Indirect cholinomimetics

Indirect acting cholinomimetic drugs

What students should know:

- Indirect acting cholinomimetics
  - Classification
  - Mechanism of action
  - Kinetics
  - Dynamics
  - Uses
  - Adverse effects & contraindications.

Indirect cholinomimetics (anticholinesterases)

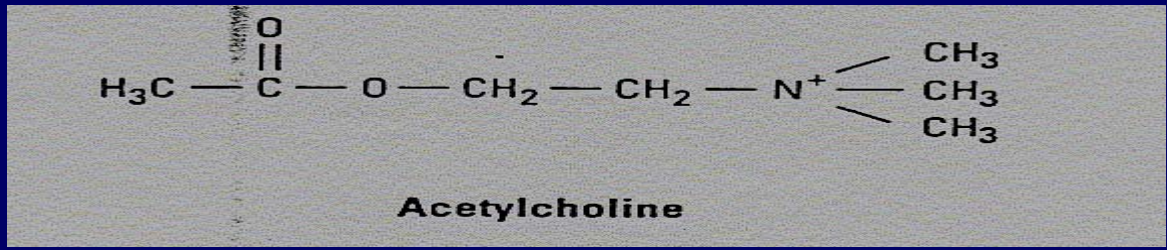
Mechanism of action:

inhibit acetylcholinesterase thus increase the Ach concentration at the cholinergic receptors (both nicotinic and muscarinic).

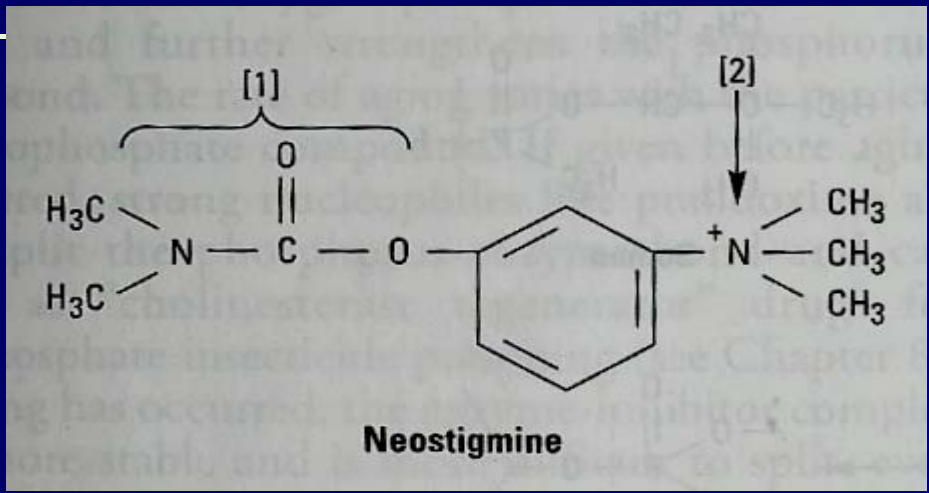
Indirect cholinomimetics

Degradation of Ach by acetyl cholinesterase:

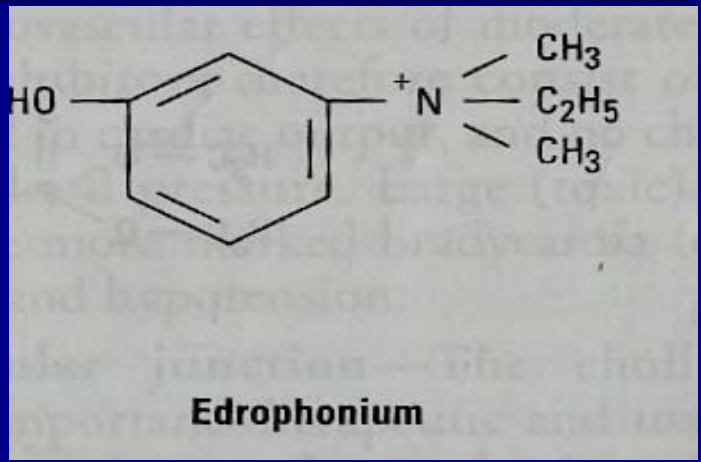
1. Ach binds to enzyme's active site and is hydrolyzed→ choline + acetylated enzyme (**binding**).
2. acetylated enzyme bond is broken by hydration→ cholinesterase enzyme + acetic acid (**Hydration**).
3. Anticholinesterases replace Ach → accumulation of Ach



