Cholinergic Drugs

Kajal P.Baviskar
Assistant Professor
Ph. Chemistry
K K Wagh College of Pharnacy


Sympathetic
'Fight & flight"
Parasympathetic
"Live & let live"

Sympathetic nervous system

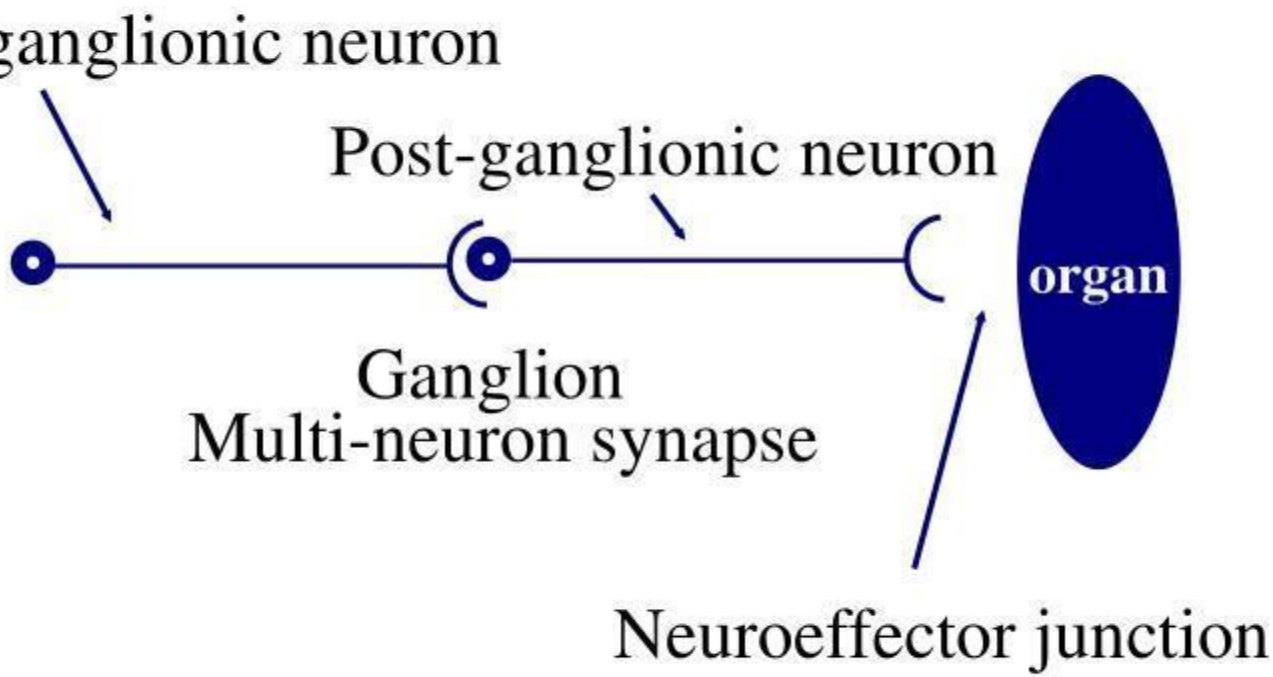
Active during fight or flight response

- Increases heart rate & breathing rate
- Dilates pupils
- Inhibits digestion and saliva production
- Contracts rectum

Parasympathetic nervous system

Active in rest and digestion

- Decreases heart rate & breathing rate
- Constricts pupils
- Stimulates digestion and saliva production
- Relaxes rectum

