

# **INDIRECT CHOLINOMIMETICS**

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# 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.*

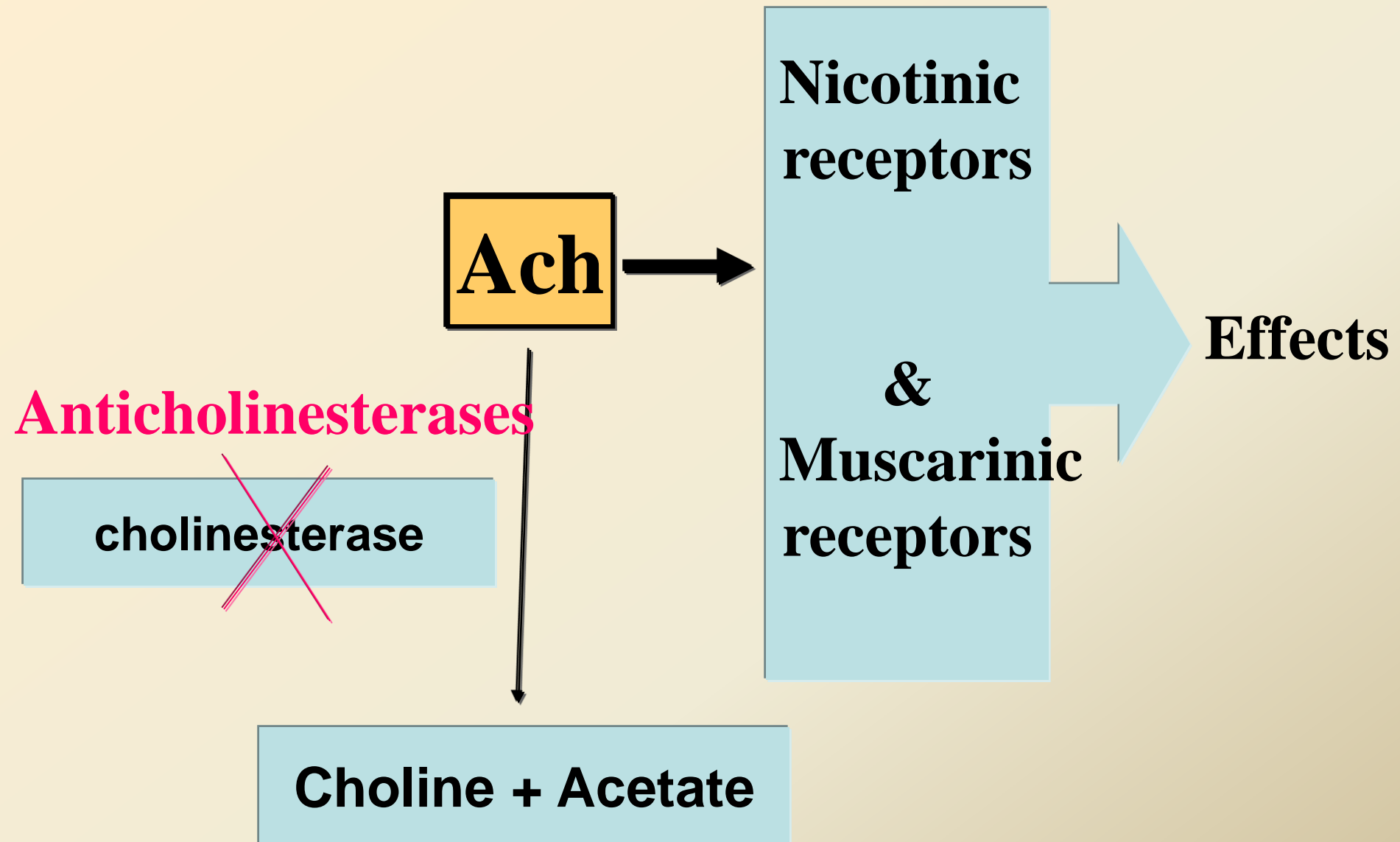
# **Indirect cholinomimetics**

**(also called anticholinesterases)**

## **Mechanism of action:**

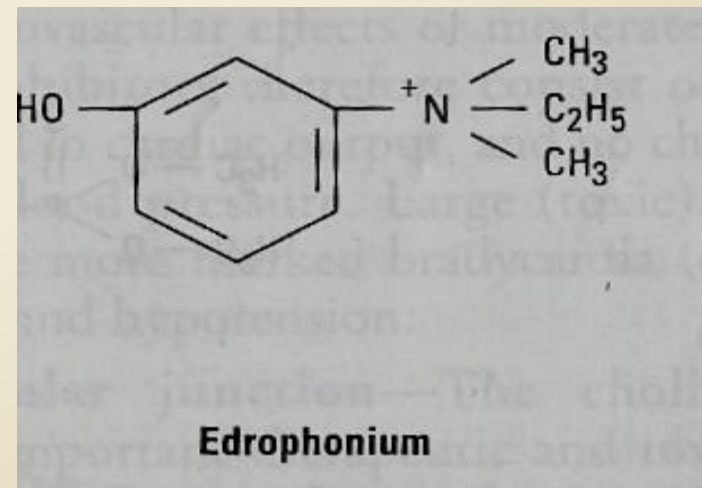
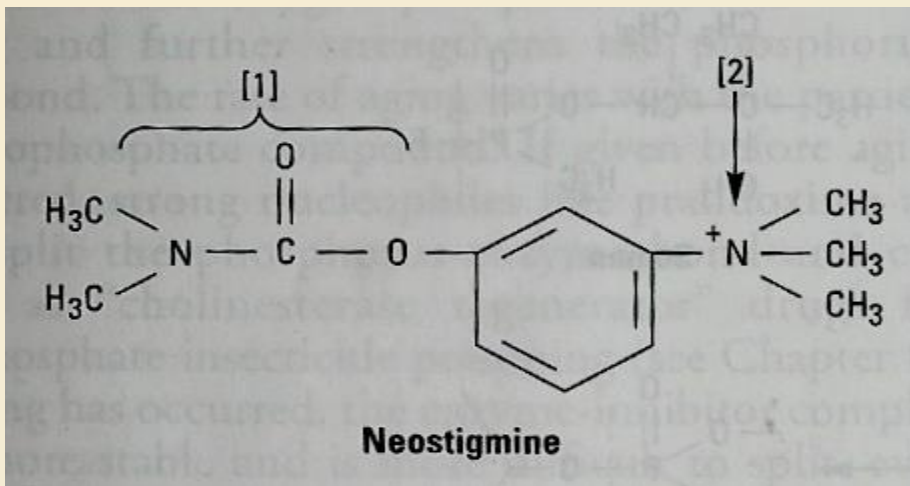
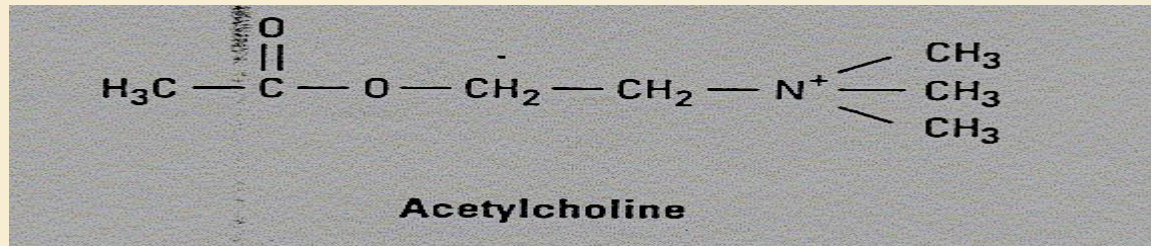
**Anticholinesterases prevent hydrolysis of Ach by inhibiting acetyl cholinesterase thus increase Ach concentrations and actions at the cholinergic receptors (both nicotinic and muscarinic).**

# 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 (**anionic site**)

## 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 – Isoflurophate**

- 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, sweating, lacrimation).**

# Pharmacological effects of anticholinesterases

- **CNS actions:**
  - **only for lipid soluble anticholinesterases**
  - **e.g. physostigmine**
  - **e.g. all phosphate ester (except ecothiophate that is polar).**
  - **Excitation, convulsion, respiratory failure, coma).**

# 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).

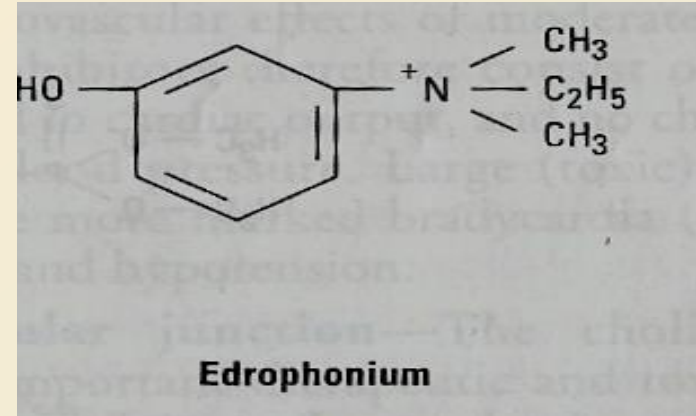
# Muscarinic actions

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

# 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

Reversible anticholinesterase

**Tertiary** ammonium compound

Non polar (lipid soluble)

