CHAPTER -6 PARA-SYMPATHOMIMETIC DRUGS

OBJECTIVES

1. Introduction- Cholinergic system
2. Biosynthesis, storage and release of acetylcholine
3. Cholinergic junction- Biosynthesis, storage and release of acetylcholine
4. Acetylcholine Receptors- A-Muscarinic Receptor and Nicotinic Receptors & their functions
5. Para-sympathomimetics Drugs- Classification
   a) Direct acting
   b) Indirect acting
   c) Cholinesterase reactivator
6. Structure Activity Relationship studies [SAR] of para-sympathomimetics Drugs
7. Para-sympathomimetics drugs and their properties
8. Acetylcholinesterase Inhibitors-
   - Reversible Acetyl cholinesterase Inhibitors, Reversible Acetyl cholinesterase Inhibitors [Alzheimer disease treatment]
   - Irreversible (Acetyl disease treatment)
9. Cholinesterase reactivator- Antidotes for Irreversible Acetyl cholinesterase Inhibitors.
10. Question bank

INTRODUCTION

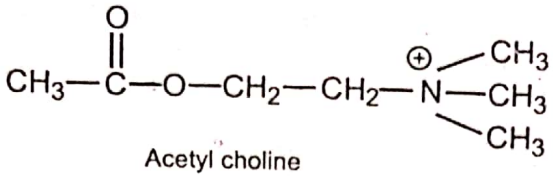
The autonomic nervous system controls various tissues like smooth muscles, cardiac muscles and glands. The autonomic nervous system is divided into two parts-

1) Sympathetic nervous system
2) Parasympathetic nervous system

Parasympathetic nervous system is also known as cholinergic system. Cholinergic system is one where is Acetylcholine (Neurotransmitter) is used or released in the body. Acetylcholine is a neurotransmitter which propagates impulse transmission in the parasympathetic nervous system. Acetylcholine has functions both in the peripheral nervous system (PNS) and in the central nervous system (CNS). Parasympathetic nervous system is characterized by its anabolic effects.

CHOLINERGIC NEUROTRANSMITTERS

Acetylcholine is the major neurotransmitter at post ganglionic synapses of cholinergic or parasympathetic nerve endings. Acetylcholine was first reported by Reid Hunt and Taveau in 1906.



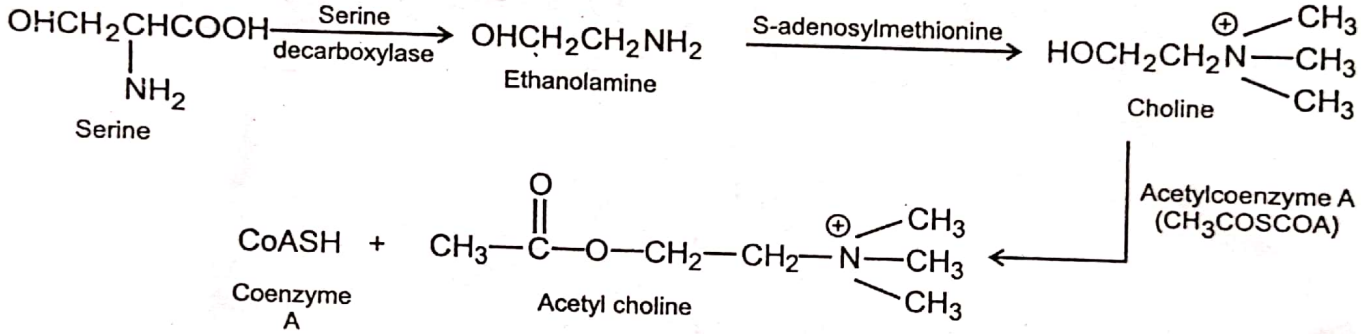
Acetyl choline

Basically, acetylcholine is an organic chemical which acts in the brain and body of animals and humans as a neurotransmitter.

It is an ester of acetic acid choline. In the brain, it acts as a neuromodulator and as a neurotransmitter.

BIOSYNTHESIS OF ACETYLCHOLINE

Synthesis of acetylcholine is done by cholinergic neurons. Acetylcholine is synthesized by choline and Accetyl coenzyme A. Choline is synthesized in the liver by the reaction between serine and ethanolamine.



It is a drug which blocks the reuptake choline by the high-affinity choline transporter at the presynapse.

The biosynthesis of Accetylcholine (ACh) depends on the uptake of Choline via a sodium dependent carrier. This uptake can be affected or blocked by hemicholinium.

Storage and Release of Ach : The highly polar choline is taken up into the axoplasm by the specific choline transporter. The newly formed ACh is loaded into the storage vesicles by the vesicular ACh transporter (VAChT). Each storage vesicle contains about 1000 to 50,000 molecules of ACh. Large amount of ACh is also present in extravesicular cytoplasm. ACh is transported into the storage vesicle by a carrier which can be inhibited by a chemical agent called vesamicol.

Release : ACh is stored in vesciels (40-50nm) along with other potential co-transmitters (Co-T) such as ATP (Ach: ATP/10:1). Release of ACh and the Co-T occcurs following depolarizatioon of the membrane, which allows the entry of Ca^{2+} through voltage-dependent Ca^{2+} channels. During activation of the nerve membrane, Ca^{2+} is though to enter the axoplasm through voltage-gated channels and to activate protein kinases that phosphorylate synapsin. As a result, vesicles close to the membrane are detached from their anchoring and allowed to fuse with the presynaptic membrane. During fusion, vesicles discharge their contents into the synaptic gap and simultaneously insert specific choline-transporter CHT

It is an experimental drug, acting presynaptically by inhibiting to synaptic vesicles and reducing its release.