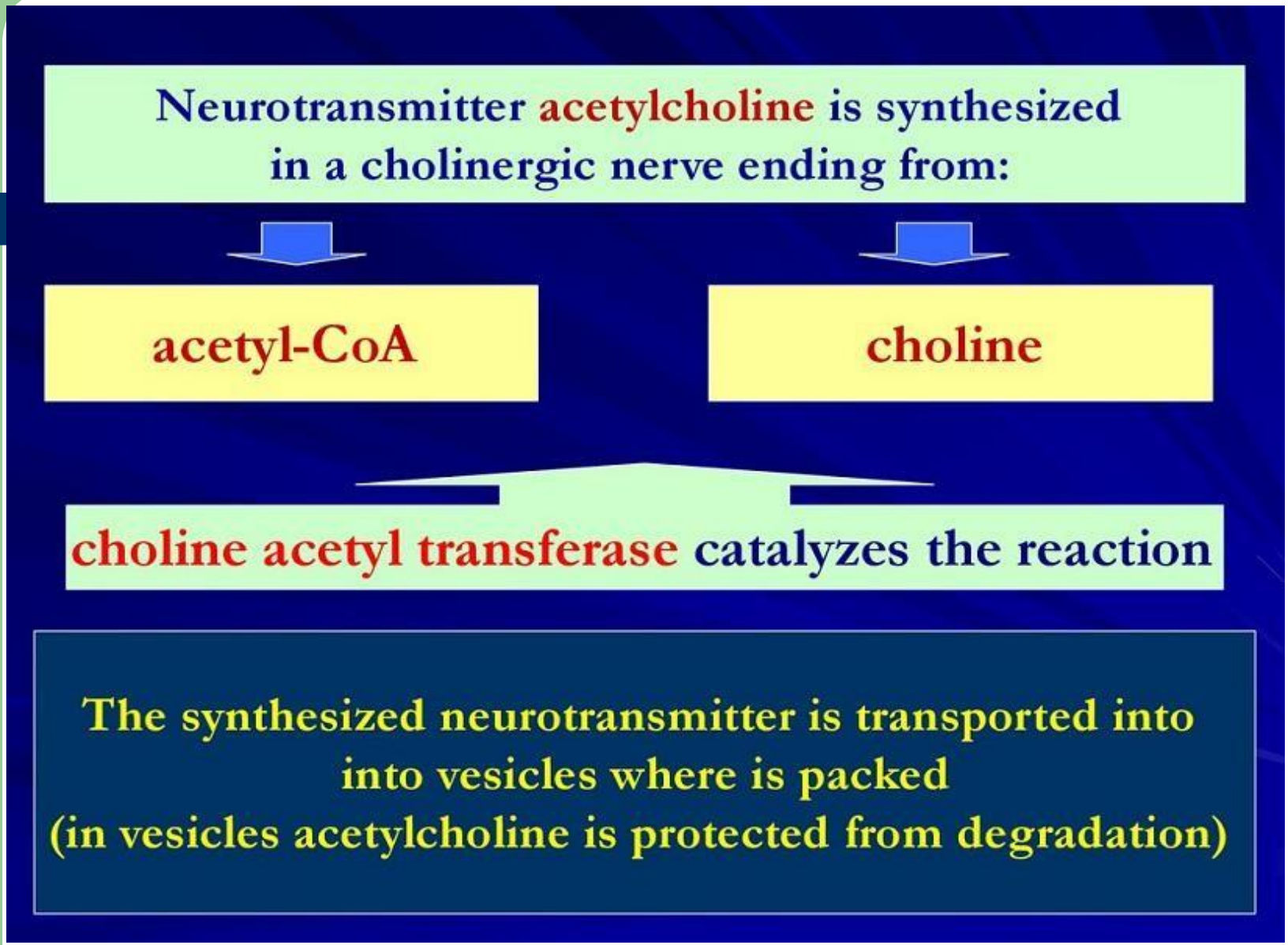

Pre-ganglionic neuron
Post-ganglionic neuron
organ
Ganglion
Multi-neuron synapse
Neuroeffector junction