Good lipid solubility

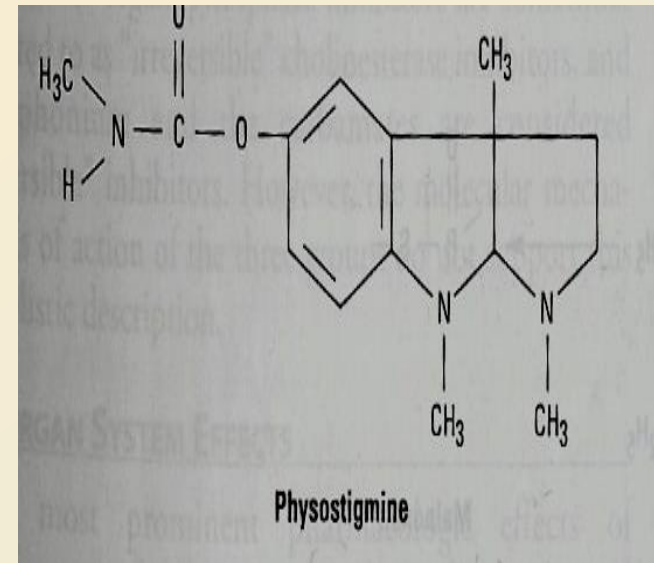
Good oral absorption

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

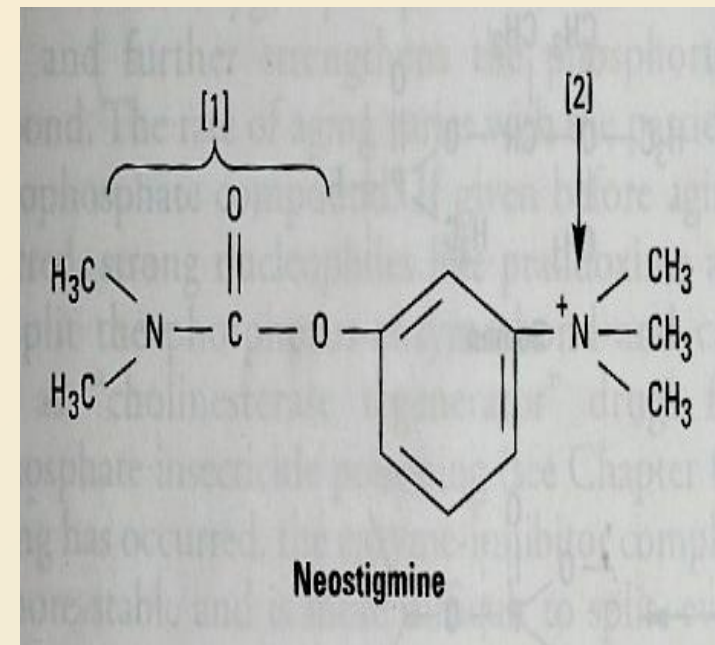
Can be used orally

**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

<b>Drug</b>	<b>Actions</b>	<b>Kinetics</b>	<b>Uses</b>
<b>Neostigmine</b>	Nicotinic & muscarinic <b>M, N</b>	0.5-2hr  polar	Myasthenia gravis treatment Paralytic ileus Urinary retention Curare toxicity
<b>Physostigmine</b>	Nicotinic muscarinic <b>M, N, CNS</b>	0.5-2hr <b>Lipid soluble</b>	Glaucoma atropine toxicity
<b>Pyridostigmine</b>	Nicotinic & muscarinic <b>M, N</b>	3-6 polar	Myasthenia gravis treatment
<b>Ambenonium</b>	Nicotinic & muscarinic <b>M, N</b>	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 makes 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.**
- **Sweating, salivation, lacrimation**
- **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 re-activator**
- **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

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

# 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:**

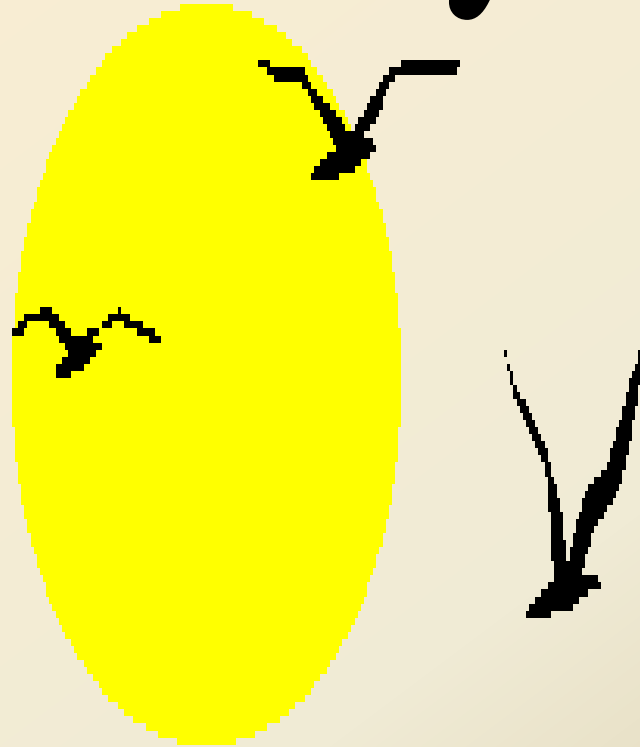
- **Bradycardia, hypotension**
- **Sweating & Salivation**
- **Bronchospasm**
- **Diarrhea**

## **Contraindications of cholinergic drugs**

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



**Thank you**



**Any Questions ?**