(Parasympathetic receptors) into the plasma membrane. ACh quickly diffuses. Exocytosis, through the synaptic gap (the acetyl choline molecule is a little longer than 0.5nm; the synaptic gap as narrow as 20-30nm). At the postsynpatic effector cell membrane, ACh reacts with its receptors i.e. muscarinic (M-) nicotinic (N) ACh receptors. Released of ACh is rapidly hydrolyzed and inactivated by a specific acetylcholinesterase an enzyme localized to pre- and postjunctional membranes or by a less specific serum cholinesterase, a soluble enzyme present in serum and interstitial fluid.

Catabolism of Acetylcholine : After the release and action of acetylcholine (Release of ACh in inhibited by Botulinium toxin) the functions and effects of ACh can be terminated by the help of enzymatic hydrolysis. Cholinesterases rapidly hydrolysis ACh into choline and acetic acid. Cholinesterases is also known as acetylcholine esterases (AChE). It only causes hydrolysis of the ACh which is released from cholinergic nerve terminals .

$$\text{Acetylcholine} \xrightarrow{\text{Cholinesterases}} \text{Choline + Acetic acid}$$

Cholinergic receptors are like other transmembrane receptors and are chemical sites at synapses through which acetylcholine exerts its action. Acetylcholine acts on two different classes of receptors.

1) Muscarinic receptors (M-receptors)
2) Nicotinic receptors (N -receptors)

Axoplasm is the cytoplasm within the axon of a neuron.

MUSCARINIC RECEPTORS

Muscarinic receptors belongs to the Super family of G-protein coupled receptors which activates other ion-channels. Muscarinic receptors are more sensitive to muscarine than to nicotine. Muscarine is a water soluble toxin derived from the mushroom Amanita muscaria which causes activation of peripheral sympathetic nervous system. Acetyl choline when binds to muscarinic receptors it causes conformational change in the receptor, causes activation of an intracellular G-protein which catalyses intracellular events.

Muscarinic receptors are of five subtypes :

1. M_1 : Present in autonomic ganglia, gastric gland and in the CNS. It causes depolarisation, histamine release, acid secretion, affects learning, memory & motor functions.
2. M_2 : Present in the heart. It decreases velocity of conduction and also decreases the strength of contractility.
3. M_3 : Present in smooth muscles of the blood vessels and of the lungs. It causes contraction of smooth muscles and releases NO (nitrous oxide) to produce vasodilation.
4. M_4 : Present in the CNS and heart and has no significantly clinical effects. It may have direct regulatory action on K^+ and Ca^{2+} ion channels.
5. M_5 : Present in the CNS and no clinical effects products by this type of receptor. It may regulate dopamine release at terminals within the striatum.

acetylcholine uptake in

Corpus
it is the critical component of the motor and reward systems.

A-Muscarinic Receptor and Their functions

Types of Receptor	Location and	Function	Nature	Transducer Mechanism via receptor interaction	Agonists	Antagonist
M1 *Neural*	Autonomic ganglia : Gastric glands : CNS :	Depolarization Histamine release, acid secretion Learning, memory, motor functions	G-protein coupled Receptor family	Inositoltriphosphate/ Diacylglycerol Increases cytosolic Ca^{2+}, PLA_2 Increase, Prostalgandins (PG) synthesis	Oxotremorine	Pirenzepine, Telenzepine
M_2 *Cardiac*	SA node AV node : Atrium : Ventricle : Cholinergic nerve endings : CNS : Visceral smooth muscle :	Hyper polarization Decrease rate of impulse generation, Decrease velocity of conduction Shortening of APD, Decrease strength of contractility Decrease ACh release Temor, analgesia contraction	G-protein coupled Receptor family	K+ channel opening, Decrease cAMP	Methacholine	Tripitramine Methoctramine,
M_3 *Glandular*	Visceral smooth Iris (*eye*) Exocrine glands : Vascular endothelium	muscle Contraction constriction of pupil Increase secretion release of NO, vasodilation	G-protein (Gq) coupled Receptor family	IP3/DAG-↑ Cytosolic Ca^{2+}, PLA_2↑, PG synthesis	Bethanechol	Darifenacin

NICOTINIC RECEPTORS

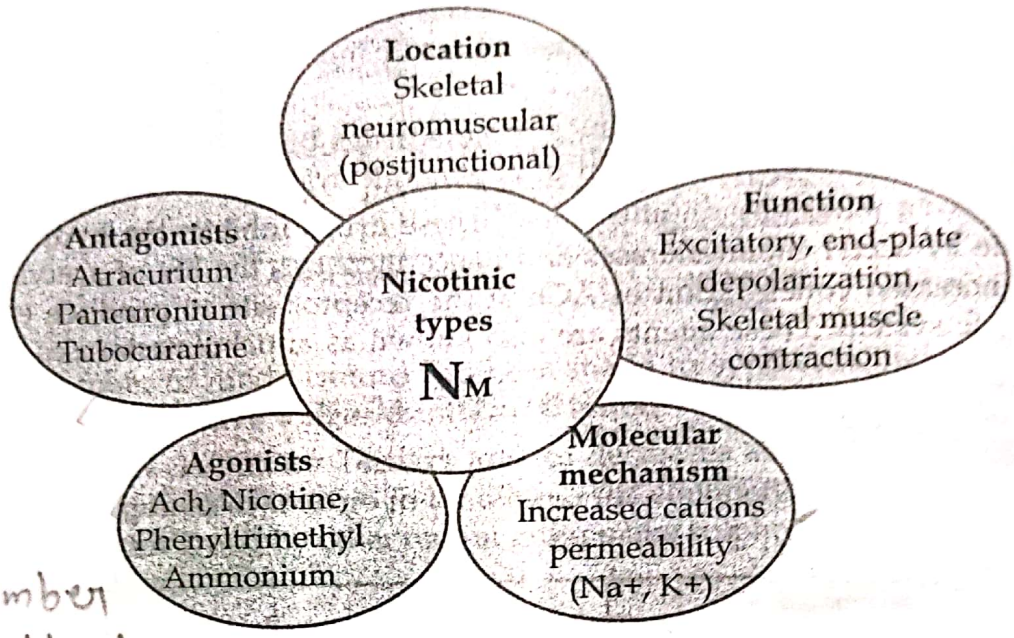
Nicotinic receptors derived their name from nicotine, which does not stimulate the nicotinic receptors but selectively binds to the receptor. It is an ionotropic receptor which is linked to ion channels. Nicotinic receptors are selectively activated by nicotine and blocked by tubocurarine or hexamethonium. These receptors are rosette like pentameric in structure which encloses a ligand gated cation channel and their activation causes opening of the channel and rapid flow of cations results in depolarization and generation of action potential. Nicotinic receptors are of two types :

