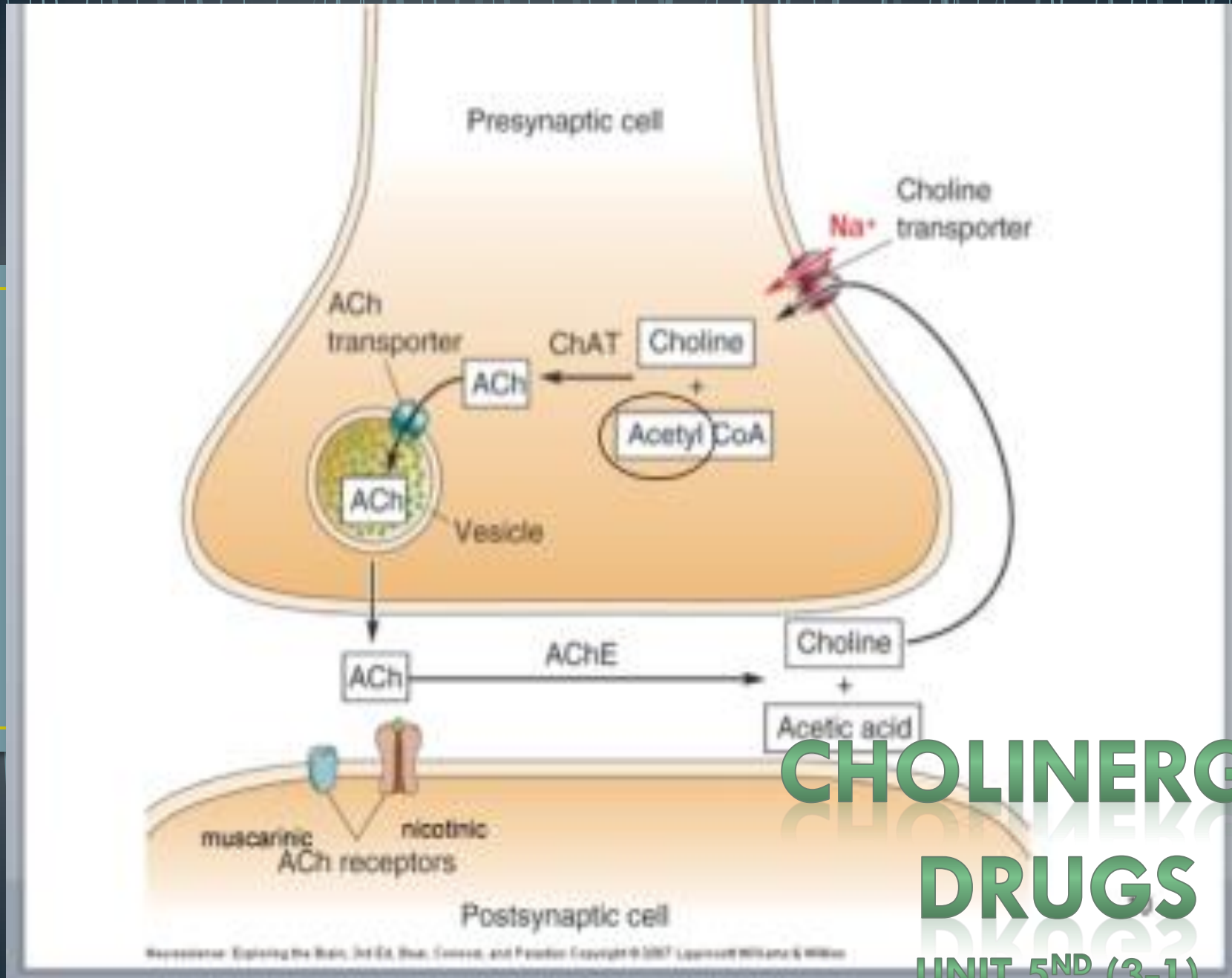



# CHOLINERGIC DRUGS

## UNIT 5ND (3-1)

# Introduction

- Drugs affecting the ANS are divided into two groups . According to the type of neurons involved in their mechanism of action

