INDIRECT ACTING CHOLINRTGIC DRUGS

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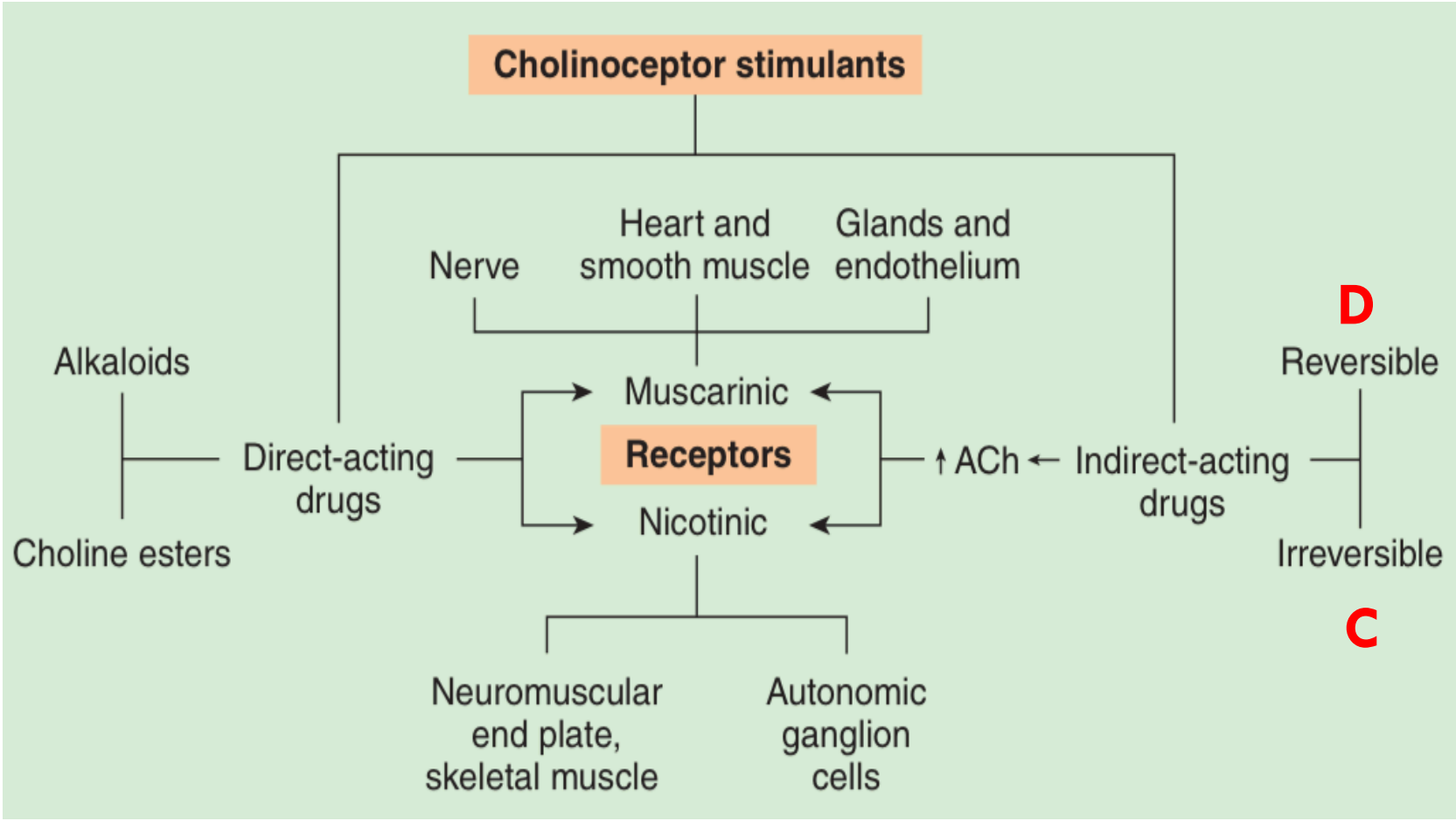
Objectives

By the end of this lecture the student should able to :

- 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.