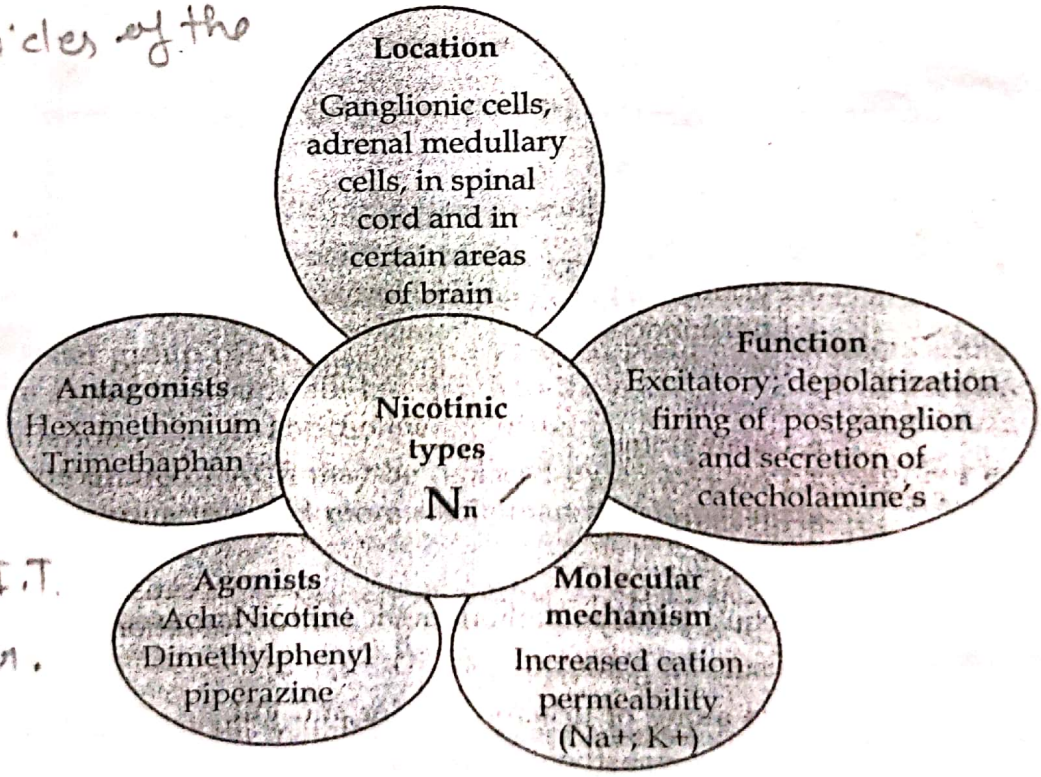
1) Muscle type nicotinic receptors (N_m)
2) Neuronal type nicotinic receptors (N_n)

1) **Muscle type nicotinic receptors (N_m)** : Are located in the skeletal neuromuscular (postjunctional) junction. It causes end plate depolarisation and skeletal muscle contraction.

2) **Neuronal type nicotinic receptors (N_n)** : Are located in adrenal medullary cells, in

spinal cord, in ganglionic cells and in certain areas of brain. It produces excitatory functions like depolarization, firing of postganglion and secretion of catecholamines.





PARASYMPATHOMIMETIC AGENTS

Parasympathomimetic agents are the compounds which mimic the actions of acetyl choline, which is the major neurotransmitter i.e. causes nerve stimulation. Parasympathomimetic agents are classified on the basis of their direct or indirect action on the acetylcholine receptor. These agents are of two types :

1. **Direct acting parasympathomimetics :** These drugs bind to the nicotinic or muscarinic receptors and causes excitation of cholinergic system.
2. **Indirect acting parasympathomimetics :** These drugs inhibits the hydrolysis of acetylcholine by acetyl cholinesterases and hence increases the life of acetylcholine and causes increased conentration of ACh at the receptor site to produce excitation of cholinergic system. These agents are also known as anticholinesterases.

CLASSIFICATION OF PARASYMPATHOMIMETIC AGENTS

Parasympathomimetic agents/Cholinergic drugs

- **Direct acting agents**
  1. Acetylcholine
  2. Carbachol
  3. Bethanechol
  4. Methacholine
  5. Pilocarpine
  6. Cevimeline
  7. Arecoline
  8. Oxotremorine
  9. Xanomeline
- **Cholinesterase inhibitors**
  - **Reversible Direct Acting**
    1. Physostigmine
    2. Neostigmine
    3. Pyridostigmine
    4. Endrophonium chloride
    5. Tacrine HCl
    6. Galantamine
    7. Donepzil
    8. Rivastigmine
  - **Irreversible Indirect Acting**
    1. Parathion
    2. Malanthion
    3. Dichlorofenthion
    4. Paraoxon
    5. Chlorpyrifos
- **Cholinesterase reactivator**
  - Pralidoxime chloride