Acetylcholine



Neostigmine



Edrophonium

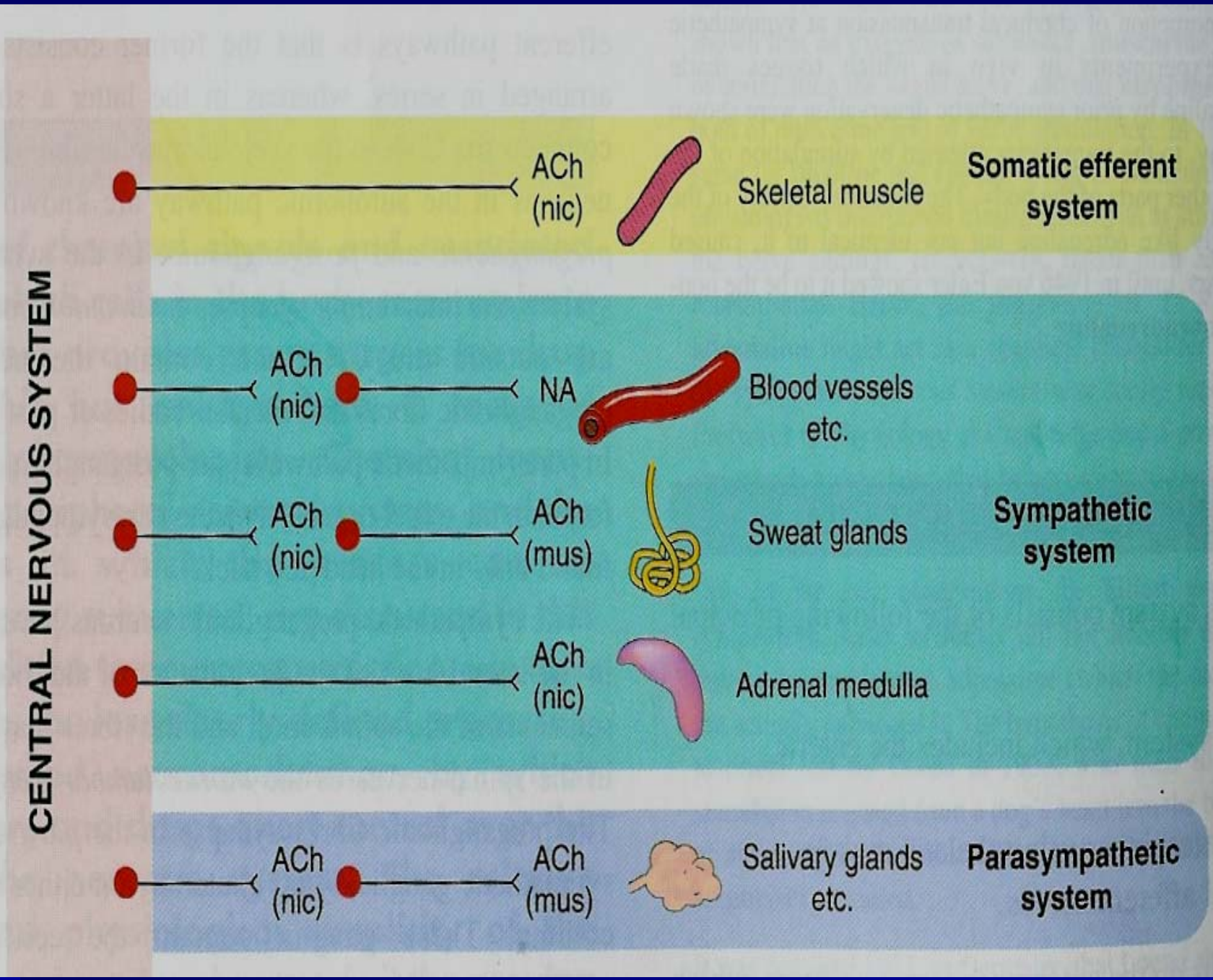
Pharmacological effects of anticholinesterases