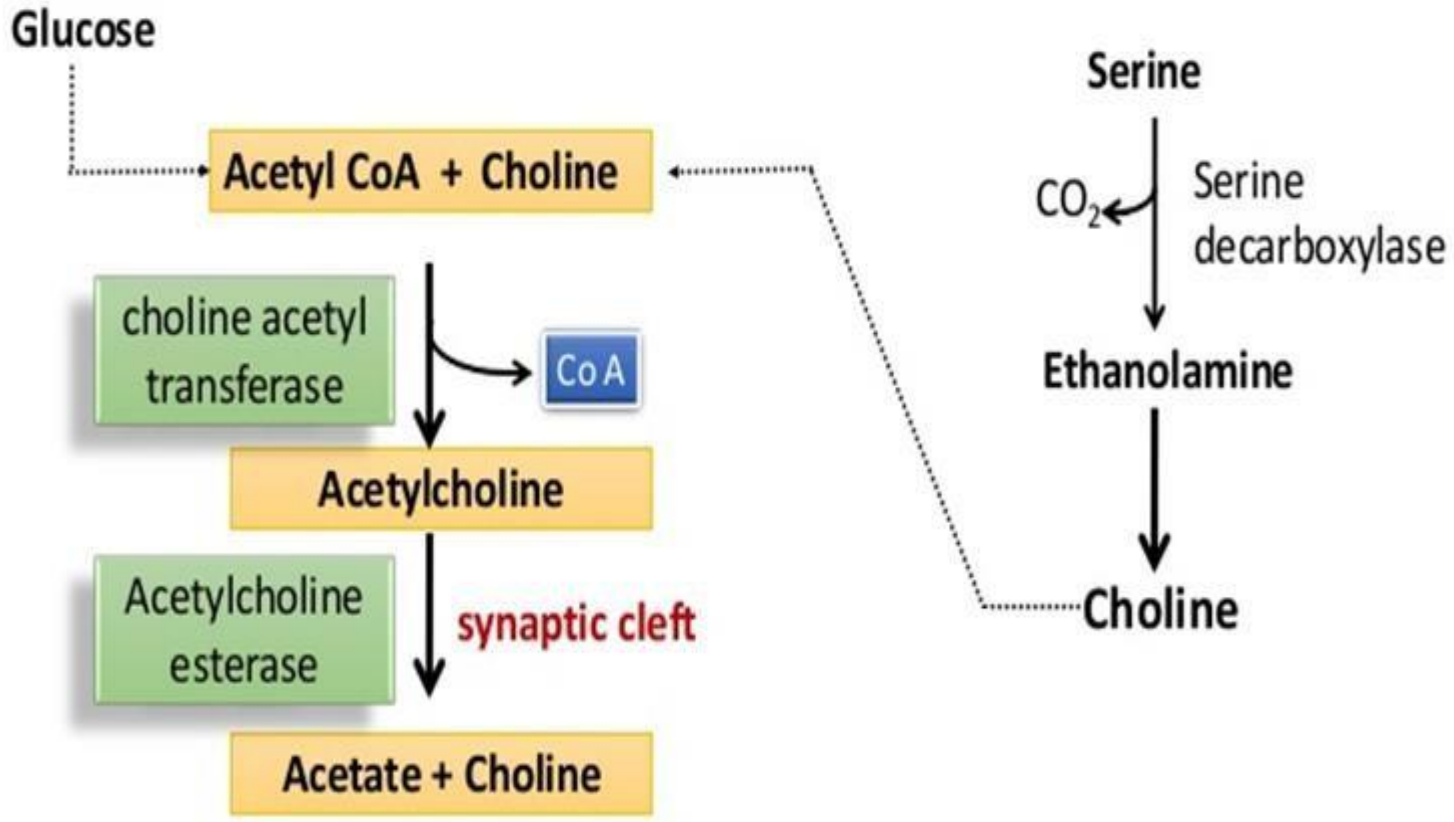
Neurotransmitter: Acetylcholine

- **Autonomic nervous system**

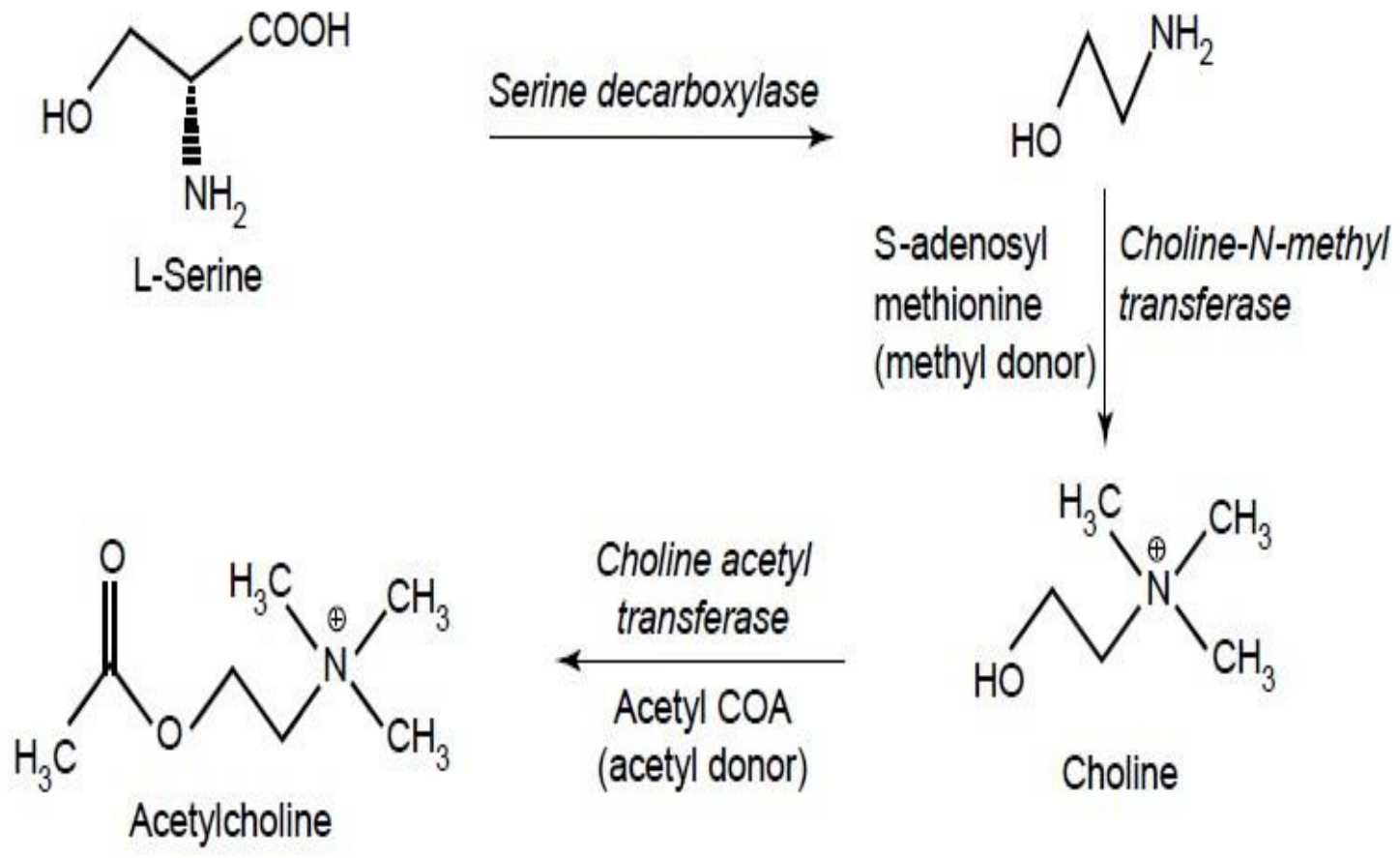
released by pre- and postganglionic fibers of the parasympathetic division, preganglionic fibers of the sympathetic division, and a few postganglionic fibers of the sympathetic division.