Ambenonium chloride
Isofluorphate
Echothiophate iodid
Echothiophate io

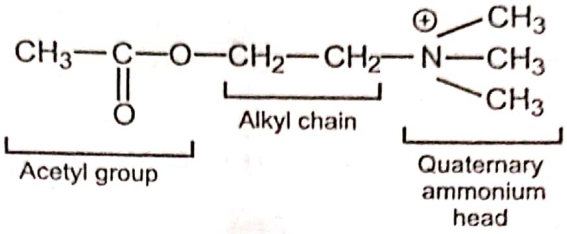
Both the direct and indirect acting parasympathomimetic agents are used-

1) In reducing intraocular pressure in glaucoma
2) In the relief of post operative atony of urinary bladder and gut, Postoperative Urin retention is comm after anesthesia and surgery.
3) It relieves muscular weakness in myasthenia gravis

यह अवस्था नसों और मांसपेशियों के बीच संचार टूटने के कारण होता है।

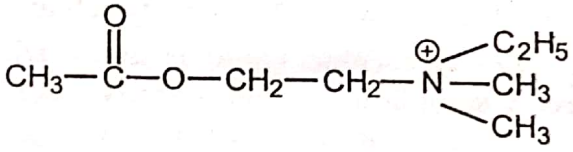
SAR OF PARASYMPATHOMIMETIC AGENTS

Acetylcholine is the prototype drug in the category of directly acting parasympathomimetics. This drug gets rapidly hydrolysed by the enzyme acetylcholinesterases.



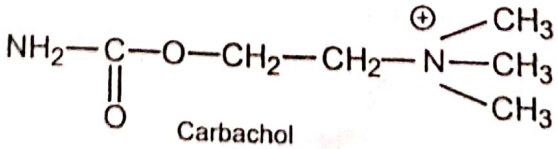
A large number of modifications has been made to synthesize new derivatives which are more selective and have longer duration of action.

1) The (Primary Secondary Tertiary amines decreases activity) quaternary ammonium group is required as it helps in binding to the cholinergic receptors. The replacement of ammonium group by other onium groups like sulphonium or phosphonium causes loss of activity.
2) The methyl group of quaternary ammonium group can be replaced by larger alkyl group. For example, dimethyl ethyl derivative of acetylcholine is more active than the parent drug.



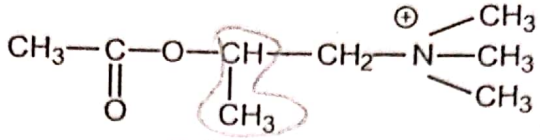
Dimethylethyl derivative of Acetylcholine

3) Replacement of more than one methyl group of quaternary ammonium group leads to complete loss of cholinergic activity.
4) The ester group of ACh helps in hydrogen bonding formation with the receptor. If large aromatic groups are inserted into the ester group it will produce ACh antagonists i.e. may act as anticholinergic drug.
5) Acetate group of ACh may be replaced by a carbamate group. For example, Carbachol is more active and more stable than the parent drug.



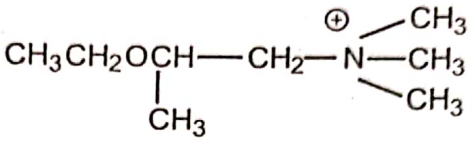
Carbachol

6) The Ethylene chain maintains the distance between the ester group and ammonium group. Increase in the chain length decreases the activity while branching in the chain produces change in activity. For example, Methacholine is more potent than acetylcholine.



Methacholine

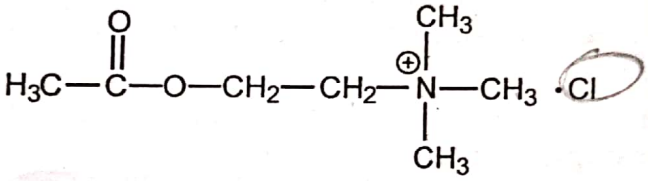
7) Ester group of acetylcholine can be replaced by other groups like ether & ketone to give compounds which are chemically stable and potent compounds and have some cholinergic activity. For example, β-Methylcholine Ethyl Ether.



β-Methylcholine Ethyl Ether

Various directly acting drugs are as follows :

1) Acetylcholine



IUPAC name : 2-Acetoxy-N, N, N-trimethyl ethanaminium chloride

Properties : A very hygroscopic, white or almost white crystalline powder, very slightly soluble in water, freely soluble in alcohol, slightly soluble in dichloromethane. It should be protected from light and store in airtight container.

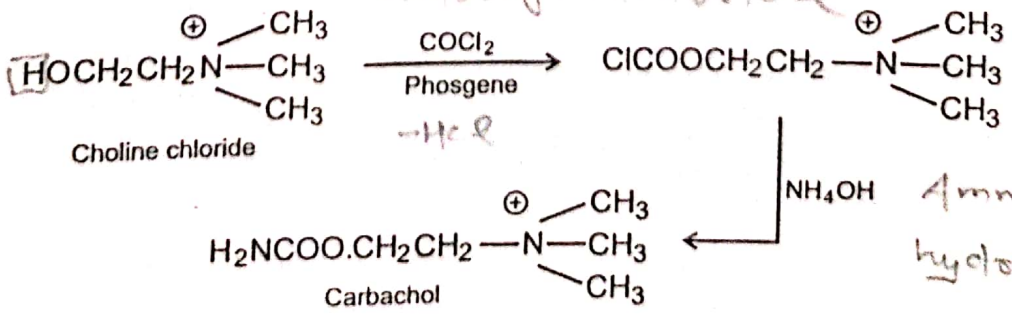
Mechanism of Action : Acetylcholine is direct acting quaterammonium cholinergic drug that has the muscarinic effects of acetylcholine. It's transit action is due to its destruction by cholinesterase.

