DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM
PART-III: CHOLINERGIC SYSTEM AND DRUGS- PARASYMPATHOMIMETIC AGENTS

Presented By:
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OUTLINE OF PRESENTATION

- **Cholinergic neurotransmitters:**
  - Biosynthesis and catabolism of acetylcholine.
  - Cholinergic receptors (Muscarinic & Nicotinic) and their distribution.
- **Parasympathomimetic agents:** SAR of Parasympathomimetic agents
  - **Direct acting agents:** Acetylcholine, Carbachol*, Bethanechol, Methacholine, Pilocarpine.
  - **Indirect acting/ Cholinesterase inhibitors (Reversible & Irreversible):** Physostigmine, Neostigmine*, Pyridostigmine, Edrophonium chloride, Tacrine hydrochloride, Ambenonium chloride, Isofluorphate, Echothiophate iodide, Parathione, Malathion.
  - **Cholinesterase reactivator:** Pralidoxime chloride.

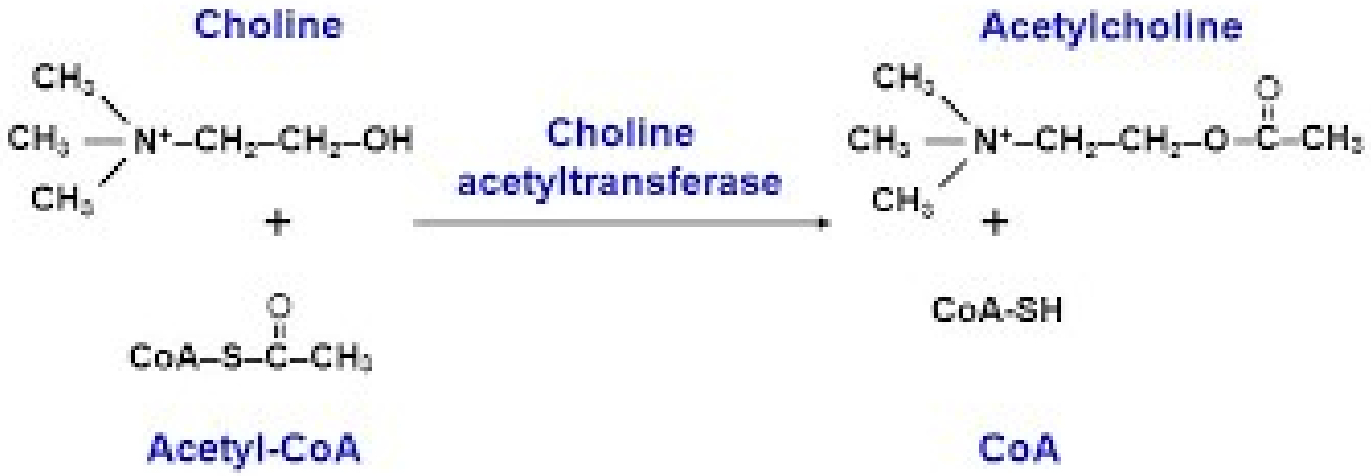
CHOLINERGIC NEUROTRANSMITTERS

- Acetylcholine (ACh) is a major neurotransmitter at autonomic, somatic as well as central sites.
- Obviously, it is a major neurotransmitter at parasympathetic nervous system.
- For this reason, parasympathetic nervous system is also known as cholinergic nervous system.

BIOSYNTHESIS AND CATABOLISM OF ACETYLCHOLINE

Synthesis:

- Acetylcholine is synthesized locally in the cholinergic nerve endings by the following pathway—



Choline is actively taken up by the axonal membrane by a Na+: choline cotransporter and acetylated with the help of ATP and coenzyme-A by the enzyme *choline acetyl transferase present* in the axoplasm.

BIOSYNTHESIS AND CATABOLISM OF ACETYLCHOLINE

Storage:

- Most of the Ach is stored in ionic solution within small synaptic vesicles, but some free ACh is also present in the cytoplasm of cholinergic terminals.

Release:

- Release of ACh from nerve terminals occurs

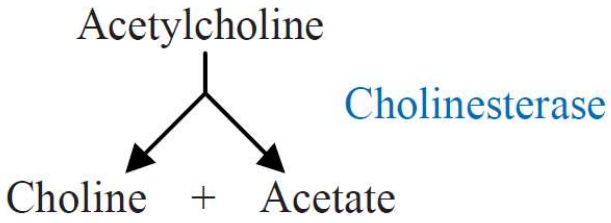
in small quanta—amount contained in individual vesicles is extruded by exocytosis.

- In response to a nerve Action Potential synchronous release of multiple quanta triggers postjunctional events.

BIOSYNTHESIS AND CATABOLISM OF ACETYLCHOLINE

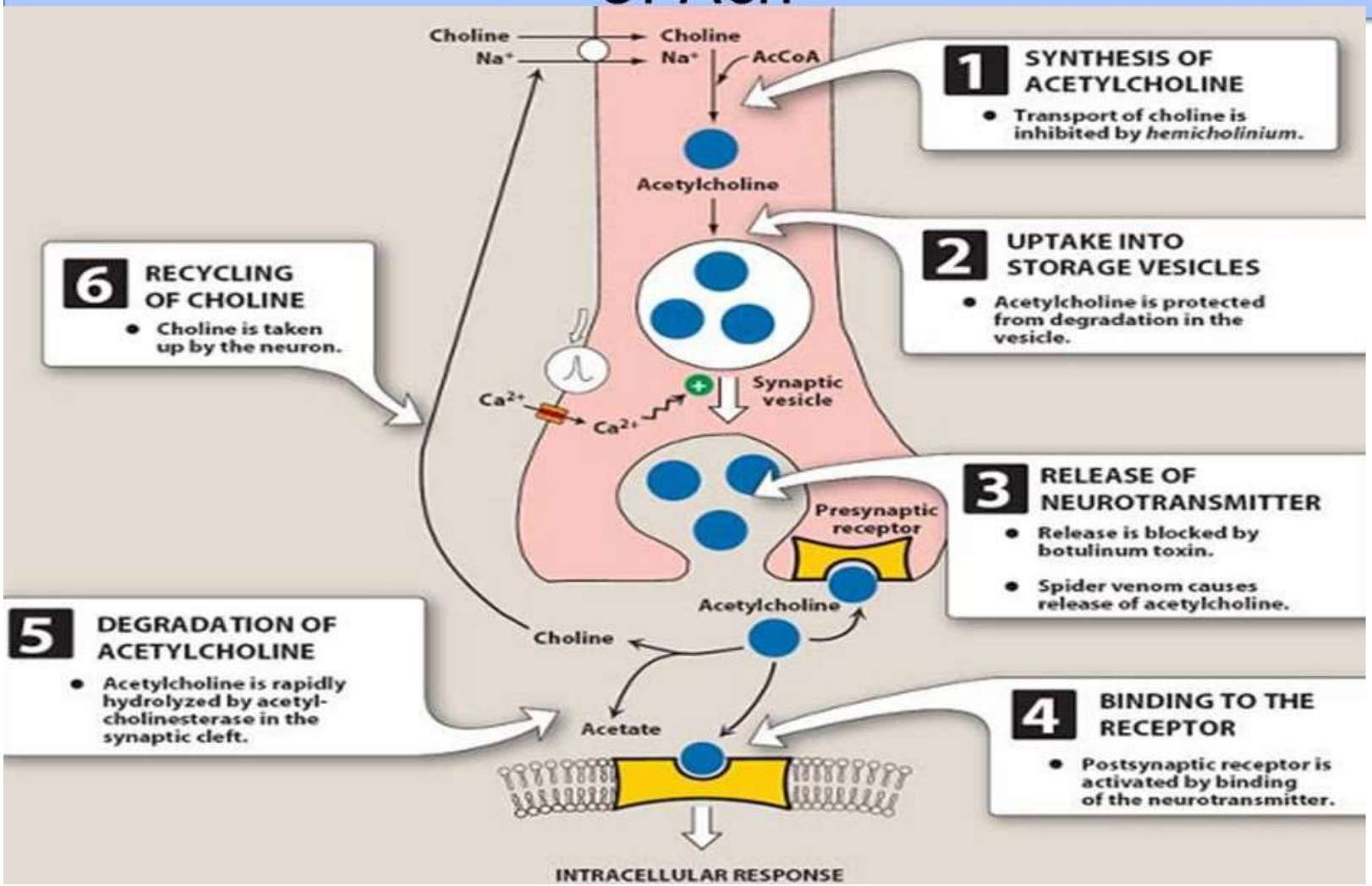
Degradation by Cholinesterase :

