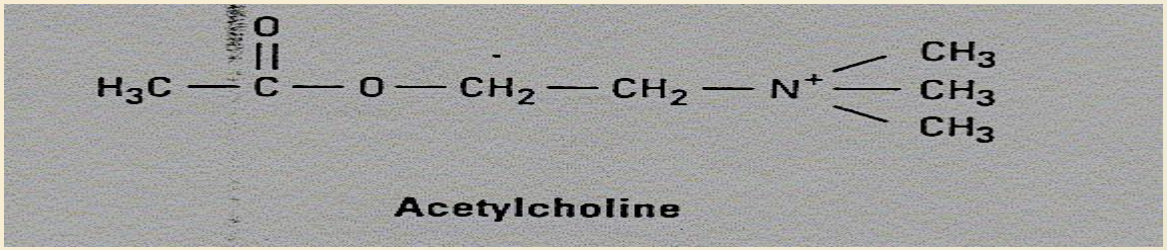
Anticholinesterases prevent hydrolysis of Ach by inhibiting acetyl cholinesterase thus increase Ach concentrations and actions at the cholinergic receptors (both nicotinic and muscarinic).

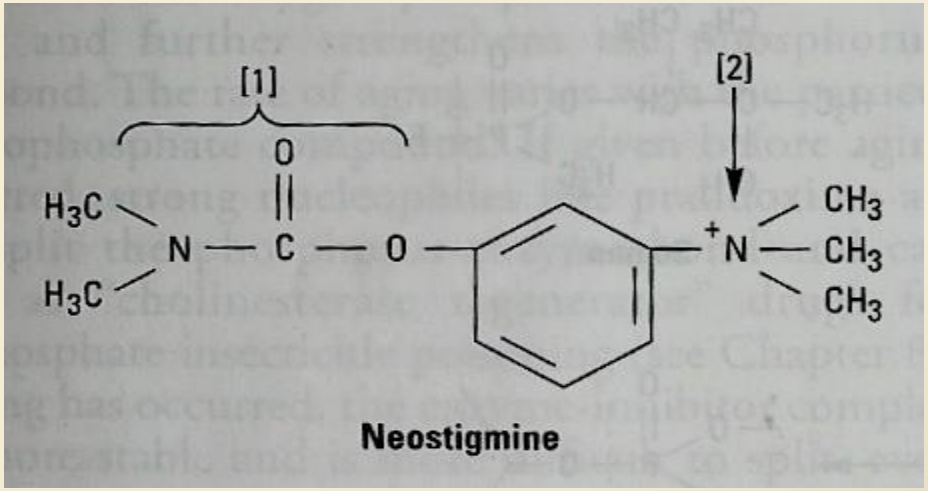
Indirect cholinomimetics (anticholinesterases)

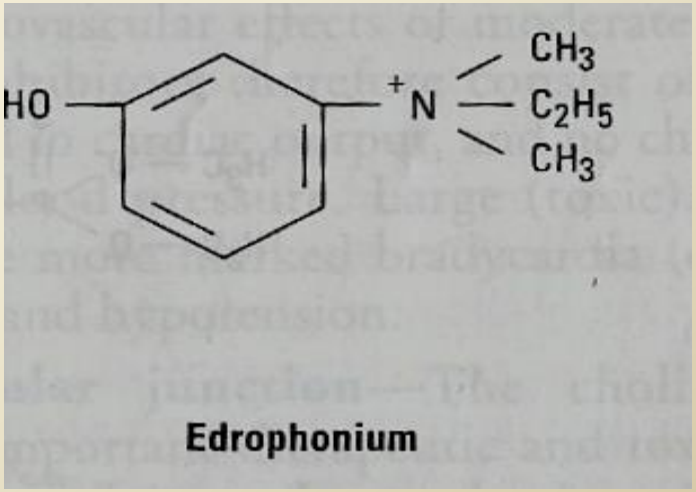


Anticholinesterases

Anticholinesterases are similar in structure to Ach so combine with cholinesterase enzyme (two sites, anionic and esteratic sites) instead of Ach.