Uses :

1. It is used as a miotic to reduce post-operative rises in intra-ocular pressure associated with cataract surgery, ridectomy and other anterior segment surgery.
2. It also used as a vasodilator and cardiac depressant, a stimulent of the vagus and the parasympathetic nervous system.
3. It has a tonic action on smooth muscle. It also increases lachrymal, salivary and other secretions.

2) Carbachol

Synthesis :



Choline chloride

Carbachol

IUPAC name : 2 carbamoyloxy-N, N, N-trimethyl ethyl ammonium chloride

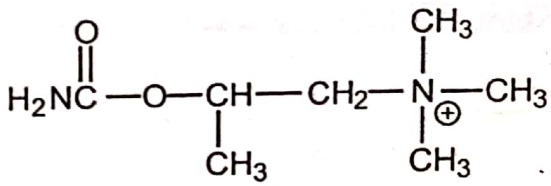
Properties : It is a white powder, freely soluble in water, sparingly soluble in alcohol, practically insoluble in chloroform and ether. Stored in airtight containers.

Mechanism of Action : Carbachol is a quaternary ammonium parasympathomimetic possesses both muscarinic and nicotinic actions of acetylcholine.

Uses :

1. It is used as an alternative to pilocarpine in the management of glaucoma.
2. Carbachol is given intra-ocularly to produce miosis in ocular surgery and to reduce post operative rises in intra-ocular pressure.
3. In some counteries it has also been used for treatment of decreased gasterointestinal motility.

3) Bethanechol



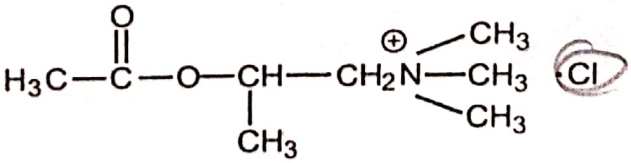
IUPAC Name : 2-carbamoyloxy-1-(N, N, N-trimethyl) propyl ammonium chloride.

Properties : Bethanechol is white or colourless crystals or white crystalline powder usually having a slight amine like odour. It is hygroscopic and exhibits polymorphism. It is freely soluble in water and in alcohol insoluble in chloroform and in ether. It is stored in air tight containers.

Mechanism of action : Bethanechol is choline ester mainly exhibits the muscarinic action of ACh. It is not inactivated by cholinesterases. It also have little nicotinic activity.

Uses : It is usually employed in stimulation of G.I. tract and urinary bladder to relieve postoperative atony. It has prolong effect than acetylcholine.

4) Methacholine



IUPAC Name : 2 (Acetoxy)-N, N, N-trimethyl propan-1-aminium chloride.

Properties : It is colourless or white crystalline powder which is hygroscopic in nature. It is soluble 1 in 1.2 of water, 1 in 1.7 of alcohol and 1 in 2.1 of chloroform. Its solutions are neutral to litmus. It is store in air tight container.

Mechanism of action : Methacholine is quaternary ammonium parasympathomimetic with the muscarinic actions of acetylcholine, It is hydrolysed by acetyl cholineesterase and

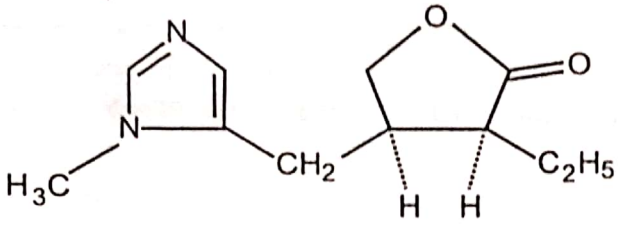
more resistant to hydrolysis by non specific cholinesterases so that its actions are more prolonged.

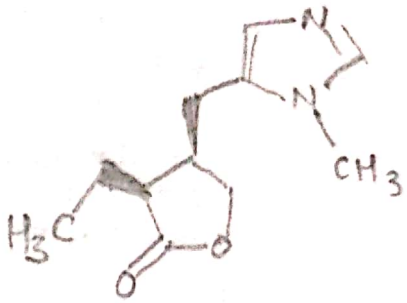
Uses :

1. It is used in treatment of reynaud's syndrome and glaucoma.
2. Methacholine chloride has been used in eye drops as a miotic for diagnostic purposes.
3. It is also used to diagnose bronchial hyper reactivity.
4. It is also used for peripheral vascular disease.

contraction of the pupil

5) Pilocarpine





IUPAC Name : 3-ethyl-4-(1-methyl-5-imidazolymethyl) tetrahydrofuran-2-one.

Properties : It occurs as colourless crystals or white or almost white crystalline powder which is hygroscopic. It is very soluble in water and in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. It is stored in airtight container and protected from light.

Mechanism of Action : Pilcocarpine is a direct acting tertiary amine cholinergic that has muscarinic effects of acetylcholine.

Uses :

1. It is used mainly in the treatment of glaucoma and in treatment of dry eye or dry mouth.
2. It is used in the treatment of open angle glaucoma.
3. Pilocarpine may be used before surgery as part of the emergency treatment of acute attacks of angle-closure glaucoma.
4. It has also been used as a diaphoretic in diagnostic tests for cystic fibrosis and leprosy.