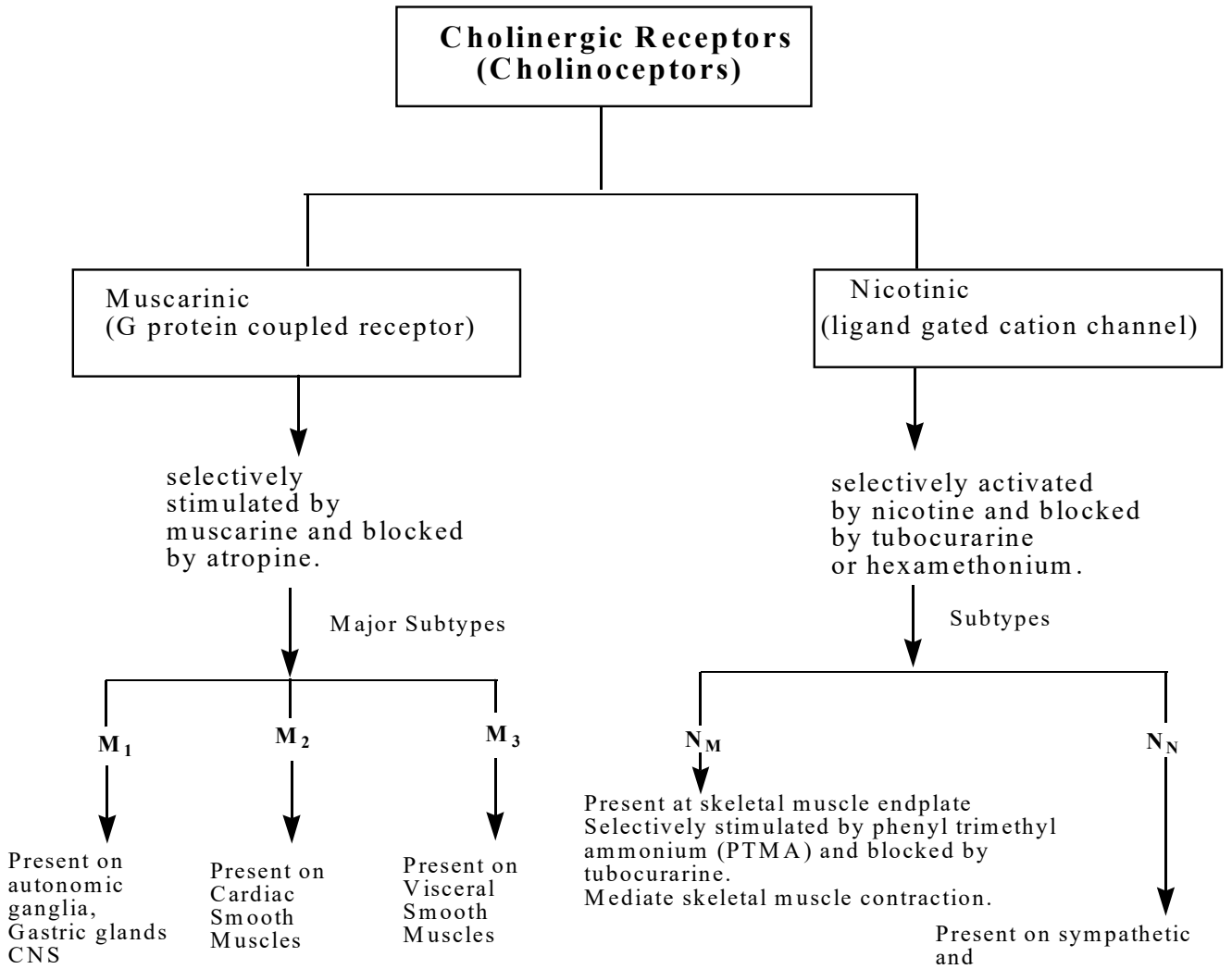
- Immediately after release, Ach is hydrolyzed by the enzyme cholinesterase and choline is recycled.



- A specific (*Acetylcholinesterase*—AChE or true cholinesterase) and a nonspecific (*Butyrylcholinesterase—BuChE or* pseudocholinesterase) type of enzyme occurs in the body; while AChE is strategically located at all cholinergic sites and serves to inactivate ACh instantaneously, BuChE present in plasma and elsewhere probably serves to metabolize ingested esters.

Synthesis, Storage, release & degradation of Ach





NOTE:
— ACh activates and atropine blocks all 3 subtypes of muscarinic receptors.
— The CNS contains all subtypes of muscarinic receptors, but M1 appear to predominate.
— Most smooth muscles and glands have both M2 and M3 subtypes; M3 predominates.