¬Cholinergics – Acts on the receptors stimulated by Ach

¬Adrenergics - Acts on the receptors stimulated by Norepinephrine

# Cholinergic agents

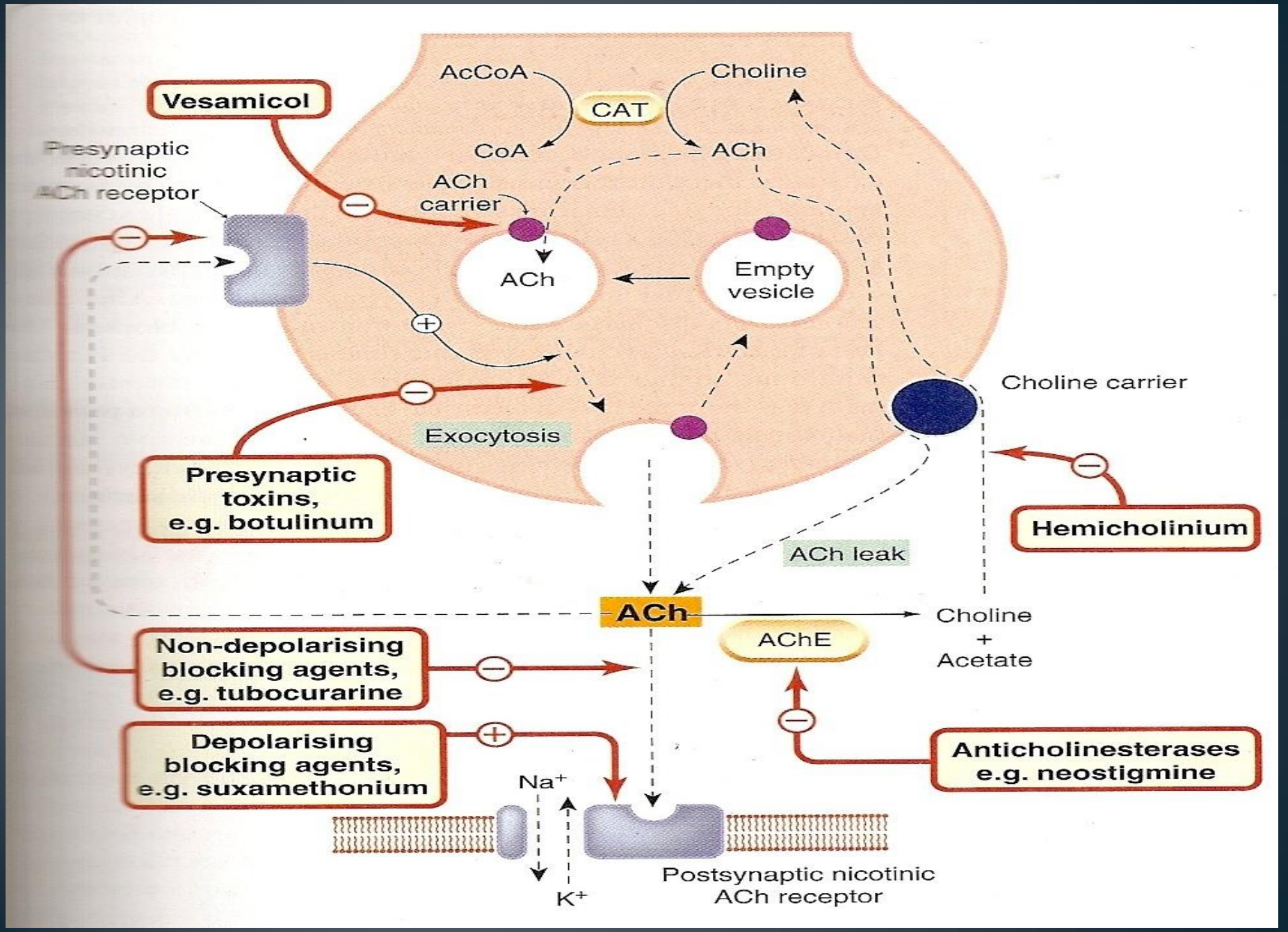
- Cholinergic agents are the drugs that either directly or indirectly produce effect similar to those elicited by Acetylcholine
- Dale while studying the pharmacological actions of Ach distinguished two types of activities which he designated as muscarinic and nicotinic