INDIRECT ACTING AGENTS/CHOLINESTERASE INHIBITORS

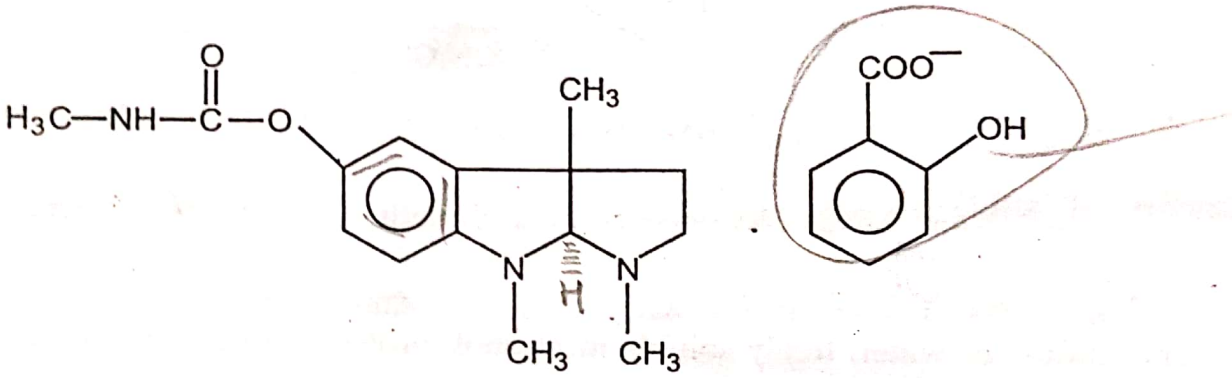
These agents are also known as acetylcholinesterase inhibitors. Acetyl cholinesterase is an enzyme which terminates the action of acetylcholine at the junctions of the various cholinergic nerve endings with their effector organs or postsynaptic sites. These drugs inhibits the AChE enzyme and causes accumulation of ACh in the vicinity of cholinergic nerve terminals. This higher concentration of the neurotransmitter increases the biological response. These agents thus produce effects similar to that of cholinergic agents. Anticholinesterase agents are of two types :

a) **Reversible Inhibitors :** As the name indicates, these drugs binds reversibally to the choline subsite. These drugs causes acylation of the hydroxyl group of the serine residue of acetylcholinesterase. These agents form an ester like carbonate or phosphate and covalently binds to the active site of the enzyme. For example, Physostigmine and Neostigmine

b) **Irreversible Inhibitors :** These drugs produces irreverisble inactivation of the acetylcholinesterase. This category includes various organophosphorus compounds. These drugs are long lasting and binds irreversbly by covalent bonding to the active site of the enzyme. The resulting phosporylated enzyme is very stable and causes inactivation of the acetylcholinestrases enzyme. For example, Parathion and Malathion.

Various drugs belonging to Indirect acting agents are as follows :

1) Physostigmine Salicylate



IUPAC Name : 1,3(a)8-trimethyl-2, 3, 3(a), 8a-tetrahydropyrrolo [2, 3-b]-indole-5-yl-N-Methyl carbamate.

Properties : It is white, shining, odourless crystals or white powder. It acquires a red tint on exposure to heat, light or air or on contact with traces of metals for long periods. It is sparingly soluble in water and stored in air tight containers at a temperature 25°, Protected from light. It is readily absorbed by G.I.T and destroyed in the body by hydrolysis of the ester linkage by cholinesterases.

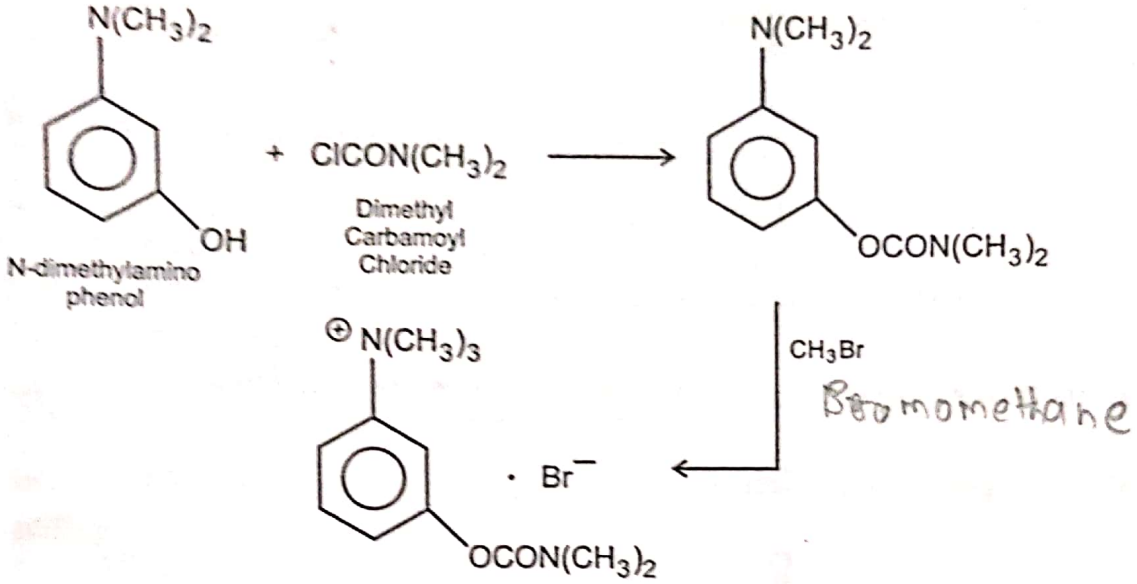
Mechanism of Action : Physostigmine is a reversible tertiary amine inhibitor of cholinestrase activity with actions similar to those of Neostigmine.

Uses :

1. Physostigmine has been used alone or more usually with other miotics such as pilocarpine, to decrease interaocular pressure in glaucoma.
2. It is more potent miotic than pilocarpine but is rarely tolerated for prolonged periods.
3. It can also be used parenterally for reversal the effects caused by anticholinergic and tricyclic antidepressants.

2) Neostigmine bromide

Synthesis



Neostigmine bromide

IUPAC Name : N,N,N-trimethyl-meta-(dimethyl-carbomoyloxy)-benzenaminium bromide.