DISTRIBUTION AND FUNCTIONS OF MUSCARINIC RECEPTORS

	M_1		M_2	M_3
1. Location and function subserved	*Autonomic ganglia:* *Gastric glands:* *CNS:*	Depolarization (late EPSP) Hist. release, acid secretion Learning, memory, motor functions	*SA node:* Hyperpolarization, ↓ rate of impulse generation *AV node:* ↓ velocity of conduction *Atrium:* shortening of APD, ↓ contractility *Ventricle:* ↓ contractility (slight) (receptors sparse) *Cholinergic nerve endings:* ↓ ACh release *CNS:* tremor, analgesia *Visceral smooth muscle:* contraction	*Visceral smooth muscle:* contraction *Iris:* constriction of pupil *Ciliary muscle:* contraction *Exocrine glands:* secretion *Vascular endothelium:* release of NO→ vasodilatation
2. Nature	Gq-protein coupled		Gi/Go-protein coupled	Gq-protein coupled
3. Transducer mechanism	IP_3/DAG—↑ cytosolic Ca^{2+}, PLA_2↑—PG synthesis		K^+ channel opening, ↓ cAMP	IP_3/DAG—↑ cytosolic Ca^{2+} PLA_2↑—PG synthesis
4. Agonists*	MCN-343A, Oxotremorine		Methacholine	Bethanechol
5. Antagonists*	Pirenzepine, Telenzepine		Methoctramine, Tripitramine	Solifenacin, Darifenacin

*Relatively selective

— ACh activates and atropine blocks all 3 subtypes of muscarinic receptors.

— The CNS contains all subtypes of muscarinic receptors, but M1 appear to predominate.

— Most smooth muscles and glands have both M2 and M3 subtypes; M3 predominates.

DISTRIBUTION AND FUNCTIONS OF NICOTINIC RECEPTORS

	N_M	N_N
1. Location and function subserved	*Neuromuscular junction:* depolarization of muscle end plate —contraction of skeletal muscle	*Autonomic ganglia:* depolarization —postganglionic impulse *Adrenal medulla:* catecholamine release *CNS:* site specific excitation or inhibition
2. Nature	Has intrinsic ion channel, pentamer of α2 β ε or γ and δ subunits, each subunit has 4 TM segments	Has intrinsic ion channel, pentamer of only α or α,β subunits, each subunit has 4 TM segments
3. Transducer mechanism	Opening of cation (Na^+, K^+) channels	Opening of cation (Na^+, K^+, Ca^{2+}) channels
4. Agonists	PTMA, Nicotine	DMPP, Nicotine
5. Antagonists	Tubocurarine, α-Bungarotoxin	Hexamethonium, Trimethaphan

PARASYMPATHOMIMETIC AGENTS (CHOLINERGIC DRUGS, CHOLINOMIMETIC DRUGS)

- These are drugs which produce actions similar to that of ACh, either by directly interacting with cholinergic receptors (cholinergic agonists) or by increasing availability of ACh at these sites *(anticholinesterases)*.

ACTIONS OF ACETYLCHOLINE

Muscarinic actions

Heart: it decreases the heart rate and cardiac output.

Blood vessels: vasodilatation and decreases BP.

GIT: It increases the salivary & intestinal secretion.Increases intestinal motility and relaxes sphincters

Respiratory system: bronchoconstriction & Increased secretions.

Eyes: Miosis (constriction of pupil). Accommodation of near vision. Decrease the IOP due to increase in the out flow of aqueoushumor.

Genitourinary tract: it causes: Urination.Erection of genital in male.

CNS: it causes excitatory effect and effect on the learning, short term memory and arousal.

Nicotinic actions

Neuromuscular Junction: contraction of skeletal muscles. Stimulates both sympathetic and parasympathetic ganglia. Stimulates the release of adrenaline from the adrenal medulla and chromoffin.

In CNS: stimulates the release of ADH at the hypothalamus.

Therapeutic uses: Used as eye drop to produce rapid and complete miosis after cataract surgery.

CLASSIFICATION OF CHOLINERGIC AGENTS

DIRECTLY ACTING

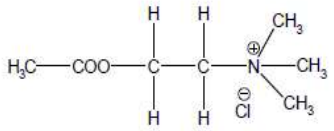
CHOLINERGIC AGONISTS

Choline esters	*Alkaloids*
Acetylcholine	Muscarine
Methacholine	Pilocarpine
Carbachol	Arecoline
Bethanechol	

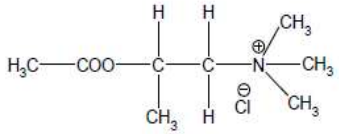
I. Directly acting cholinergic drugs

A. Choline esters

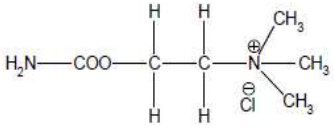
i. Acetyl choline



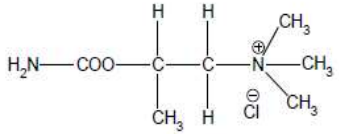
ii. Methacholine



iii. Carbachol

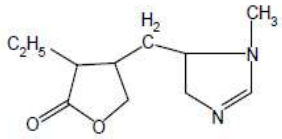


iv. Bethanechol

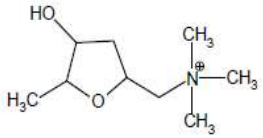


B. Cholinomimetic alkaloids

i. Pilocarpine



ii. Muscarine



INDIRECTLY ACTING

ANTICHOLINESTERASES

Reversible

Carbamates	*Acridine*
Physostigmine (Eserine)	Tacrine
Neostigmine	
Pyridostigmine	
Edrophonium	
Rivastigmine, Donepezil	
Galantamine	

Irreversible

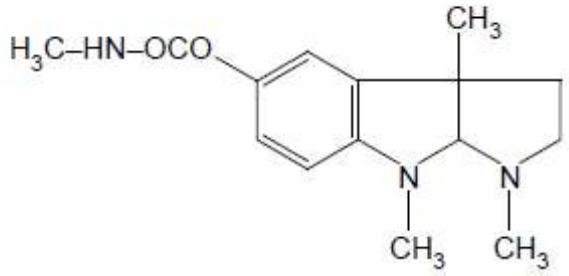
Organophosphates	*Carbamates*
Dyflos (DFP)	Carbaryl* (SEVIN)
Echothiophate	Propoxur* (BAYGON)
Malathion*	
Diazinon* (TIK-20)	
Tabun[£], Sarin[£], Soman[£]	