# Synthesis of Ach

- Choline is taken up into the nerve terminals by special choline transport system mediated by a carrier that cotransports sodium.
- The choline transport appears to be the rate limiting step
- It can be inhibited by hemicholinium.
- The choline is acetylated by the enzyme choline acetyl transferase to form Ach The acetyl group source is acetyl-coA

# Storage and Release of ach

- The Ach is packaged into vesicles by an active transport process coupled with the efflux of protons
- The mature vesicles also contain ATP and Proteoglycon
- When an action potential propagated voltage sensitive calcium channels in the presynaptic membrane opens causes an intracellular increase in calcium.
- Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and release of their contents into the synaptic cleft.
- This release can be blocked by botulinum toxin.
- Ach is degraded by acetylcholinesterase and forms choline and acetate in the synaptic cleft.


AcCoA
Choline
CAT
CoA
ACh
Vesamicol
Presynaptic nicotinic ACh receptor
ACh carrier
ACh
Empty vesicle
Choline carrier
Exocytosis
Presynaptic toxins, e.g. botulinum
Hemicholinium
ACh leak
ACh
Choline + Acetate
AChE
Non-depolarising blocking agents, e.g. tubocurarine
Depolarising blocking agents, e.g. suxamethonium
Anticholinesterases e.g. neostigmine
Na+
K+
Postsynaptic nicotinic ACh receptor

# Cholinoceptors

- Cholinergic receptors have been characterized as nicotinic and muscarinic on the basis of their ability to be bound by naturally occuring alkaloids nicotine and muscarine respectively

  NICOTINIC RECEPTORS
- It is a ligand gated cationic channel
- It is stimulated by nicotine and blocked by d-tubocurarine or hexamethonium.
- It is of two types

¬ N1: It is located at skeletal muscle end plate (neuro muscular junction ) .

It causes depolarisation of muscle end plate and contraction of skeletal muscles.

Agonist-nicotine,PTA

Antagonist-tubocurarine

¬ N2 :It is located at atonomic ganglia (depolarisation), adrenal medulla ( catechol release )and cns.

Agonist-hexamethonium.

# Muscarinic receptors

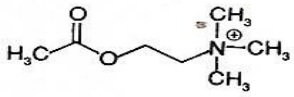
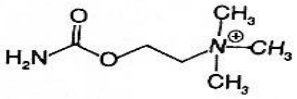
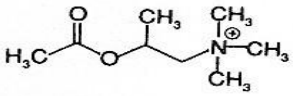
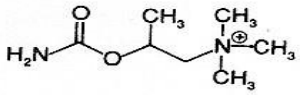
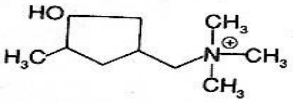
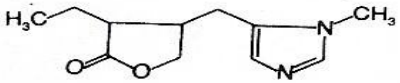
- M1:Neuronal receptors located on ganlion cells , cortex ,
- hippocampus and corpus striatum.
- Antagonist : pirenzepine  Agonist : oxotremorine
- Functions : learning , salivary secretions , memory , motor functions .
- M2 : Cardiac receptors
- Agonist : methacholine
  Antagonist : methoctramine
  Functions : vagal bradicardia, auto receptors
- M3 : It causes vasodilation through EDRF and smooth muscle contraction

¬ All the muscarinic receptors are G-protein couple receptors can be blocked by atropine .