Classification of anticholinesterases

Reversible anticholinesterases

Short acting (Alcohols) edrophonium

Intermediate acting (Carbamates esters)
Physostigmine, Neostigmine, Pyridostigmine

Irreversible anticholinesterases

Long acting

Phosphates esters e.g. insecticides, gas war

e.g. Ecothiophate & Isoflurophate

Reversible indirect cholinomimetics

Short acting, reversible

- drugs as edrophonium, it is an alcohol
- forms weak hydrogen bond with acetylcholinesterase enzyme

Intermediate acting, reversible

- Carbamates esters
- binds to two sites of cholinesterase enzyme
- All polar except physostigmine
  - Physostigmine
  - Pyridostigmine
  - Neostigmine

Irreversible indirect cholinomimetics

Very long acting, Phosphate esters

e.g. Ecothiophate – Isofluorophate

- very long duration of action
- form very stable covalent bond with cholinesterase
- All phosphates are lipid soluble **except ecothiophate which is polar.**

Pharmacological effects of anticholinesterases

- **ALL Anticholinesterases have muscarinic and nicotinic actions (N & M actions) and some have CNS effects (only lipid soluble drugs).**
- **Nicotinic actions**
- **Muscarinic actions: similar to Ach (miosis, bradycardia, bronchoconstriction, increased motility, secretion of exocrine glands).**

Pharmacological effects of anticholinesterases

- **CNS actions:**

(excitation, convulsion, respiratory failure, coma).

- **only for lipid soluble anticholinesterases**
- **e.g. physostigmine & phosphate ester (except ecothiophate that is polar).**

Nicotinic actions

Neuromuscular junction

Therapeutic dose: **muscle contraction**

Toxic dose: **relaxation or paralysis of skeletal muscles.**

Ganglia: **stimulation of sympathetic and parasympathetic ganglia**

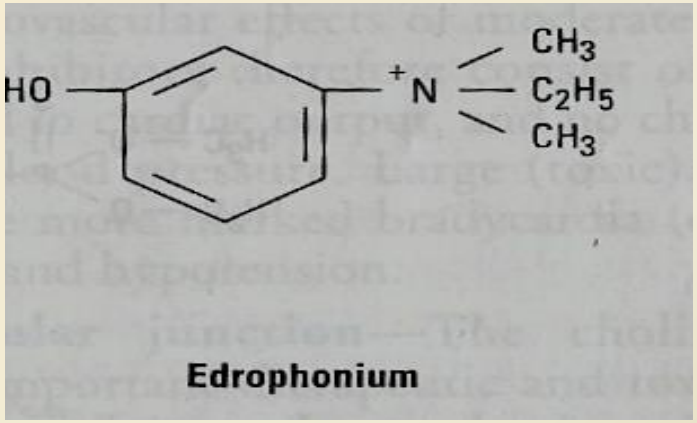
Adrenal medulla **release of catecholamines (A & NA).**

Muscarinic actions

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

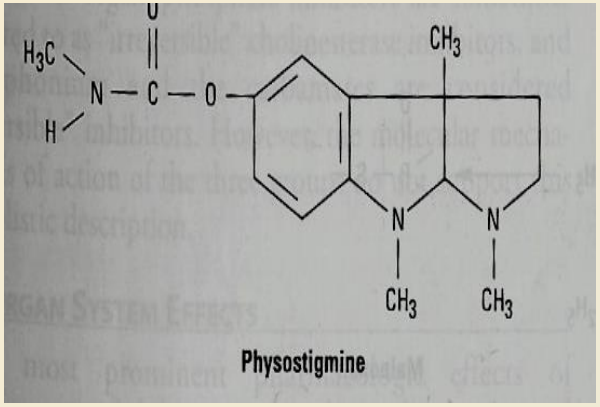
Indirect Cholinomimetics

Edrophonium



- Reversible anticholinesterase
- alcohol
- Polar
- NOT absorbed orally (must be given by injection)
- attach mainly to acetyl cholinesterase by weak hydrogen bond.
- Has short duration of action (5-15 min.)
- Used for diagnosis of myasthenia gravis.