*Insecticides
[£]Nerve gases for chemical warfare

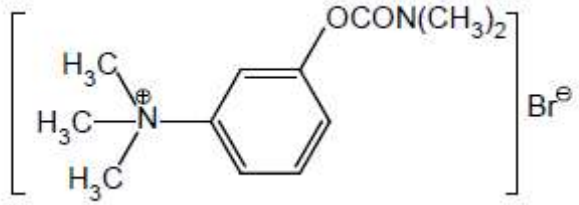
II. Indirectly acting cholinergic drugs

A Reversible cholinesterase inhibitors

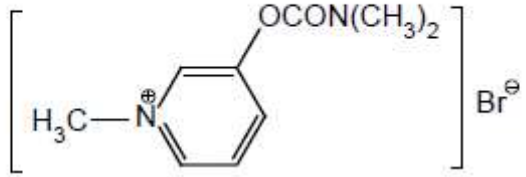
i. Physostigmine (Eserine)



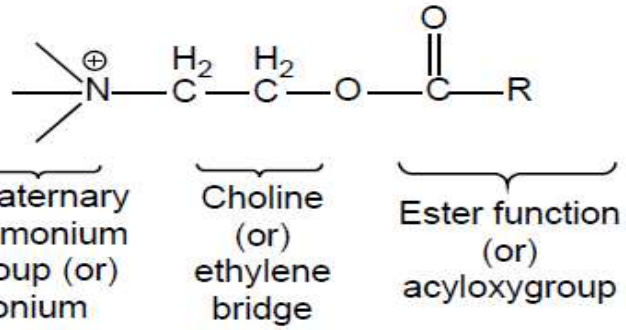
ii. Neostigmine bromide (Pristigmine)



iii. Pyridostigmine bromide (Mestinon)



SAR OF PARASYMPATHOMIMETIC AGENTS



- Acetylcholine can exist in a number of conformations. Four of these conformations are synplanar, synclinal, anticlinal, and antiplanar.
- The most active isomer is the (+) *trans enantiomer and it is identical to synclinal conformation of* acetylcholine.
- The muscarinic receptors and acetylcholinesterase display stereoselectivity, the (S) enantiomer of methacholine is equipotent with acetylcholine, while the R (–) enantiomer is about 20-fold less potent.

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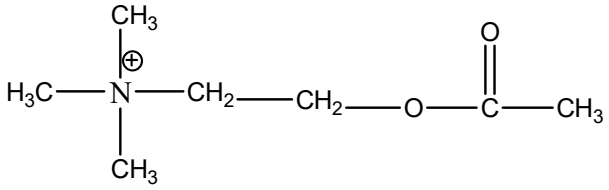

Acetylcholine

I. Modification of Quaternary Ammonium Group

- The quaternary ammonium group is essential for intrinsic activity, and contributes to the affinity of the molecule for the receptors, partially through the binding energy and partially because of its action as a detecting group.
- The trimethyl ammonium group is the optimal functional moiety for the activity, although some exceptions are known (e.g. pilocarpine, nicotine, and oxotremorine), and it shows maximal muscarinic activity.
- Placement of primary, secondary, or tertiary amines leads to decrease in activity.

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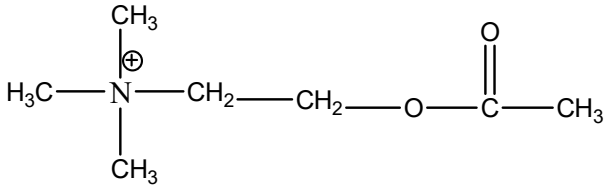

Acetylcholine

II. Modification of acyloxy group

- The ester group of ACh contributes to the binding of the compound to the muscarinic receptor.
- Replacement of methyl group by ethyl or large alkyl groups produces inactive compounds.
- Esters of aromatic or higher molecular weight acids possess cholinergic antagonist activity.

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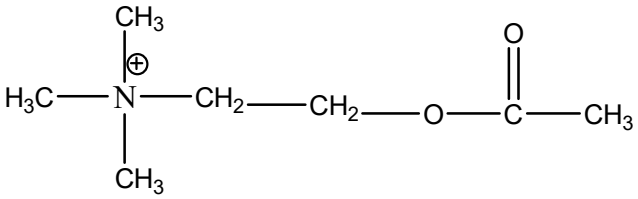


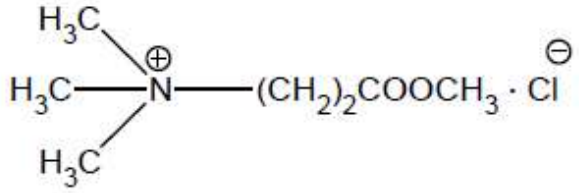
Acetylcholine

III. Modification of ethylene bridge

- The methyl ester is rapidly hydrolyzed by cholinesterase to choline and acetic acid. To reduce susceptibility to hydrolysis, carbamate esters of choline (carbachol) were synthesized and were found to be more stable than carboxylate esters.
- Placement of α-substitution in choline moiety results in a reduction of both nicotinic and muscarinic activity, but muscarinic activity to a greater extent.
- Incorporation of ß-substitution leads to reduction of nicotinic activity to greater extent.
- Replacement of ester group with ether or ketone produces chemically stable and potent compounds.

DIRECT-ACTING CHOLINERGIC AGENTS

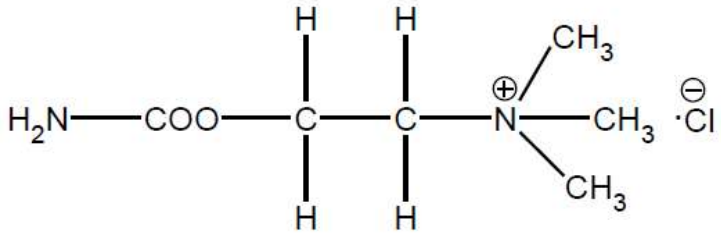
ACETYLCHOLINE



(2-Acetoxyl ethyl)-trimethyl ammonium chloride

- It is a direct-acting cholinergic agent which exerts its effects by stimulating muscarinic/nicotinic receptors.
- It is a topical ophthalmic drug to induce miosis, during certain intraocular surgical procedures, such as cataract surgery, ridectomy, penetrating keratoplasty, and other anterior-segment surgery.
- Systemically administered Ach is rapidly hydrolyzed by acetylcholinesterase, hence, it has no clinical use.
- It is a cardiac depressant and effective vasodilator.