# Classification
## cholinergic agonists

- Choline esters
  - Acetyl choline
  - Methacholine
  - Carbachol
  - Bethanechol
- Alkaloids
  - Muscarine
  - Pilocarpine
  - Arecoline

**Table 10.3** Muscarinic agonists

| Drug | Structure | Receptor specificity | | Hydrolysis by AChE | Clinical uses |
|---|---|---|---|---|---|
| | | *Musc* | *Nic* | | |
| Acetylcholine |  | +++ | +++ | +++ | None |
| Carbachol |  | ++ | +++ | — | None |
| Methacholine |  | +++ | + | ++ | None |
| Bethanechol |  | +++ | — | — | Bladder* and GI |
| Muscarine |  | +++ | — | — | None† |
| Pilocarpine |  | ++ | — | — | Glaucoma |
| Oxotremorine |  | ++ | — | — | None |

Musc, muscarinic; Nic, nicotinic.

*Necessary first to ensure that bladder neck is not obstructed.

†Cause of mushroom poisoning.

# Anticholinesterases

## Reversible

### Carbamates

Physostigmine
Neostigmine
edrophonium,

### Acridine

Tacrine

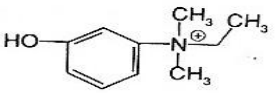
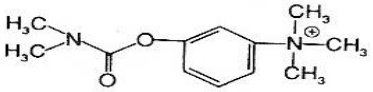
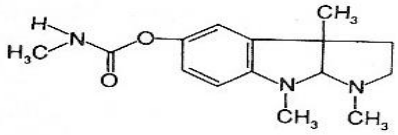
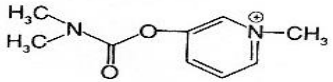
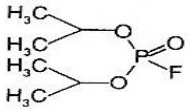
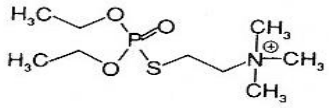
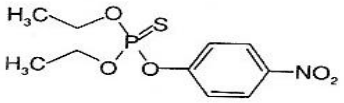
## Irreversible

### Organophosphates carbamates

Dyflos
Ecothiophate
Parathion
Tabun

Carbaryl

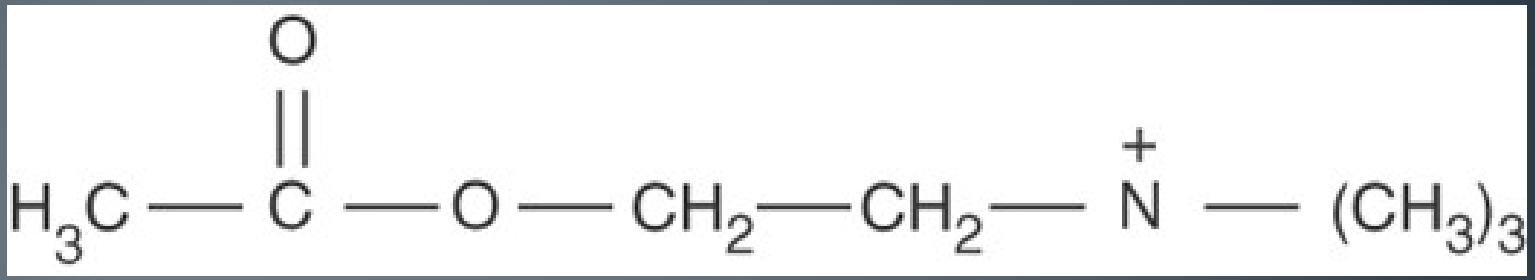
**Table 10.8** Anticholinesterase drugs

| Drug | Structure | Duration of action (long/medium/short) | Main site of action | Notes |
|---|---|---|---|---|
| Edrophonium |  | S | NMJ | Used mainly in diagnosis of myasther<br>Too short acting for therapeutic use |
| Neostigmine |  | M | NMJ | Used i.v. to reverse competitive neuromuscular block<br>Used orally in treatment of myasthenia<br>Visceral side-effects |
| Physostigmine |  | M | P | Used as eye drops in treatment of glau |
| Pyridostigmine |  | M | NMJ | Used orally in treatment of myasthenia<br>Better absorbed than neostigmine and longer duration of action |
| Dyflos |  | L | P | Highly toxic organophosphate, with very prolonged action<br>Has been used as eye drops for glauco |
| Ecothiopate |  | L | P | Used as eye drops in treatment of glauc<br>Prolonged action; may cause systemic e |
| Parathion |  | L | — | Converted to active metabolite by replac of sulfur by oxygen<br>Used as insecticide but commonly cause *poisoning in humans* |