Parasympathomimetic/ cholinomimetics (Cholinergic Drugs)



Indirect-acting on Ach receptors

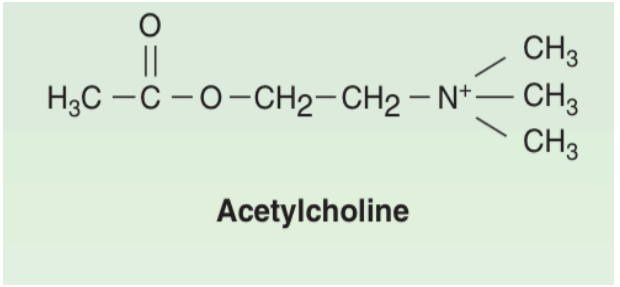
(also called anticholinesterases)

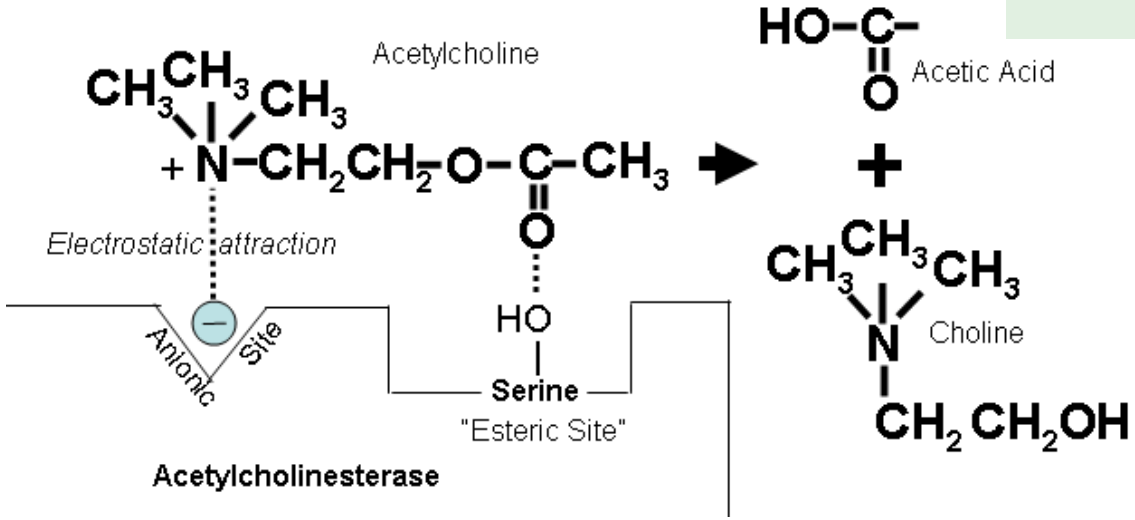
Mechanism of action:

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

Indirect-acting on Ach receptors

- Mechanism of action :
  - Normally





Indirect-acting on Ach receptors

Reversible anticholinesterases

Short acting (Alcohols) edrophonium

Intermediate acting (Carbamates esters)
Physostigmine, Neostigmine, Pyridostigmine