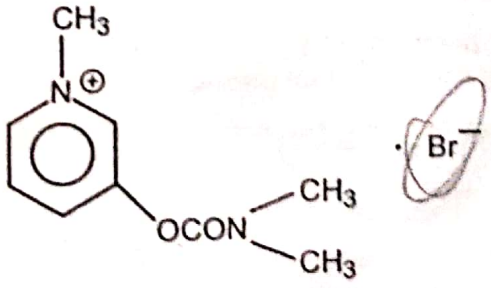
Properties : It is colourless, white or almost white hygroscopic, crystalline powder. It is very soluble in water, freely soluble in alcohol, protected from light. It is poorly absorbed by G.I.T.

Mechanism of Actoin : Neostigmine indirectly stimulates both muscarinic and nicotinic receptors. It binds to the anionic and esteric site of cholinesterase and block the activity of acetylcholinesterase.

Uses :

1. It is used in the treatment of myasthenia gravis.
2. It is used in the treatment of paralytic ilens and postoperative urinary retention.
3. It has also been used to lower intra-ocular pressure in the management of glaucoma.

3) Pyridostigmine



IUPAC Name : 3-[(Dimethylamino carbonyl)oxy]-1-methyl pyridinium bromide

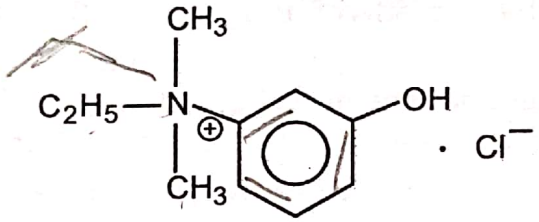
Properties : It is white or practically white, hygroscopic crystalline powder having an agreeable characteristic odour. It is freely soluble in water, alcohol and in chloroform but practically insoluble in ether. It is stored in air tight containers. It is poorly absorbed from the G.I.T. It is excreted mainly in the urine.

Mechanism of action : Pyridostigmine block acetyl cholienstrase enzyme and inhibit the destruction of released acetylcholine.

Uses :

1. Pyridostigmine is mainly used in the treatment of myasthenia gravis.
2. It has also been used as prophylaxis against the neuromuscular effects of nerve gas poisoning.
3. It has been used in management of postoperative urinary.
4. Pyridostigmine is used to reverse the neuromuscular blockade produced by competitive neuromuscular blockers but it is generally considered less satisfactory than neostigmine.

4) Edrophonium chloride



IUPAC Name : Ethyl-(3-hydroxyphenyl)dimethyl-ammonium chloride.

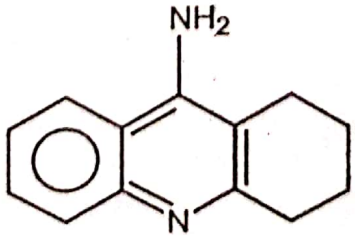
Properties : A white odorless crystalline powder very soluble in water. A 10% solution in water is practically colourless and the pH is between 4.0 and 5.0. It should be kept in a well closed container and protected from light.

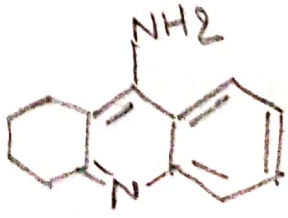
Mechanism of Action : It is a quaternary ammonium compound that is reversible inhibitor of cholinesterase activity. It has shorter duration of action than neostigmine and pyridostigmine.

Uses :

1. It is mainly useful for the treatment of myasthenia gravis but due to its short duration of action it is not suitable for routine treatment of myasthenia gravis.
2. Edrophonium chloride also used in the treatment of snake bite.

5) Tacrine Hydrochloride





IUPAC Name : 1, 2, 3, 4-tetrahydroacridin-9-amine

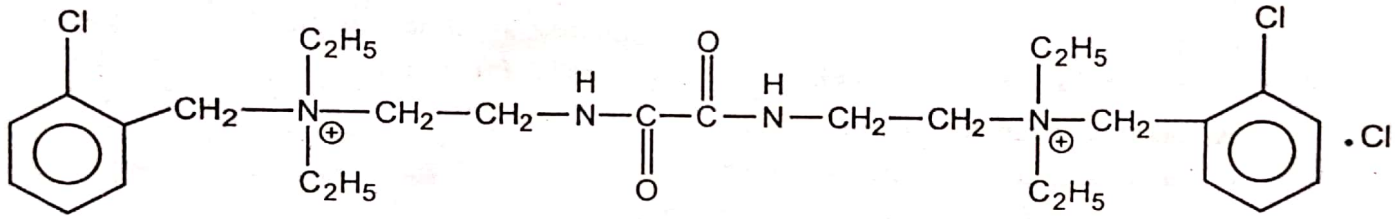
Properties : The monohydrate occurs as a white powder. It is freely soluble in water, alcohol, methyl alcohol and in propylene glycol, sparingly soluble in linoleic acid and in macrogol 400. It is metabolised in liver. The major metabolite 1-hydroxy-tacrine is active.

Mechanism of Action : Tacrine is a centrally acting anticholinesterase and indirect cholinergic agonist.

Uses :

1. It is used in the treatment of mild to moderate severe dementia in Alzheimer's disease.
2. It has also used as an analeptic agent used to promote mental alertness.
3. Tacrine has been used intravenously to antagonize competitive neuromuscular blockers and as a postoperative respiratory stimulant.

6) Ambenonium chloride



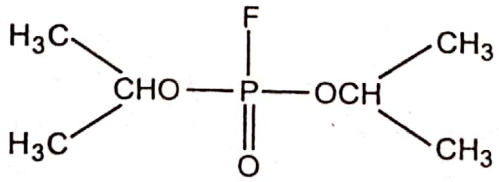
IUPAC Name : 2,2-'[(1,2-Dioxoethane-1,2-diyl)diimino]bis [N-(2-chlorobenzyl)-N,N-diethylethanaminium] chloride

Properties : It is a white crystalline powder, freely soluble in water, having a molecular mass of 537.564g/mol.