*NMJ, neuromuscular junction; P, postganglionic parasympathetic junction; i.v., intravenous.*

# SAR

- structure of ach




## Modification of Quaternary Ammonium Group

- Methyl groups substituted with higher alkyl groups are inactive as agonist
- If all methyl groups are ethylated it shows antagonistic activity
- The positive charge is necessary for its activity
- If all methyl groups are replaced by H ion it losts its activity

# Modification of ethylene bridge

- Introduction of alkyl group will rapidly reduce activity
- Rule of five : Ing postulated that there should not be more than five atoms between nitrogen and the terminal hydrogen atom for maximal activity
- Introduction of methyl group on the beta carbon forms methacholine
- Introduction of methyl group on alpha carbon will leads to less active compound
- Addition of one or two ethyl groups will form chiral molecules

# Modification of acloxy group

- As predicted by the rule of five If the acetyl group is replased by higher homologues the resulting esters are less potent and instead they have antagonistic activity
- The esters derived from carbamic acid are referred to as carbamates and they are more stable than carboxylate esters to hydrolysis

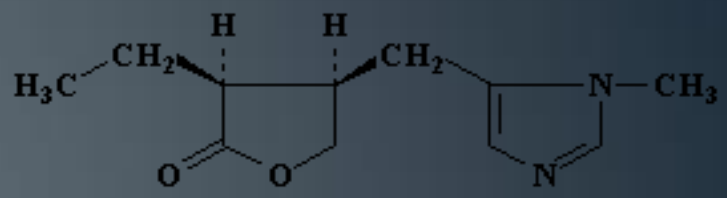
  Ex: carbachol
- Carbachol is less hydrolyzed by AchE, gastric acid and butyryl cholinesterase so it can be given orally

# Pilocarpine

- Structure

Pilocarpine

$C_{11}H_{16}N_2O_2$



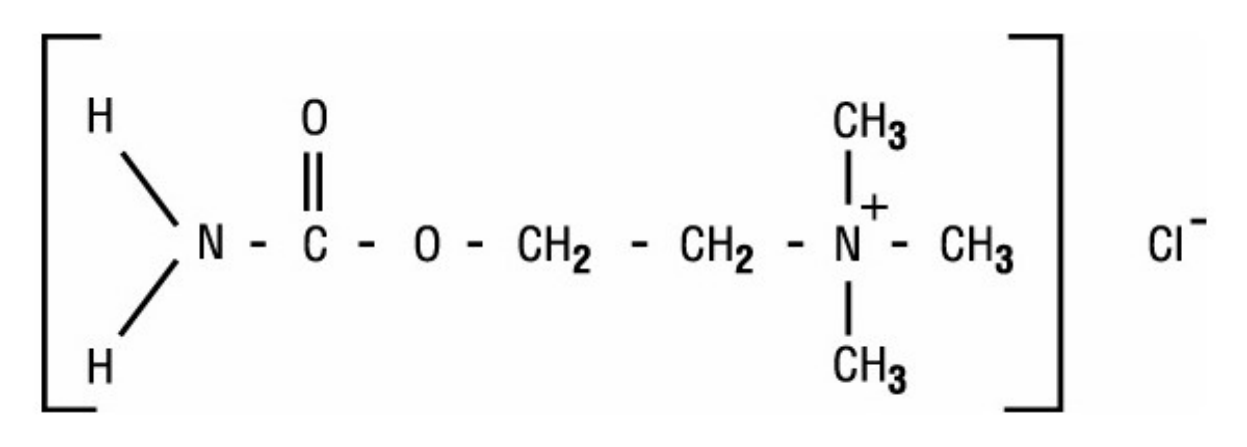

- preparation: The alkaloid is extracted from leaves of P.microphyllus with alcohol and Hcl .the solvents is evaporated and residue is treated with ammonia the acquous filtrate isbasified with strong ammonia. Then treated with chloroform and the solvent is distilled and add dil. Nitric acid and allow to crystallise
- Uses : It is a non selective agonist and acts on all muscarinic receptors mainly on M3 and causes smooth muscles to contract in gut,trachea and eye