Physostigmine



Physostigmine

Reversible anticholinesterase

Tertiary ammonium compound

Non polar (lipid soluble)

Good lipid solubility

Good oral absorption

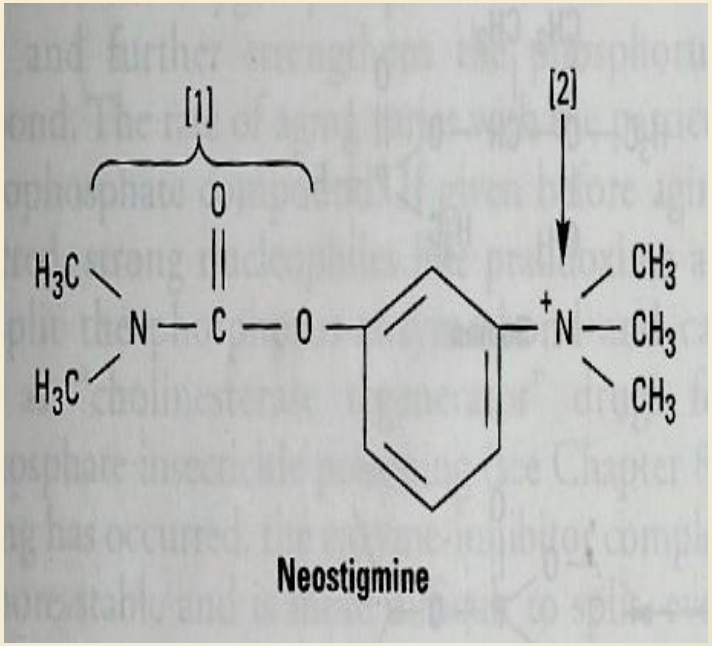
Has muscarinic & nicotinic actions

cross BBB (has CNS effects)

Uses

- **Glaucoma**
- **atropine toxicity (atropine is anticholinergic drug)**

Neostigmine



Reversible anticholinesterase

Quaternary ammonium comp.

Polar compound

Can be used orally

No CNS effect

Has muscarinic & nicotinic actions (prominent on GIT & urinary tract).

Uses

- Treatment of myasthenia gravis
- Paralytic ileus & Urinary retention
- Competitive neuromuscular blockers intoxication

Carbamate esters

Drug	Actions	Kinetics	Uses
Neostigmine	Nicotinic & muscarinic M, N	0.5-2hr polar	Myasthenia gravis treatment Paralytic ileus Urinary retention Curare toxicity
Physostigmine	Nicotinic muscarinic M, N, CNS	0.5-2hr Lipid soluble	Glaucoma atropine toxicity
Pyridostigmine	Nicotinic & muscarinic M, N	3-6 polar	Myasthenia gravis treatment
Ambenonium	Nicotinic & muscarinic M, N	4-8 polar	Myasthenia gravis treatment

Indirect Cholinomimetics (Organophosphorous compounds)

Ecothiophate

Mechanism

- Irreversible anticholinesterase
- Binds to cholinesterase by strong covalent bond.
- Have very long duration of action
- Aging make bond extremely stable
- All are highly lipid soluble except ecothiophate
- Used for glaucoma.