Mechanism of Action : It competitively reversibly inhibit the acetylcholinesterase enzyme responsible for hydrolysis of acetylcholine.

Uses : It is used in the management of myasthenia gravis.

7) Isoflurophate



IUPAC Name : bis(Propan-2-yl) fluorophosphonate

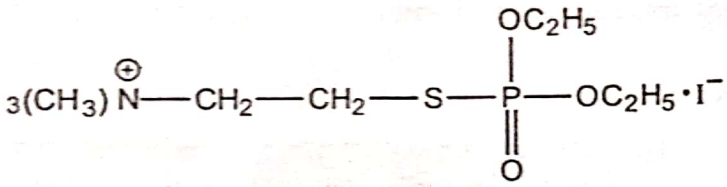
Properties : It is an oily colourless liquid. It is stable but undergoes hydrolysis when subjected to moisture producing hydrofluoric acid.

Mechanism of Action : It produces virtually irreversible inactivation of the acetyl cholinesterase.

Uses :

1. It is used as a miotic agent in treatment of glaucoma.
2. It is used in civilian laboratories to mimic lethal nerve gas exposure or organo phosphate toxicities.
3. It also inhibit some proteases enzyme. So it is useful for additive for protein or cell isolation procedure.

8) Ecothiophate Iodide



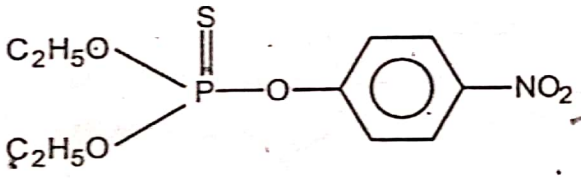
IUPAC Name : 2-(Diethoxy phosphorylsulfanyl) ethyl-N, N, N-trimethylazanium iodide.

Properties : It is a white crystalline powder with molecular mass of 383.228 g/mol. It is soluble in water.

Mechanism of Action : It is an irreversible acetyl cholinesterase inhibitor. It covalently binds to cholinesterase and permanently inactive the enzyme.

Uses : It is used as an ocular antihypertensive in the treatment of chronic glaucoma.

9) Parathion



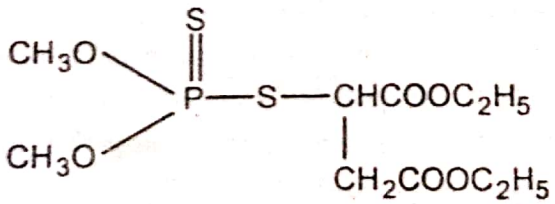
IUPAC Name : O,O-Diethyl-O-(4-nitrophenyl) phosphorothioate

Properties : It is brown to yellow liquid with odour of garlic. It is soluble in water and insoluble in petroleum ether. On metabolism in liver it forms p-nitrophenol and 4-nitrophenyl phosphate by oxidation and hydrolysis reaction.

Mechanism of Action : It indirectly acts on the acetyl cholinesterase enzyme.

Uses : It is used as insecticide in agriculture. It is often applied by spraying to cotton, rice and fruit trees.

10) Malathion



IUPAC Name : Diethyl-2-[(Dimethoxy Phosphorothioyl) Sulfanyl] butanediote

Properties : Malathion is a colorless to yellow brown liquid with a characteristic unpleasant odour. It is soluble in most organic solvents except paraffin hydrocarbons and practically insoluble in water.

Mechanism of Action : It inhibits the acetylcholinesterase activity by binding serine residue on the cholinesterase enzyme and irreversibly deactivates the enzyme.

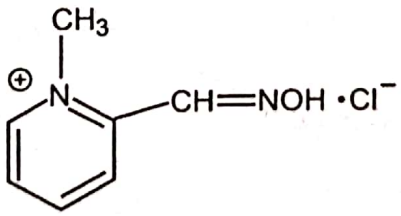
Uses :

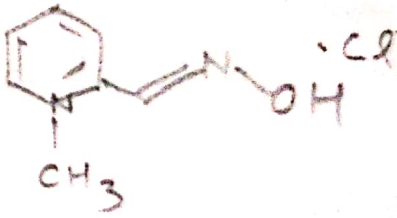
1. Malathion in low doses (0.5%) is used in treatment of head lice and body lice.
2. It is also used for treatment of scabies (contagious skin infestation by mite sarcoptes scabiei)
3. It is also used as insecticide.

CHOLINESTERASE REACTIVATORS

These are the drugs which causes the reverse of the inactivation of cholinesterases produced by organophosphates or irreversible agents i.e. these agents causes reactivation of cholinesterases. These drugs are used in the treatment of poisoning produced by organophosphorus compounds. These reacts with alkylphosphorylated form of cholinesterase to free the active part of the enzyme. These reactivators are mainly used in the treatment of poisoning by organophosphates, sulfonates and acetylcholinesterase inhibitors. For example, Pralidoxime chloride.

1) Pralidoxime chloride





IUPAC Name : 2-[(Hydroxyamino)methyl]-1-methyl pyridin-1-ium chloride

Properties : It is a white to pale yellow, odourless crystalline powder which is freely soluble in water.

Mechanism of Action : It reactivate the acetyl cholinesterase enzyme rapidly by binding to the anionic site of enzyme and displaces the phosphate from the serine residue.

Uses :

1. It is mainly used for the treatment of poisoning by organophosphorus compounds.
2. It is also used for the treatment of overdose by anticholinesterase drugs, including those used to treat myasthenia gravis such as neostigmine. However it is slightly effective and its use is not generally recommended.
3. It is not effective in the treatment of poisoning due to phosphorous, inorganic phosphates or organophoshates without anticholinesterase activity.