1. **Nicotinic actions**
2. **Muscarinic actions**
3. **Actions on CNS :**

   Excitation, convulsion, respiratory failure, coma

Sites of Ach release

1. Neuromuscular junction.
2. **Autonomic ganglia:** all preganglionic nerve fibers of both sympathetic and parasymp nerves.
3. **Parasympathetic** postganglionic fibers.
4. **Sympathetic** postganglionic fibers to sweat glands.
5. **Preganglionic** sympathetic nerve to **Adrenal medulla.**


CENTRAL NERVOUS SYSTEM
ACh (nic)
Skeletal muscle
Somatic efferent system
ACh (nic)
NA
Blood vessels etc.
ACh (nic)
ACh (mus)
Sweat glands
Sympathetic system
ACh (nic)
Adrenal medulla
ACh (nic)
ACh (mus)
Salivary glands etc.
Parasympathetic system

NICOTINIC ACTIONS OF ACH

Skeletal muscles:

- stimulation → muscle fasciculation (twitching).
- High conc → persistent depolarization & paralysis.

Ganglia: stimulation of sympathetic and parasympathetic ganglia

Adrenal medulla release of catecholamines (A & NA).

Muscarinic actions

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period.
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period.
Ventricles	Small decrease in contractile strength

Blood vessels Arteries	Dilation (via EDRF). Constriction (high-dose direct effect).
Veins	Dilation (via EDRF). Constriction (high-dose direct effect).
Lung Bronchial muscle	Contraction (bronchoconstrictor)
Bronchial glands	Stimulation
Gastrointestinal tract Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands Sweat, salivary, lacrimal, nasopharyngeal	Secretion

Classification of Anticholinesterases

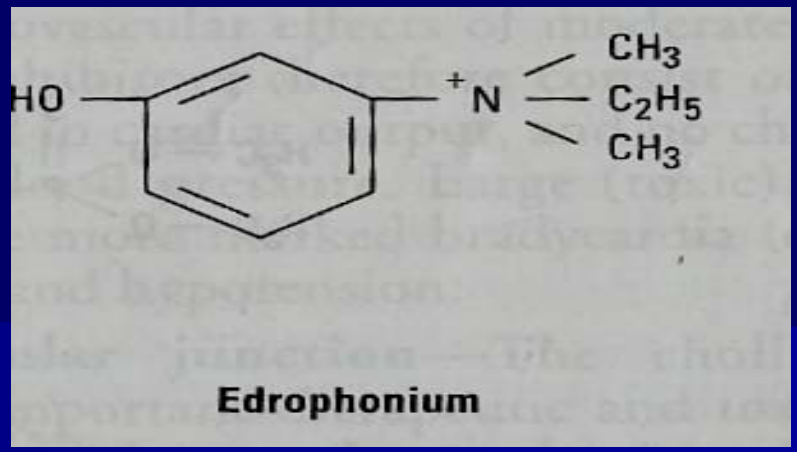
I- Reversible indirect cholinomimetics

- Edrophonium (Quaternary alcohol)
- Carbamates (esters)
  - Physostigmine
  - Pyridostigmine
  - Neostigmine
  - Ambenonium

II. Irreversible indirect cholinomimetics

- Organophosphorous compounds (esters)
  - Ecothiophate
  - Isoflurophate

Indirect Cholinomimetics



Edrophonium

Edrophonium

Simple alcohol

Reversible anticholinesterase

Not substrate for enzyme

attach mainly to anionic site.

Has very short duration of action (5-15 minutes)

Pharmacokinetics

Polar

NOT absorbed orally (Should be given by injection)