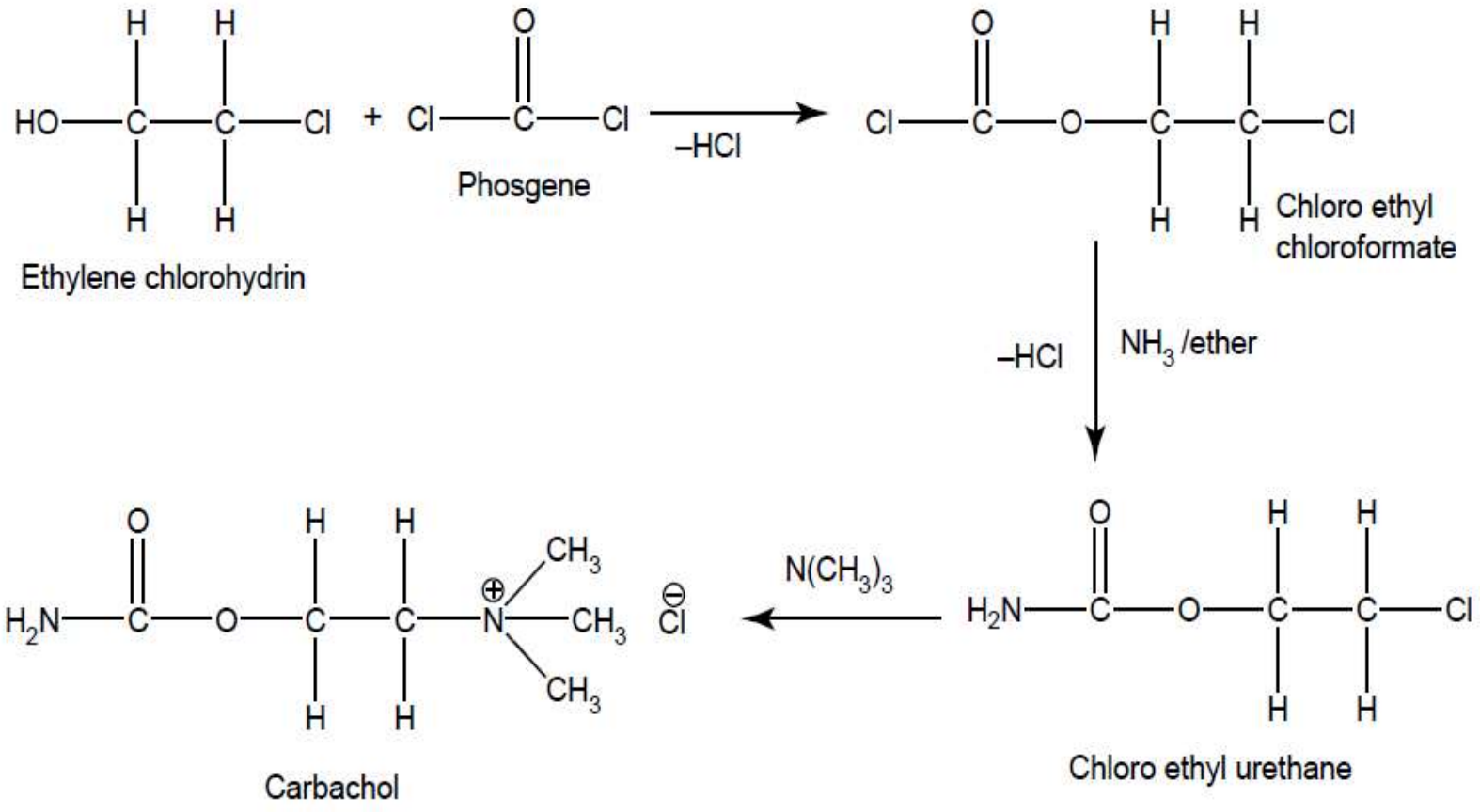
CARBACHOL*



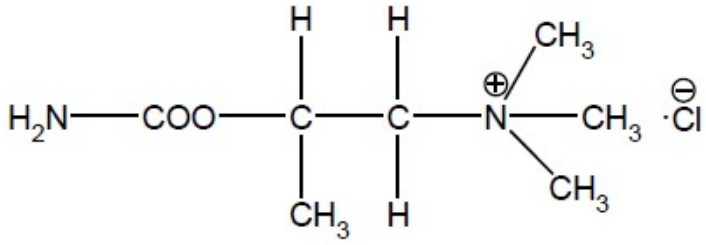
2-[(Amino carbonyl oxy]-*N*,*N*,*N*-trimethyl ethan ammonium chloride

- **Carbachol** is an ester of carbamic acid with the terminal methyl group of Ach is replaced by amino group.
- It possesses both muscarinic and nicotinic properties by cholinergic receptor stimulation.
- It is more slowly hydrolyzed by acetylcholinesterase.
- It is used for its miotic actions in the treatment of glaucoma to reduce intraocular pressure.

SYNTHESIS OF CARBACHOL



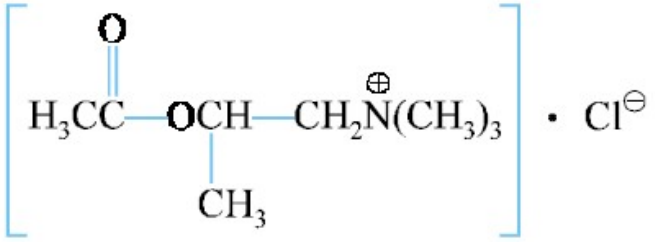
BETHANECHOL CHLORIDE



2-[(Amino carbonyl) oxy] *N, N, N trimethyl propan ammonium chloride*

- **Bethanechol** chloride is a synthetic ester which is structurally and pharmacologically related to acetylcholine.
- Unlike acetylcholine, **bethanechol** is not hydrolyzed by cholinesterase and will therefore have a long duration of action.
- The presence of –CH3 gives prolonged activity due to steric hindrance.
- It produces smooth muscle contractions.
- It is not well absorbed from the gastro-intestinal tract.
- It can be given subcutaneously, but not by intramuscular (IM) or intravenous (IV) because of its severe side effects.
- It is used to relieve urinary retention and abdominal distention after surgery.
- This is one of the postvagotomy gastric drug.

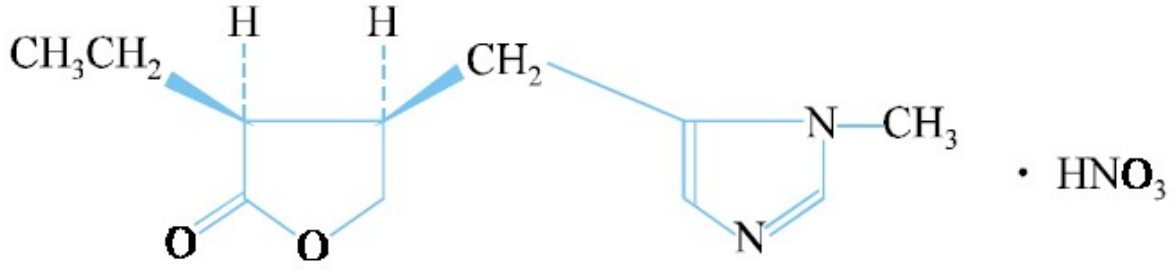
METHACHOLINE CHLORIDE



(2-Hydroxypropyl)trimethylammonium chloride acetate;

- **Methacholine** chloride is the ß-methyl homolog of acetylcholine and differs from the latter primarily in its greater duration and selectivity of action.
- It is found to be more muscarinic than nicotinic in its actions.
- Its actions on the cardiovascular system are more marked and pronounced.
- It has been used successfully to terminate attacks of supraventricular paroxysmal tachycardia.