- Somatic (voluntary) nervous system and by some neurons in the CNS.


Neurotransmitter acetylcholine is synthesized in a cholinergic nerve ending from:
acetyl-CoA
choline
choline acetyl transferase catalyzes the reaction
The synthesized neurotransmitter is transported into into vesicles where is packed
(in vesicles acetylcholine is protected from degradation)


Glucose
Acetyl CoA + Choline
choline acetyl transferase
CoA
Acetylcholine
Acetylcholine esterase
synaptic cleft
Acetate + Choline
Serine
CO_2
Serine decarboxylase
Ethanolamine
Choline

Biosynthesis



- **Storage**

Most newly biosynthesized acetylcholine is actively transported into cytosolic storage vesicle, where it is maintained with adenosine triphosphate (ATP) (10:1 ratio) along with calcium and magnesium ions until it is released.

Some acetylcholine remains in the cytosol and eventually is hydrolyzed. Only the stored form serves as the functional neurotransmitter.

Each synaptic vesicle contains a **quantum of acetylcholine;** one quantum represents between **12,000 and 60,000** molecules.

A single action potential causes release of several hundred quanta of acetylcholine into the synapse.

- **Release**

When action potential arrives at the nerve endings, voltage sensitive calcium channels open in presynaptic nerve membranes, leading to influx of calcium ions.

Increase in endocellular concentration of calcium occurs and in turn, it causes the fusion of vesicles with membrane surface and **release of their content (Ach, co-transmitters- ATP)** into the synaptic cleft by **exocytosis.**

When a nerve impulse is chemically conducted (by acetylcholine action), the acetylcholinesterase terminates the Ach action by its hydrolysis with formation of:

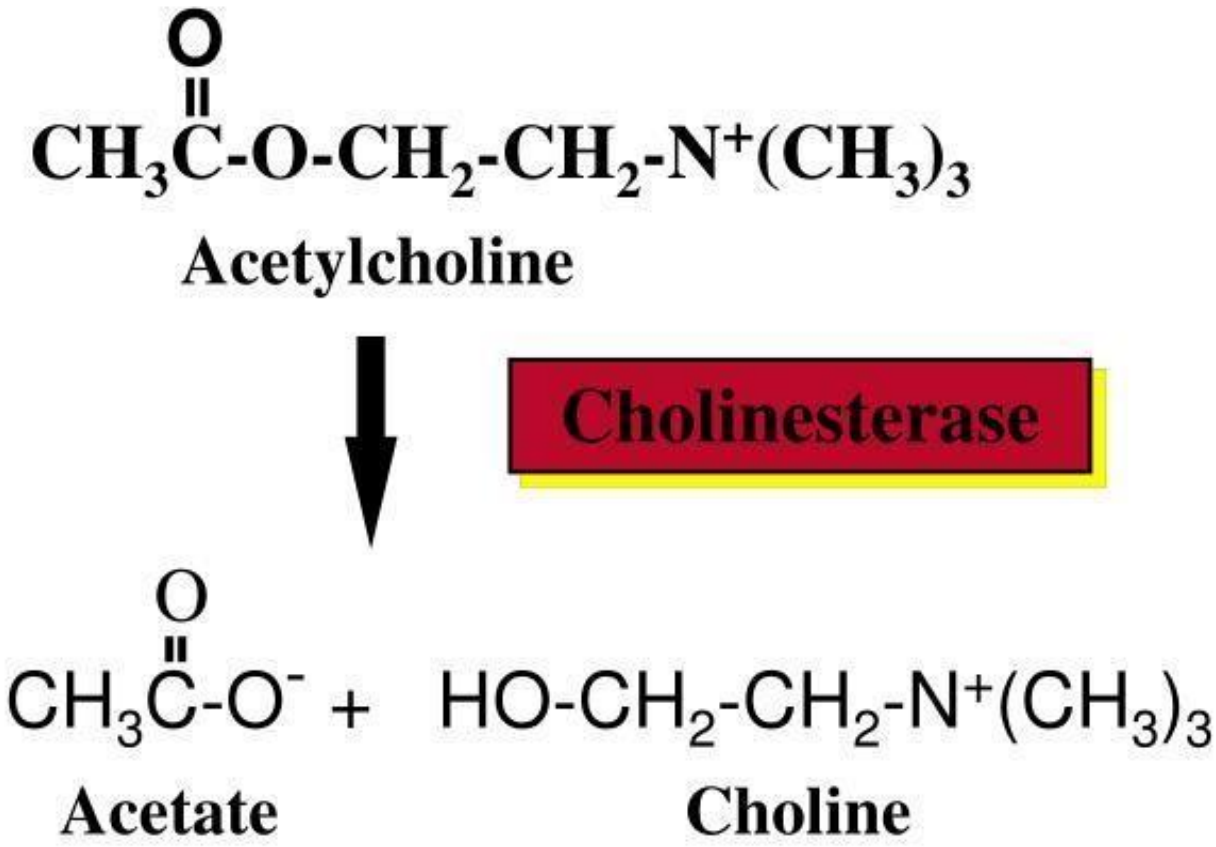
choline

acetate

Choline formed is actively uptaken by the axonal membrane (by a Na+:choline cotransporter) and is used for acetylcholine resynthesis again.

Is removed

Acetylcholine Catabolism



The released acetylcholine binds to:

postsynaptic receptors

presynaptic receptors

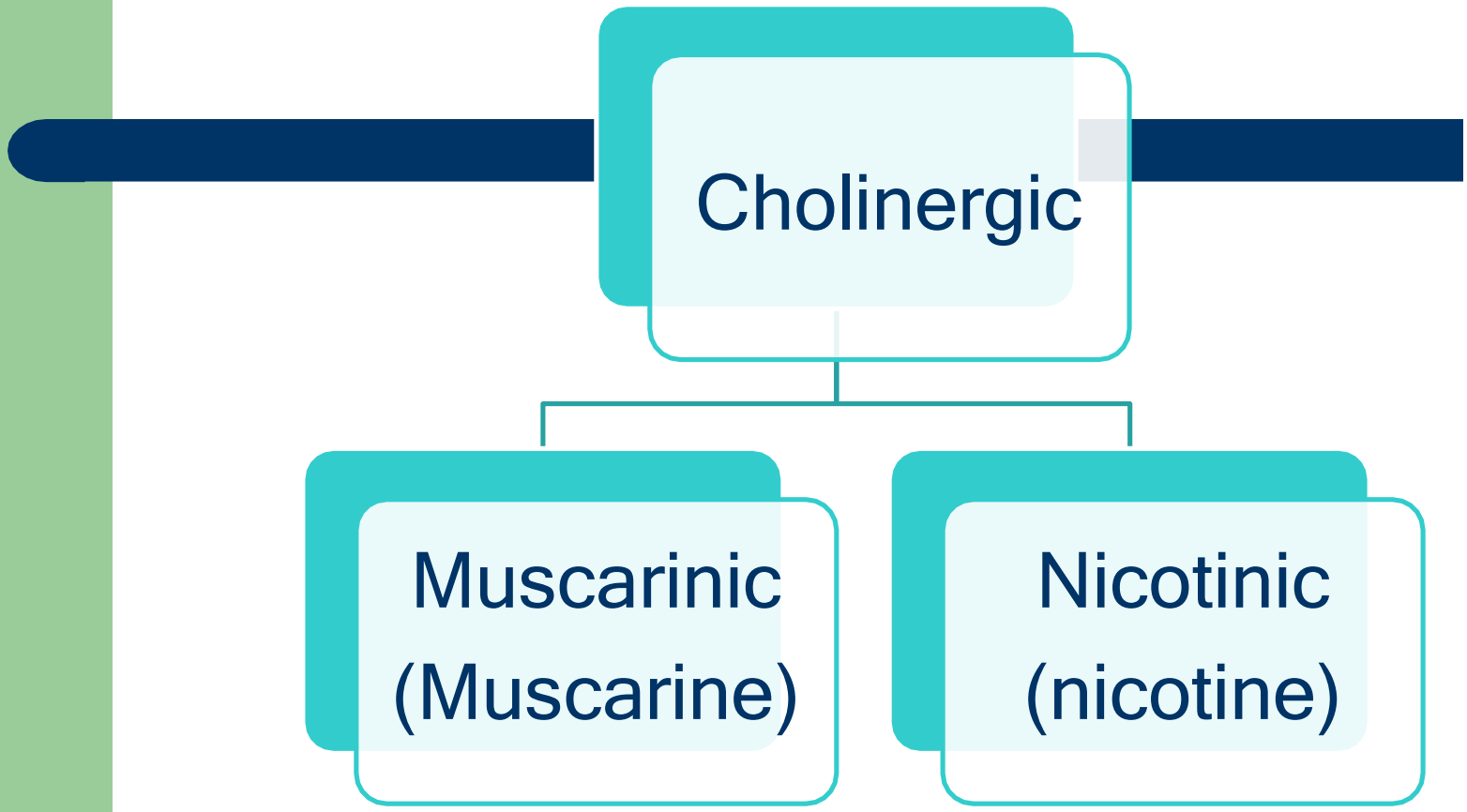
muscarinic

nicotinic

Binding of acetylcholine to postsynaptic receptors results in a biological response within cells of target organs (the myocardium, g.i.t., excretory glands, eyes, etc)

Binding of acetylcholine to presynaptic receptors results in discontinuation of its release (negative feedback mechanism)

Cholinergic receptors: chemical sites in effector cells or at synapses through which acdetylcholine exerts its action.


Cholinergic
Muscarinic (Muscarine)
Nicotinic (nicotine)