NOT hydrolyzed by cholinesterases

Excreted unchanged in the urine

USES

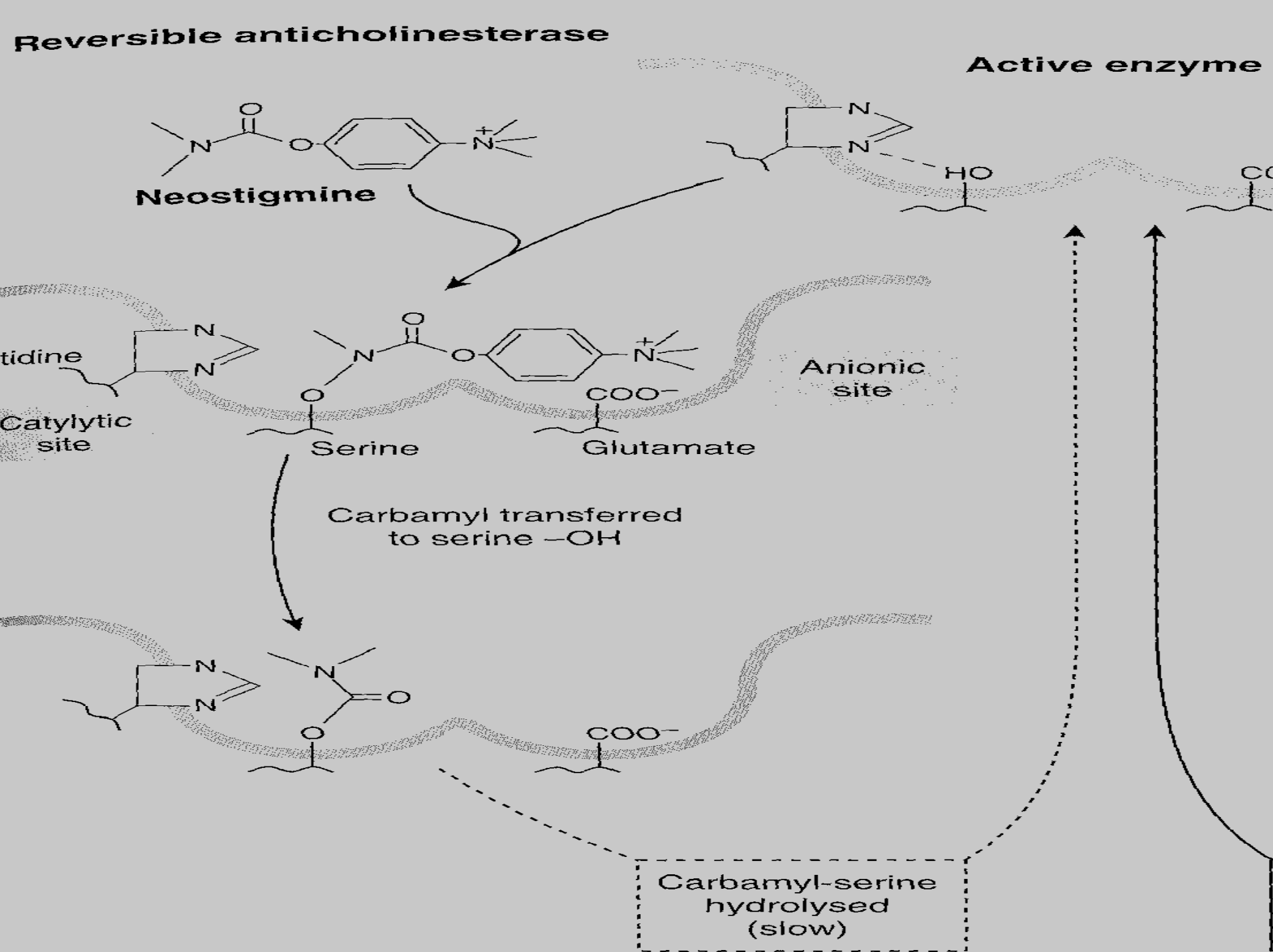
Diagnosis of myasthenia gravis

Anticholinesterases

Carbamates

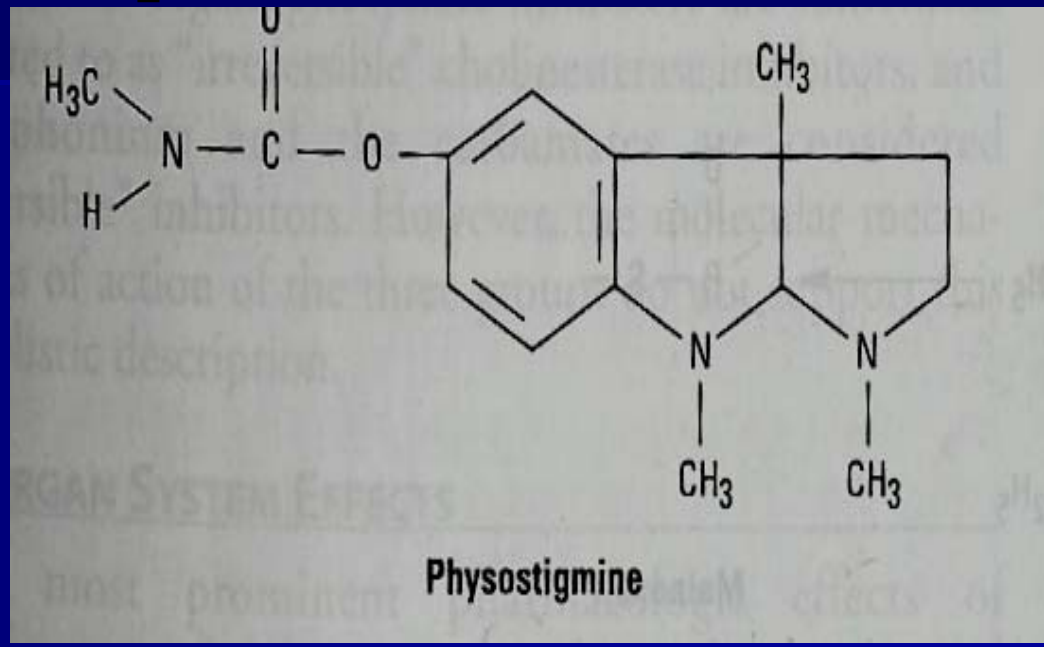
Mechanism of action:

1. Attach at both sites of the cholinesterase enzyme.
2. Hydrolyzed at slower rate than Ach.
3. Substrate for true cholinesterase enzyme and non specific esterases.
4. longer half life, 4-8 hr
5. All are polar EXCEPT **Physostigmine.**


Reversible anticholinesterase
Active enzyme
Neostigmine
HO
tidine
Catylytic site
Serine
Glutamate
Anionic site
Carbamyl transferred to serine –OH
Carbamyl-serine hydrolysed (slow)

Physostigmine

Tertiary ammonium compound



Physostigmine

Pharmacokinetics

Non polar

Good lipid solubility

Good oral absorption

Good BBB penetration

Hydrolyzed by cholinesterases (True & Pseudo).

Pharmacodynamics

- Attach at both sites of the enzyme
- Intermediate duration of action
- Indirect action (reversible anticholinesterase)
- Has muscarinic (see table of Ach) & nicotinic actions
- CNS stimulant action
- No direct action on NMJ

USES

- Glaucoma
- To counteract the effect of mydriatics
- Atropine intoxication (I.V.)

Neostigmine

Reversible anticholinesterase

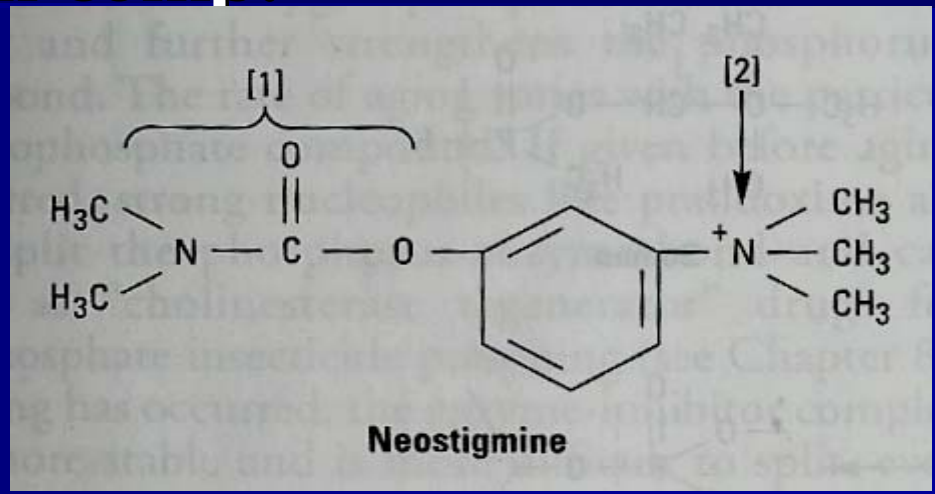
Quaternary ammonium comp.

Pharmacokinetics

Polar compound

Poor lipid solubility

Can be used orally



Neostigmine

NO BBB penetration (No CNS effect)

Intermediate duration of action

Hydrolyzed by cholinesterases (True & Pseudo)

Pharmacodynamics

- **Indirect action.**

Has muscarinic & nicotinic actions

(More prominent on GIT & urinary tract than CVS).