Organophosphates toxicity

- **Sever bradycardia, hypotension.**
- **bronchospasm.**
- **Increased GIT motility → cramps & diarrhea.**
- **CNS effects → convulsion, coma and respiratory failure.**
- **Initial twitching of skeletal muscles → muscle weakness & paralysis.**

Treatment of organophosphate toxicity

- **Support respiration**
- **Cholinesterase reactivators (Oximes)**
- **Atropine (to block muscarinic actions & CNS effects).**

Cholinesterase reactivators

OXIMES

Pralidoxime (PAM)

- cholinesterase reactivator
- Acts by regeneration of cholinesterase enzyme.
- reactivates recently inhibited enzymes before aging.

Uses

I.V. → over 15-30 min for organophosphate intoxication.

Donepezil

– is a centrally acting reversible acetyl cholinesterase inhibitor.

– Given orally.

– used for treatment of dementia of Alzheimer’s disease.

Indirect Cholinomimetic

Edrophonium **M, N**	**Very Short** **5-15 min, Polar**	**Diagnosis of Myasthenia gravis**
Neostigmine **M, N**	**Short 0.5-2hr** **polar**	**Myasthenia gravis treatment** **Paralytic ileus** **Urinary retention** **curare toxicity**
Physostigmine **M,N, CNS**	**Short 0.5-2hr** **Lipid soluble**	**Glaucoma** **atropine toxicity**
Ambenonium **Pyridostigmine** **M, N**	**Short 3-6, polar**	**Myasthenia gravis treatment**
Ecothiophate **M, N**	**Long 100hr, polar**	**Glaucoma.**
Donepezil **M, N**	**Lipid soluble**	**dementia of Alzheimer's disease**

Summary for cholinomimetics & their uses

Eye : treatment of glaucoma
Pilocarpine (direct muscarinic agonist)
Physostigmine -Ecothiophate (indirect cholinomimetics)

Urinary retention and paralytic ileus
Bethanechol (direct)
Neostigmine (indirect)

Myasthenia gravis (only indirect cholinomimetics)
Pyridostigmine, Neostigmine, Ambenonium

Xerostomia
Pilocarpine – Cevimeline (Sjogren's syndrome)

Alzheimer's disease: Donepezil

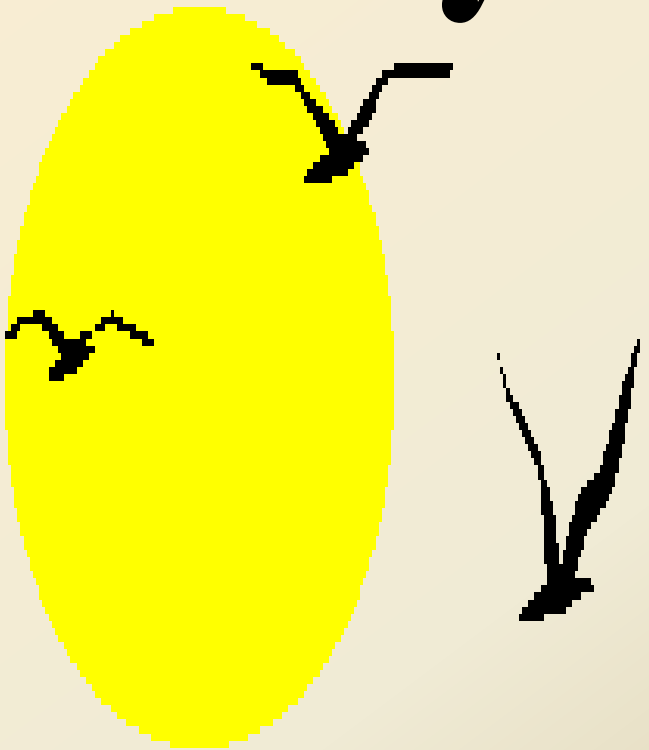
Adverse effects of cholinergic drugs:

- Bradycardia
- Sweating & Salivation
- Bronchoconstriction
- Diarrhea

Contraindications of cholinergic drugs

- Bronchial asthma
- Peptic ulcer
- Angina pectoris
- Incontinence
- Intestinal obstruction

Thank you



Any Questions ?