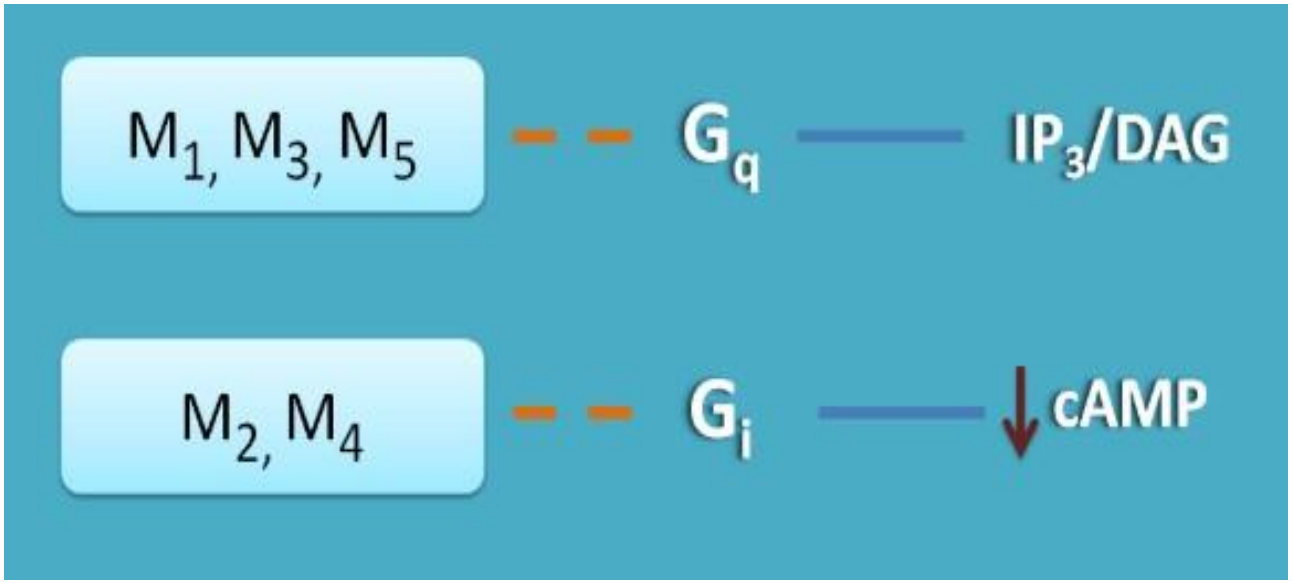
Muscarinic receptors

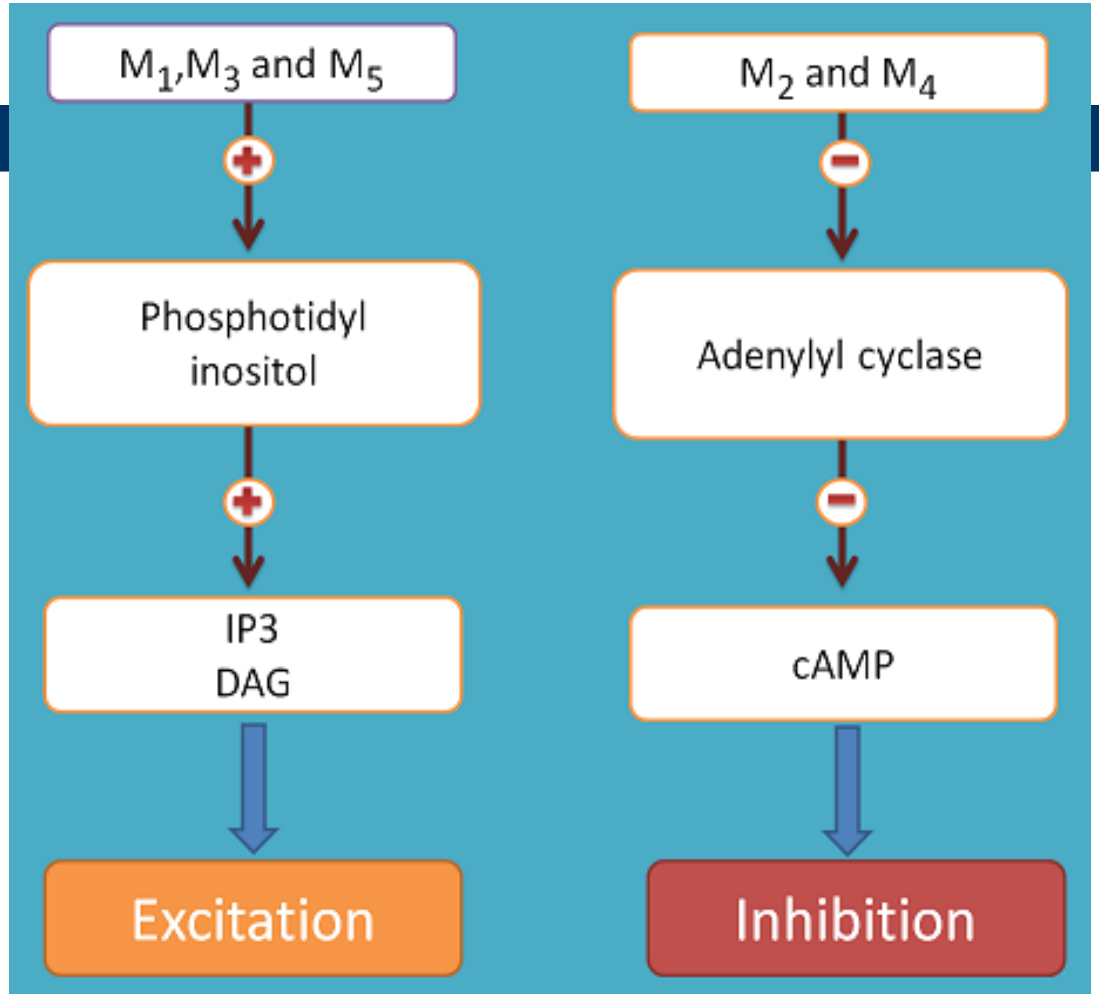
Receptor	Organs
M_1	salivary glands, enteric nerves
M_2	heart, smooth muscle
M_3	smooth muscle, salivary glands
M_4	brain (diffuse), lung
M_5	brain (substantia nigra), eye

All Muscarinic receptors- G protein coupled.

Excitatory - M1, M3, M5

Inhibitory – M2, M4




M1,M3 and M5
Phosphotidyl inositol
IP3
DAG
Excitation
M2 and M4
Adenylyl cyclase
cAMP
Inhibition

IP3/DAG----------increase intracellular calcium level----------excitaion and contraction in smooth muscles.