- **Direct action on NMJ**

USES

- **Treatment of myasthenia gravis (+ atropine)**
- **Paralytic ileus & Urinary retention**
- **Curare intoxication**

Ambenonium & Pyridostigmine

- reversible anticholinesterase
- Similar to neostigmine
- Treatment of myasthenia gravis

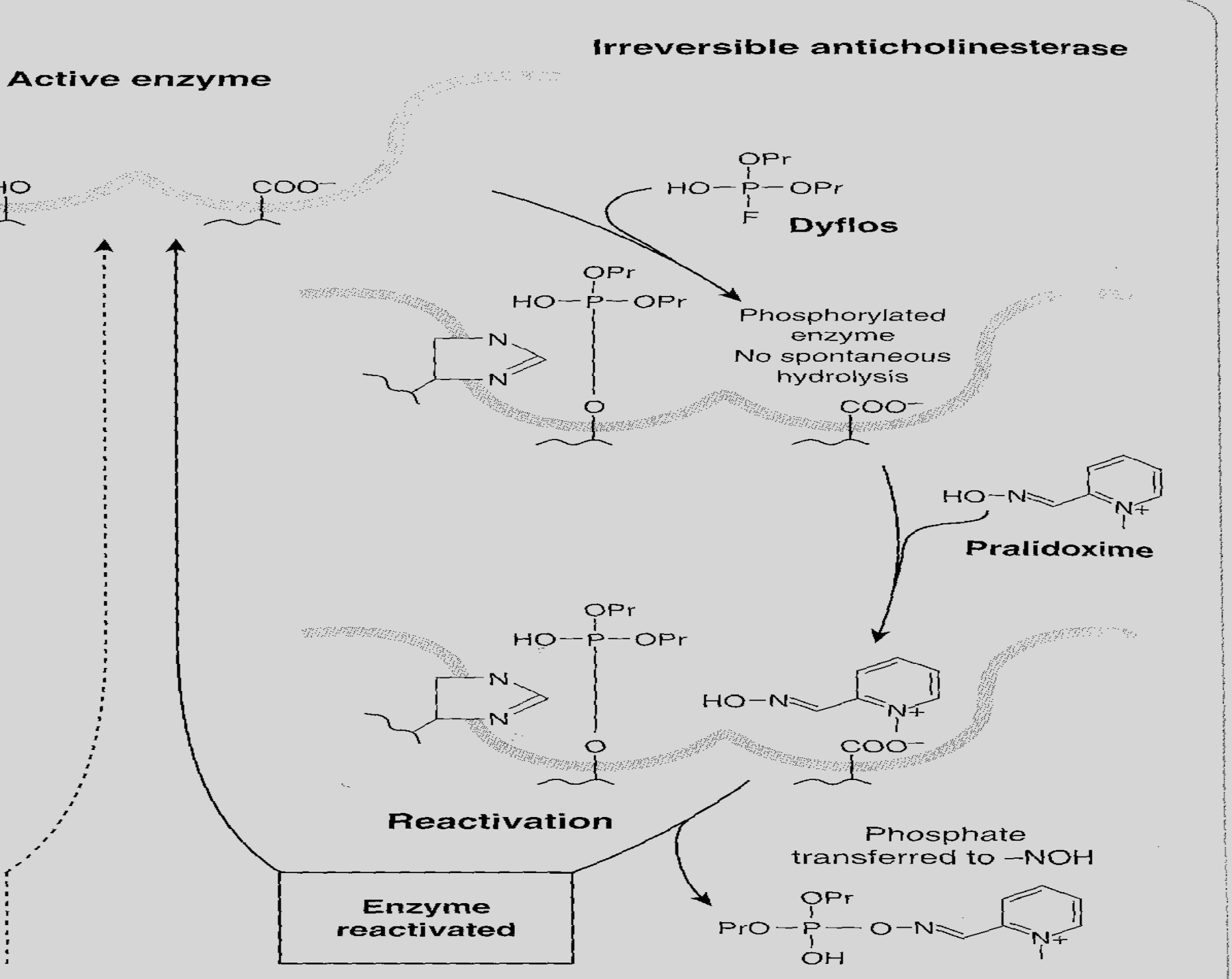
Indirect Cholinomimetics
(Organophosphorous compounds)

Ecothiophate

Isoflurophate (DFP)

Mechanism

- Indirectly by inhibition of cholinesterase
- Binds to esteratic site of cholinesterase forming covalent bond (the phosphorous atom).
- Long duration of action
- Aging make bond extremely stable
- All are highly lipid soluble except ecothiophate
- Used for glaucoma.