In eye it produces pupillary constriction and spasm of accomidation (cycloplegia)

The pupillary constriction and spasm of accomidation will reduce intra ocular tension by establishing better drianage of occular fluid through the canal of schlemm so used in treatment of glaucoma

# Carbachol

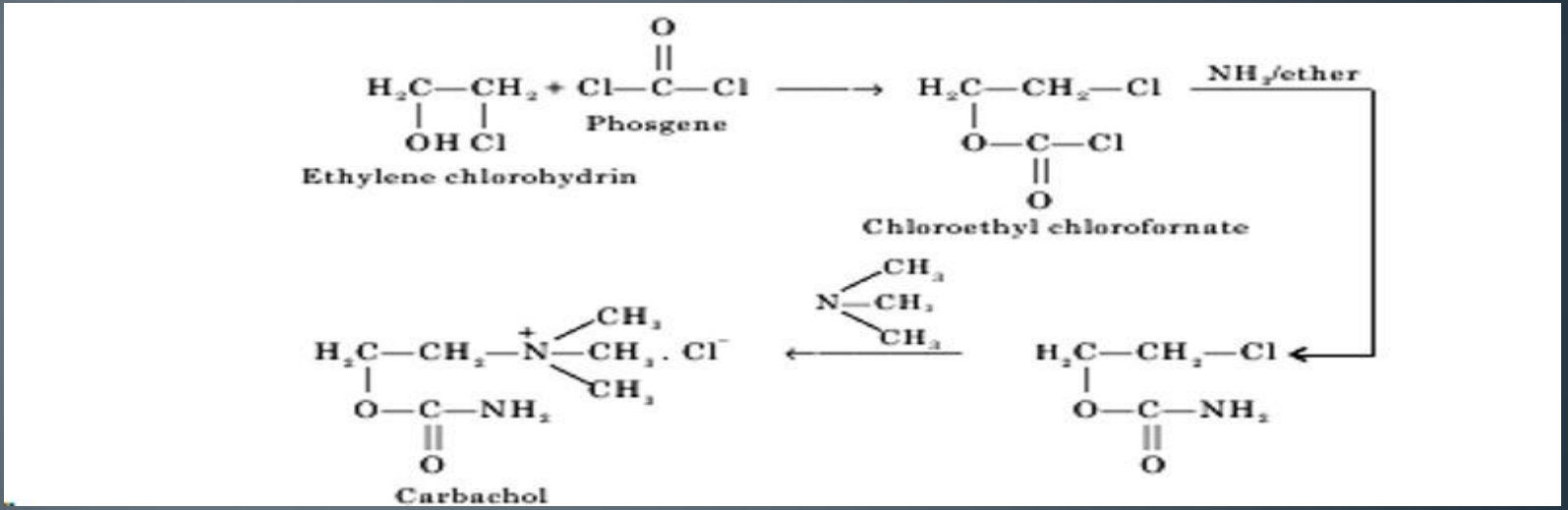
- Structure



- Ethanaminium 2-[(aminocarbonyl) oxy]- N, N, N-trimethyl-chloride

# Carbachol

- SYNTHESIS




- Properties : Faintly yellow crystalline ,hygroscopic powder
  Melts at 200 to 204 degrees
  Pka : 4.8

# Uses of Carbachol

- Narrow angle glaucoma
- To induce miosis prior to occular surgery
- It is less suceptible to hydrolysis so it is more stable in aqueous solution

# CONCLUSION

- The cholinergic drugs are the drugs that mimics the actions of the parasympathetic system and used in treating many diseases like glaucoma , xerostomia , myasthenia gravis etc

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3) S.N.Pandeya text book of medicinal chemistry
4) Text book of Pharmacology by Rang and Dale