Irreversible anticholinesterases

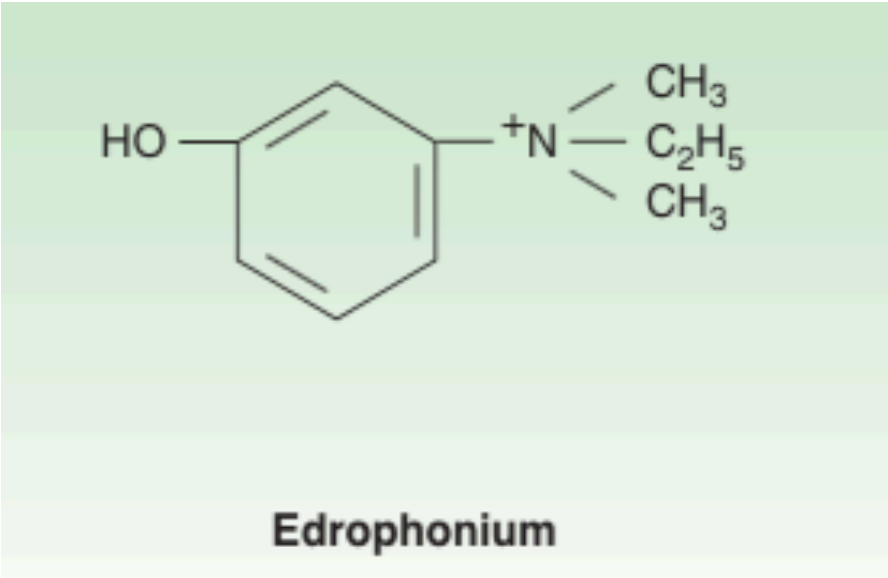
Long acting

Phosphates esters e.g. insecticides, gas war

e.g. Ecothiophate & Isoflurophate

Indirect-acting on Ach receptors

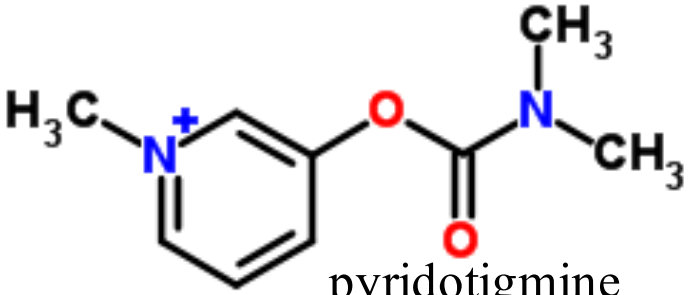
- Structure: (Reversible anticholinesterases)
  - 1- Simple alcohols (Short Acting)
  - Forms weak hydrogen bond with acetylcholinesterase enzyme



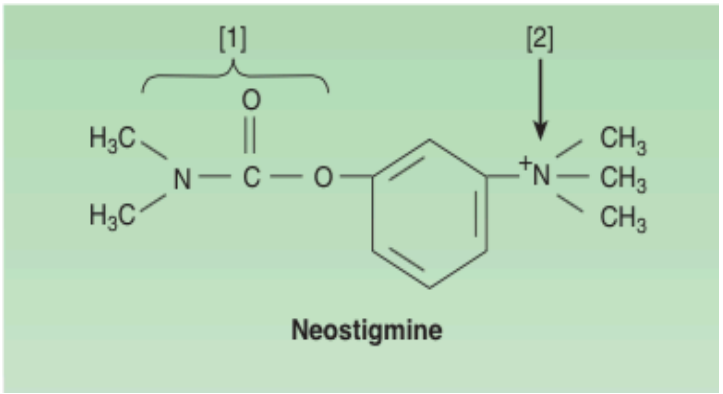
Edrophonium

Indirect-acting on Ach receptors

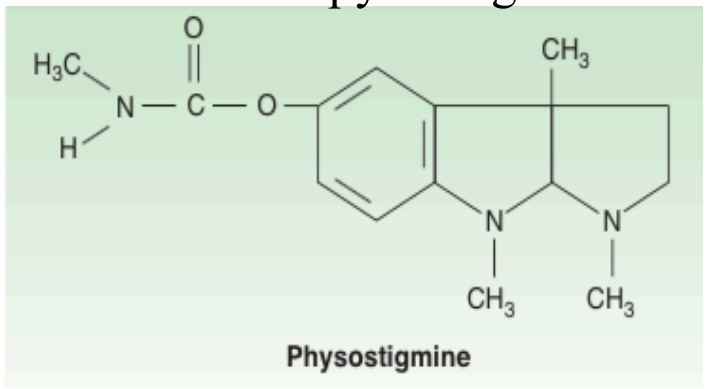
- Structure (Reversible anticholinesterases)
  - 2- Carbamic acid esters (Intermediate acting)
  - binds to two sites of cholinesterase enzyme
  - All polar and synthetic except physostigmine
    - Physostigmine
    - Pyridostigmine
    - Neostigmine