PILOCARPINE NITRATE



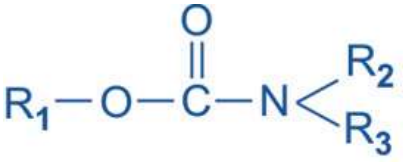
2(3H-Furanone, 3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl) methyl]-(3S-*cis)-*, *mononitrate*

- Pilocarpine is an alkaloid obtained from the dried leafl ets of *Pilocarpus jaborandi and Pilocarpus microphyllus in which it occurs to the extent of about 0.5% together with other* alkaloids.
- Pilocarpine is a nonselective agonist on the muscarinic receptors.
- It is mostly used as a solution (1 to 5%) to exert an action on the eye to cause miosis and retard intraocular tension in the treatment of open-angle glaucoma.

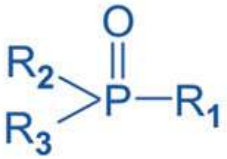
INDIRECT ACTING/ CHOLINESTERASE INHIBITORS

CHOLINESTERASE INHIBITORS (ANTICHOLINESTERASES)

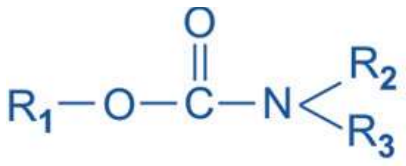
- Anticholinesterases (anti-ChEs) are agents which inhibit ChE, protect ACh from hydrolysis—produce cholinergic effects *in vivo and potentiate* ACh both *in vivo and in vitro*.
- *Some anti ChEs* have additional direct action on nicotinic cholinoceptors.
- Anti-ChEs are either esters of carbamic acid or derivatives of phosphoric acid.



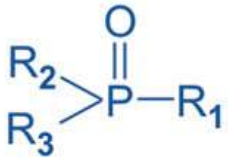
CARBAMATES



ORGANOPHOSPHATES



CARBAMATES

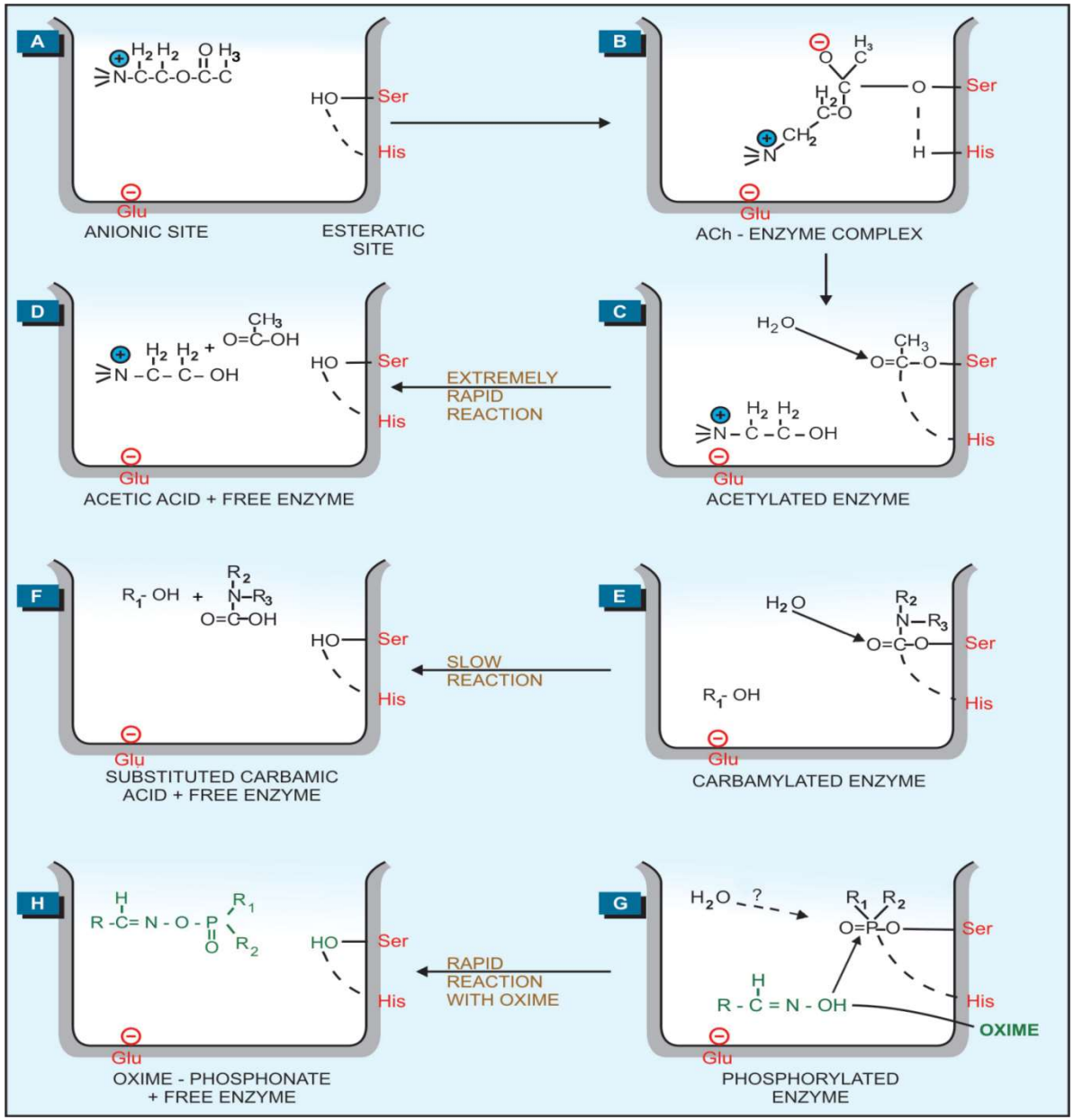


ORGANOPHOSPHATES

- In some carbamates R_1 may have a nonpolar tertiary amino N, e.g. in physostigmine, making the compound lipid soluble.
- In others, e.g. neostigmine, R1 has a quaternary N^+—making it water soluble.
- All organophosphates are highly lipid soluble except echothiophate which is water soluble.