Irreversible anticholinesterase
Active enzyme
HO
COO⁻
OPr
HO—P—OPr
F
Dyflos
OPr
HO—P—OPr
N
N
O
Phosphorylated enzyme
No spontaneous hydrolysis
COO⁻
HO—N
N+
Pralidoxime
OPr
HO—P—OPr
N
N
O
HO—N
N+
COO⁻
Reactivation
Enzyme reactivated
Phosphate transferred to —NOH
OPr
PrO—P—O—N
OH
N+

Pharmacological effects of organophosphorous

1. **Muscarinic actions** (see table of Ach).
2. **Nicotinic actions**

- Ganglia
- NMJ

Therapeutic dose ----- Increase action of Ach, contraction

Toxic dose------Muscle twitching & paralysis

3. CNS Excitation, convulsion, respiratory failure, coma

Organophosphorous compounds toxicity

- Sever bradycardia, hypotension.
- bronchospasm.
- Increased GIT motility → cramps & diarrhea.
- CNS effects → convulsion, coma and respiratory failure.
- Twitching of skeletal muscles → depolarization block → muscle weakness.

Treatment of organophosphate toxicity

- Prevent further absorption
- Support respiration
- Cholinesterase reactivators
- Atropine (to block Muscarinic & Central actions).

Cholinesterase reactivators (Oximes)

Pralidoxime (PAM)

- accelerate the hydrolytic regeneration of cholinesterase enzyme.
- They reactivate recently inhibited enzymes before aging.

Uses

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

New cholinergic Drugs

Cevimeline

- Direct acting cholinomimetics
- It is given orally.
- Increased salivation.
- Used for treatment of dry mouth symptom associated with Sjogren's syndrome.

Anticholinesterase drugs.

- Donepezil
- Tacrine
- Given orally.
- Treatment of dementia of Alzheimer's disease.

Indirect Cholinomimetic

Edrophonium.-	**Very Short 5-15min**	**Diagnosis of Myasthenia. Supraventricular tachycardia**
Neostigmine	**Short 0.5-2hr**	**Myasthenia gravis treatment Paralytic ileus Urinary retention curare toxicity**
Physostigmine	**Short 0.5-2hr**	**Glaucoma atropine toxicity**
Pyridostigmine	**Short 3-6**	**Myasthenia gravis treatment**
Ambenonium	**Short 4-8**	**Myasthenia gravis treatment**
Ecothiophate	**Long 100hr**	**Glaucoma.**

Anticholinergic drugs

What students should know:

Student should be able to describe:

- Kinetics of muscarinic antagonists
- The effects of atropine on the major organ systems.
- To list the clinical uses of muscarinic antagonists
- To know adverse effects & contraindications.
- To identify one antimuscarinic agent for each of the following special uses: mydriasis, cycloplegia, peptic ulcer & parkinsonism.

Anticholinergic Drugs (Cholinoreceptor blockers)

Nicotinic blockers.

- **Ganglionic blockers.**
- **Neuromuscular blockers.**

Muscarinic blockers (Parasympatholytics)

Classification of Antimuscarinics

1. Naturally occurring alkaloids.

   Atropine – Hyoscine

2. Synthetic atropine substitutes.

Naturally occurring alkaloids

Atropine

Hyoscine

Pharmacokinetics

- Tertiary amine ?
- Orally absorbed - Cross BBB
- Metabolized in the liver, excreted in urine.
- Has short duration of action on most organs except eye.

Mechanism of action

- Reversible competitive blockade of all muscarinic receptors **(NOT SELECTIVE).**

- Block muscarinic actions of Ach and other parasympathomimetics.

Pharmacological Effects

CNS

- CNS sedative action
- Vagal nucleus (CIC):

  Initial bradycardia & Tachycardia.
- Antiemetic effect (block vomiting center).
- antiparkinsonian effect (block basal ganglia).
- Toxic dose:

  Hyperthermia - excitement-hallucination.

Eye

- Passive mydriasis

  paralysis of circular muscle.
- Cycloplegia (loss of accommodation)

  paralysis of ciliary muscle.
- Loss of light reflex.
- ↑ I.O.P # glaucoma.
- ↓ Lacrimal secretion → sandy eye.

CVS

1. Heart

- Initial bradycardia followed by tachycardia.
- ↑ AV conduction (+ ve dromotropic effect).