pyridotigmine



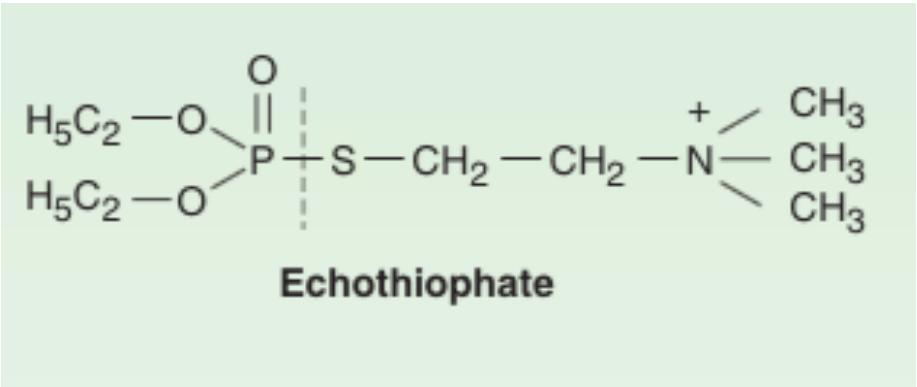
Neostigmine



Physostigmine

Indirect-acting on Ach receptors

- Structure: Irreversible anticholinesterases
  - 3- Organic derivatives of phosphoric acid (Long Acting) **e.g. Ecothiophate – Isoflurophate**
  - used as insecticides(malathion) or nerve gases (sarin)
  - Form very stable covalent bond with cholinesterase
  - All phosphates are lipid soluble except ecothiophate which is polar.



Echothiophate

Pharmacological effects of anticholinesterases

- ALL Anticholinesterases

Action on	Yes/No
muscarinic	YES
nicotinic	YES
CNS effects	only lipid soluble drugs

Pharmacological effects of anticholinesterases

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).

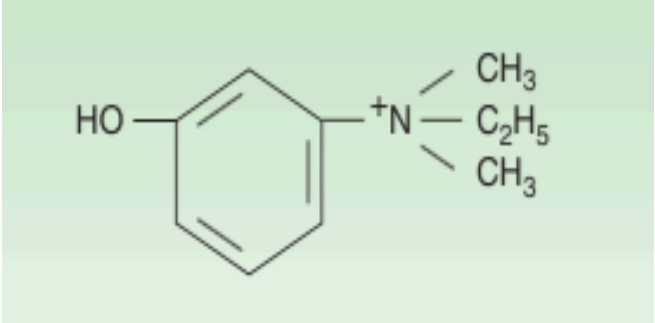
Pharmacological effects of anticholinesterases

Muscarnic 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

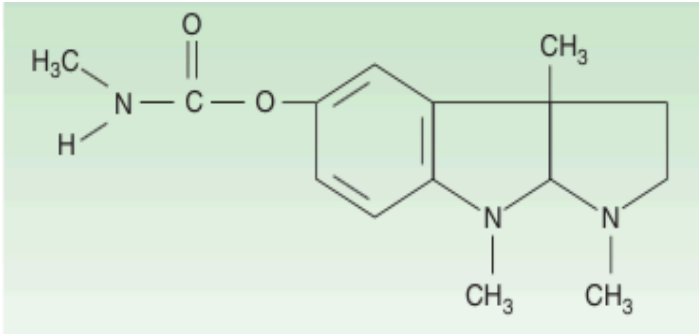
Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

- Edrophonium
  - Reversible anticholinesterase
  - alcohol
  - Polar
  - NOT absorbed orally (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.



Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

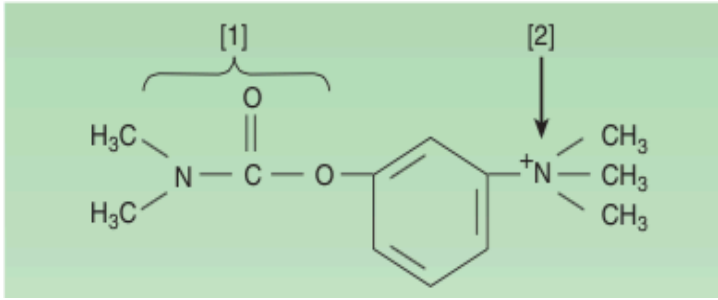
- Physostigmine
  - Reversible anticholinesterase
  - Tertiary ammonium compound
  - Non polar (lipid soluble)
  - Good lipid solubility
  - Good oral absorption
  - Has muscarinic & nicotinic actions
  - cross BBB (has CNS effects)



- Uses
  - Glaucoma
  - Atropine toxicity (atropine is anticholinergic drug)

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

- Neostigmine
  - Reversible anticholinesterase
  - Quaternary ammonium comp.
  - Polar compound
  - Can be used orally
  - No CNS effect
  - Has muscarinic & nicotinic actions (prominent on GIT & urinary tract).



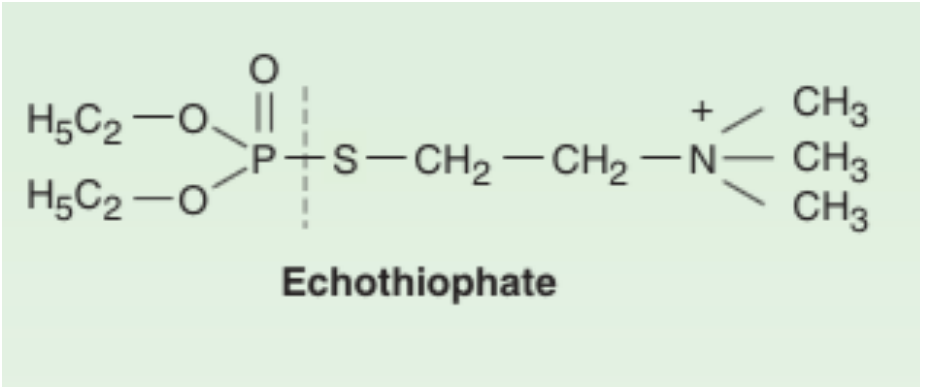
- Uses
  - Treatment of myasthenia gravis
  - Paralytic ileus & Urinary retention
  - Competitive neuromuscular blockers intoxication

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

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

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

- Ecothiophate (**Organophosphorous compounds**)
  - Irreversible anticholinesterase
  - Binds to cholinesterase by strong covalent bond.
  - Have very long duration of action
  - Aging make bond extremely stable
  - Not lipid soluble
- Used
  - for glaucoma.



Echothiophate

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

- **Organophosphates toxicity**

  - Heart:
  - Lung:
  - GIT:
  - CNS:
  - Skeletal muscles :

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

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.

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

- Donepezil
- Anticholinesterase drugs.
- Given orally.
- used for treatment of dementia of Alzheimer's disease

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS)

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		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

Drugs indirect-acting on Ach receptors (CHOLINOCEPTORS

- Adverse effects of cholinergic drugs:
- Bradycardia
- Sweating & Salivation
- Bronchoconstriction
- Diarrhea

- Contraindications of cholinergic drugs
  - Bronchial asthma
  - Peptic ulcer
  - Angina pectoris
  - Incontinence
  - Intestinal obstruction