MECHANISM OF ACTION OF ANTICHOLINESTERASES

- The anti-ChEs react with the enzyme essentially in the same way as ACh. The carbamates and phosphates respectively carbamylate and phosphorylate the esteratic site of the enzyme.
- Whereas the acetylated enzyme reacts with water extremely rapidly and the esteratic site is freed in a fraction of a millisecond, the carbamylated enzyme (reversible inhibitors) reacts slowly (Fig. F) and the phosphorylated enzyme (irreversible inhibitors) reacts extremely slowly or not at all (Fig.G).

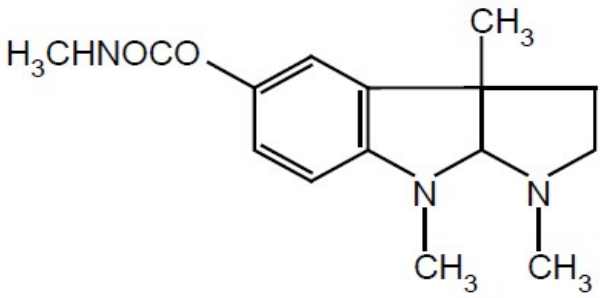


Schematic representation of reaction of acetylcholine (A–D), or carbamate anticholinesterase (E, F), or organophosphate anticholinesterase (G) with cholinesterase enzyme; and reactivation of phosphorylated enzyme by oxime (G, H). Ser—Serine; His—Histidine; Glu—Glutamic acid.

COMPARATIVE FEATURES OF PHYSOSTIGMINE AND NEOSTIGMINE

	Physostigmine	*Neostigmine*
1. Source	Natural alkaloid from *Physostigma venenosum* (Calabar bean)	Synthetic
2. Chemistry	Tertiary amine derivative	Quaternary ammonium compound
3. Oral absorption	Good	Poor
4. CNS actions	Present	Absent
5. Applied to eye	Penetrates cornea	Poor penetration
6. Direct action on N_M cholinoceptors	Absent	Present
7. Prominent effect on	Autonomic effectors	Skeletal muscles
8. Important use	Miotic (glaucoma)	Myasthenia gravis
9. Dose	0.5–1 mg oral/parenteral 0.1–1.0% eye drops	0.5–2.5 mg i.m./s.c. 15–30 mg orally
10. Duration of action	Systemic 4–6 hrs In eye 6 to 24 hrs	3–4 hrs.

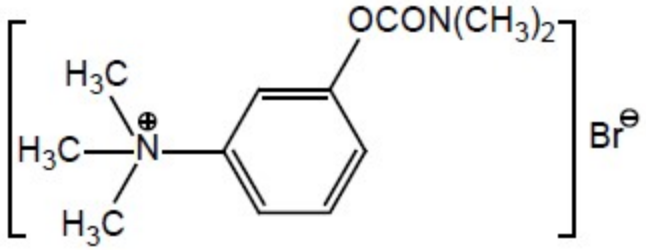
PHYSOSTIGMINE



[(3*aR*,8*bS*)-3,4,8*b*-trimethyl-2,3*a*-dihydro-1*H*-pyrrolo[2,3-b]indol-7-yl] *N*-methylcarbamate

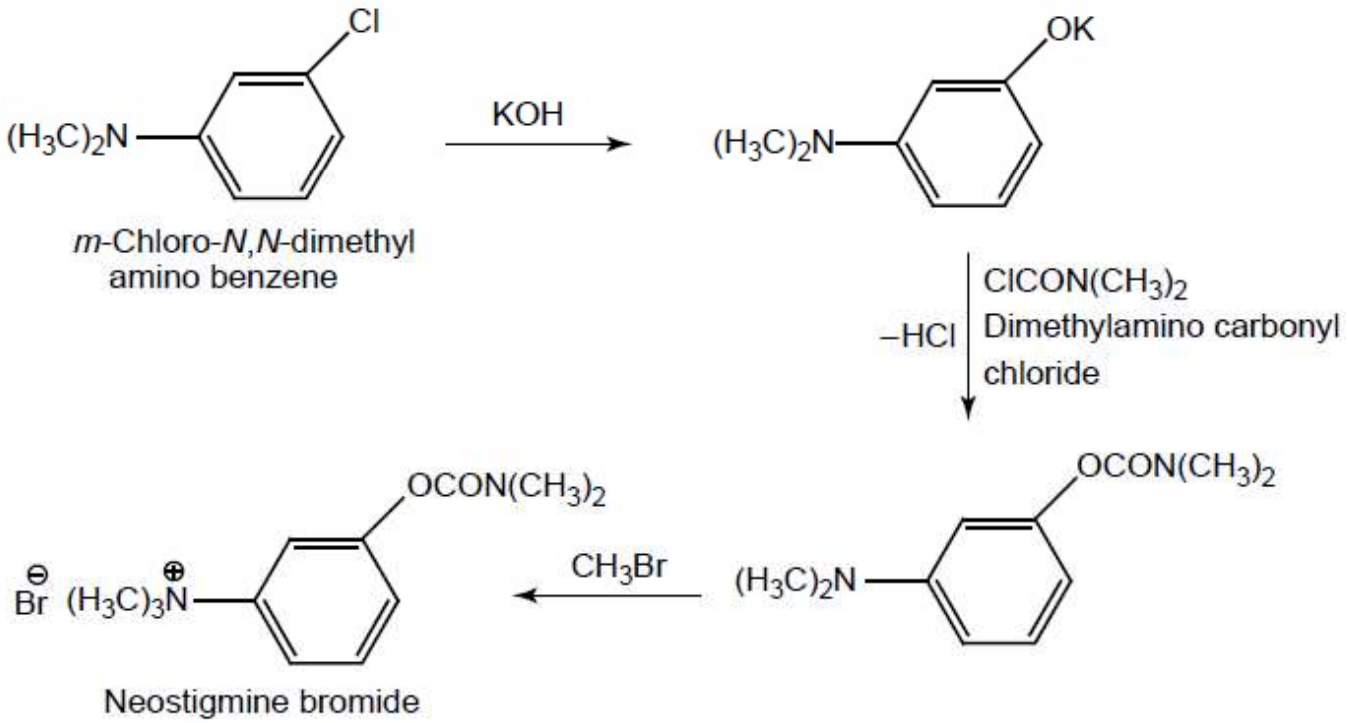
- It is an alkaloid obtained from the dried ripe seeds of *Physostigma venenosum*.
- **Physostigmine** is a parasympathomimetic, specifically, a reversible cholinesterase inhibitor which effectively increases the concentration of acetylcholine at the sites of cholinergic transmission.
- It is a carbamate ester and an indole alkaloid.
- It has a role as a miotic (for treatment of glaucoma) and an antidote to curare poisoning.
- It can penetrate the blood brain barrier and is employed to antagonize the toxic CNS effects of antimuscarinic drugs, tricyclic depressants, H1 antihistamines, and benzodiazepines.
- It is also used in the treatment of Alzheimer's disease.