2. Blood vessels

- **Therapeutic dose:** ↓ Vasodilatation induced by cholinomimetics.
- **Toxic dose:** Cutaneous vasodilatation → (atropine flush).

Secretions

- ↓ Salivary secretion → (Dry mouth).
- ↓ Sweating → Dry skin → Fever in infants and children.
- ↓ Bronchial secretion → ↑ Viscosity.
- ↓ Lacrimal secretion → Sandy eye.
- ↓ Gastric secretion → ↓ Gastric motility

GIT

- Relaxation of smooth muscles (constipation).
- ↓ GIT motility → Antispasmodic effect.
- ↑ Sphincter contractions.

Urinary Tract

- Relaxation of the ureter smooth muscles.
- Sphincter contraction.
- Urinary retention.

Bronchial Muscles

- Bronchial Relaxation
- ↓ Bronchial secretion → ↑ viscosity

Uses

1. preanesthetic medication to :
   - ↓ Salivary & bronchial secretion.
   - Protect the heart from excessive vagal tone.
2. Antispasmodic in renal & intestinal colics.
3. Cholinomimetic or organophosphorous poisoning.
4. Bradycardia (Myocardial infarction).

Adverse effects & Toxicity

- Blurred vision – Mydriasis
- Tachycardia - Atropine flush
- Urinary retention - Constipation.
- Dryness of mouth , Sandy eye
- Malignant hyperthermia.
- Hallucination, Excitationa (Toxic dose).

Treatment

- Gastric lavage.
- Anticonvulsant.
- Cooling blanket.
- **Antidote:** Physostigmine (IV slowly).

Contraindications

- Glaucoma.
- Tachycardia.
- Prostate hypertrophy in old patients.
- Constipation & paralytic ileus.
- Children

Hyoscine (SCOPOLAMINE)

What is difference between atropine and hyoscine?

Hyoscine

- Rapid onset of action
- Short duration
- Less mydriatic action (2-4 days).
- More CNS depressant action

  Sedation – Inhibition of vomiting center.
- Has amnesic action.
- Less CVS effect

Uses

- Preanesthetic medication
- Antiemetic action (Motion sickness).

Synthetic Atropine Substitutes

Eye For Funduscopic Examination of the eye.

Atropine	7 days.
Homatropine	24 hours.
Cyclopentolate	12 hours.
Tropicamide	6 hours.

GIT

Peptic ulcer

Pirenzepine (Selective M1 blocker)

Antispasmodic

Hyoscine butyl bromide

Oxyphenonium.

Propantheline.

Glycopyrrolate.

Parkinsonism

- Benztropine.
- Trihexphenidyl.

Bronchial Asthma

Ipratropium bromide

- Quaternary compound.
- Taken by inhalation (bronchodilator).
- Little effect on viscosity.

USES of antimuscarinics

- AS mydriatics.
- Bronchial asthma.
- Antispasmodic for intestinal and renal colics
- Traveller 's diarrhea
- Peptic ulcer
- Antiparkinsonian.
- Antiemetic, motion sickness (Hyoscine).
- Pre-anesthetic medication.
- Cholinomimetics intoxication

Direct cholinomimetic drugs

ACh	___
Methacholine	___
Carbachol	Paralytic ileus Urinary retention Glaucoma
Bethanechol	Paralytic ileus Urinary retention
Pilocarpine	Glaucoma
Cevimeline	Sjogren's syndrome.

Indirect cholinomimetic drugs (Anticholinesterases)

Edrophonium.-	Diagnosis of Myasthenia gravis. Supraventricular tachycardia
Neostigmine	Myasthenia gravis treatment , Paralytic ileus Urinary retention
Physostigmine	Glaucoma atropine toxicity
Ambenonium Pyridostigmine	Myasthenia gravis treatment
Ecothiophate Isofluorophate	Glaucoma.
Donepezil Tacrine	Alzheimer disease

Antimuscarinic drugs

Atropine	Preanesthetic medication - Antispasmodic
Hyoscine	Motion sickness - Preanesthetic medication Antispasmodic
Pirenzepine	Peptic ulcer
Ipratropium	Asthma
Benztropine	Parkinsonism
Dicyclomine Oxyphenonium	Antispasmodics
Tropicamide Cyclopentolate Homatropine	Fundus examination


Thank you