NEOSTIGMINE BROMIDE*



3-{[(Dimethyl amino) carbonyl] oxy}-*N, N, N-trimethyl benzene ammonium bromide*.

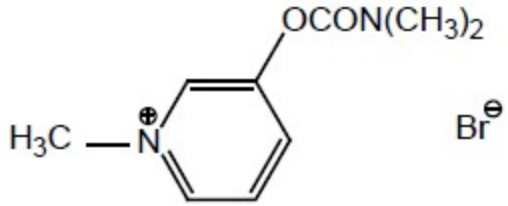
Synthesis:



NEOSTIGMINE BROMIDE

- Neostigmine is used in the treatment of Myasthenia gravis.
- Myasthenia gravis is an autoimmune disorder affecting about 1 in 10,000 population, due to development of antibodies directed to the nicotinic receptors (NR) at the muscle endplate which causes reduction in number of free NM cholinoceptors to 1/3 of normal or less and structural damage to the neuromuscular junction.
- This results in weakness and easy fatigability on repeated activity, with recovery after rest.
- Neostigmine and its congeners improve muscle contraction by allowing Ach released from prejunctional endings to accumulate and act on the receptors over a larger area, as well as by directly depolarizing the endplate.

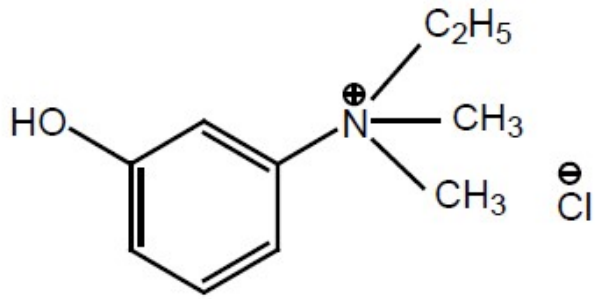
PYRIDOSTIGMINE



3-{[(Dimethyl amino) carbonyl] oxy}-1- methyl-pyridinium bromide

- Pyridostigmine is a reversible cholinesterase inhibitor with a slightly longer duration of action than neostigmine.
- It is used in the treatment of myasthenia gravis and it antagonizes the effects of neuromuscular blocking (NMB) agents.

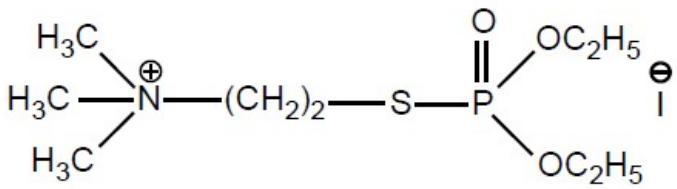
EDROPHONIUM CHLORIDE



Ethyl (*m-hydroxy phenyl) dimethyl ammonium chloride*

- **edrophonium**, a short and rapid-acting cholinesterase inhibitor with parasympathomimetic activity.
- On parenteral administration, edrophonium has a more rapid onset and shorter duration of action than neostigmine, pyridostigmine, or ambenonium.
- It is used as an antiarrhythmic drug in paroxymal atrial tachycardia.
- It is also used in the diagnosis of myasthenia gravis.

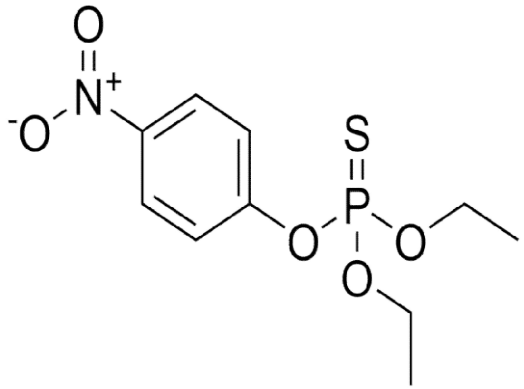
ECHOTHIOPHATE IODIDE



2-[(Diethoxyphosphonyl) thio] *N,N,N-trimethyl ethanammonium iodide*

- It is a long-acting irreversible anti-AchE drug, used in the treatment of glaucoma.

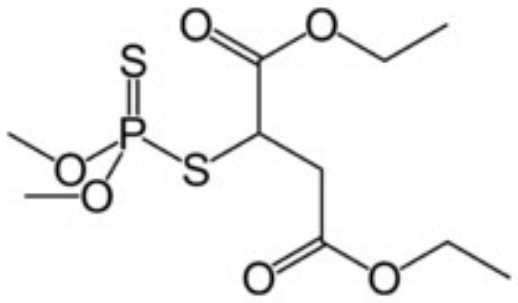
PARATHION



diethoxy-(4-nitrophenoxy)-sulfanylidene-λ^5-phosphane

- It is an organic phosphate insecticide which acts as an inhibitor of cholinesterase, and as such it is highly toxic by all routes of exposure.
- It may be found as a liquid or as a dry mixture where the liquid is absorbed onto a dry carrier.

MALATHION

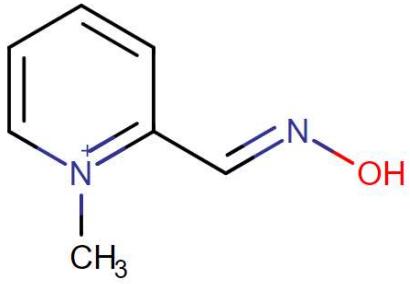


diethyl 2-dimethoxyphosphinothioylsulfanylbutanedioate

- **Malathion** is a pesticide that is widely used in agriculture, residential landscaping, public recreation areas, and in public health pest control programs such as mosquito eradication.
- In the US, it is the most commonly used organophosphate insecticide.

CHOLINESTERASE REACTIVATOR

PRALIDOXIME CHLORIDE



2-[(hydroxyimino)methyl]-1-methylpyridin-1-ium

- Pralidoxime (2-pyridine aldoxime methyl chloride) or 2-PAM, usually as the chloride or iodide salts, belongs to a family of compounds called oximes that bind to organophosphate inactivated acetylcholinesterase
- It has a role as a cholinesterase reactivator.
- Pralidoxime is an antidote to organophosphate pesticides and chemicals.
- Organophosphates bind to the esteratic site of acetylcholinesterase, which results initially in reversible inactivation of the enzyme. If given within 24 hours,after organophosphate exposure, pralidoxime reactivates the enzyme cholinesterase by cleaving the phosphate-ester bond formed between the organophosphate and acetylcholinesterase.

THANK YOU….