M2/M4-------inhibit adenylyl cyclase and thus inhibit cAMP (which is required for activation of protein kinases)

M1 receptors

- CNS excitation
- Increase in memory
- Increase in locomotor activity
- Gastric acid secretion
- Salivary secretion

M2 receptors

- Decrease rate of contraction
- Decrease force of contraction
- Decrease in AV conduction
- Increse in smooth muscle contraction
- hypothermia,
- Analgesia

M3 receptors

M3 receptors mainly produce contraction of smooth muscle and secretion of exocrine glands

- Smooth muscle
  - Pupilary constriction
  - Broncho constriction
  - Increase in GI motility
  - Bladder constriction
  - Vasodilatation
- Exocrine glands
  - Salivary secretion
  - Lacrimal secretion
  - Bronchial secretion
  - Gastric secretion
  - Sweat secretion

- Increase in food intake, body fat deposits
- Synthesis of nitric oxide

M4 receptors

- Inhibition of neurotransmitter release
- Analgesia
- Cataleptic activiy
- Facilitates dopamine release

M5 receptors

- Facilitates dopamine release
- Augments drug seeking behaviour
- Dilation of cerebral arteries

Nicotinic receptors (nAChRs)

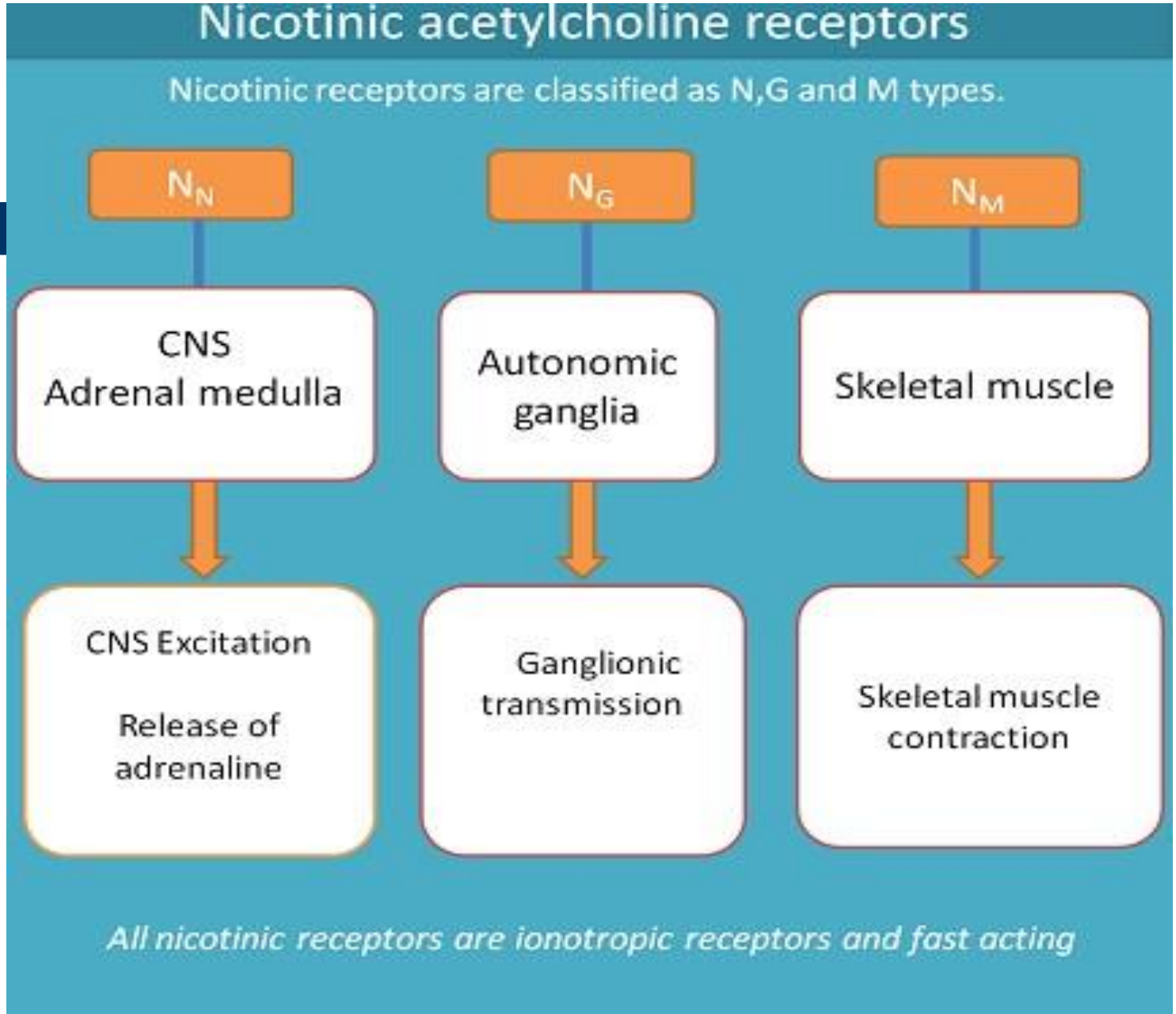
- Location

CNS

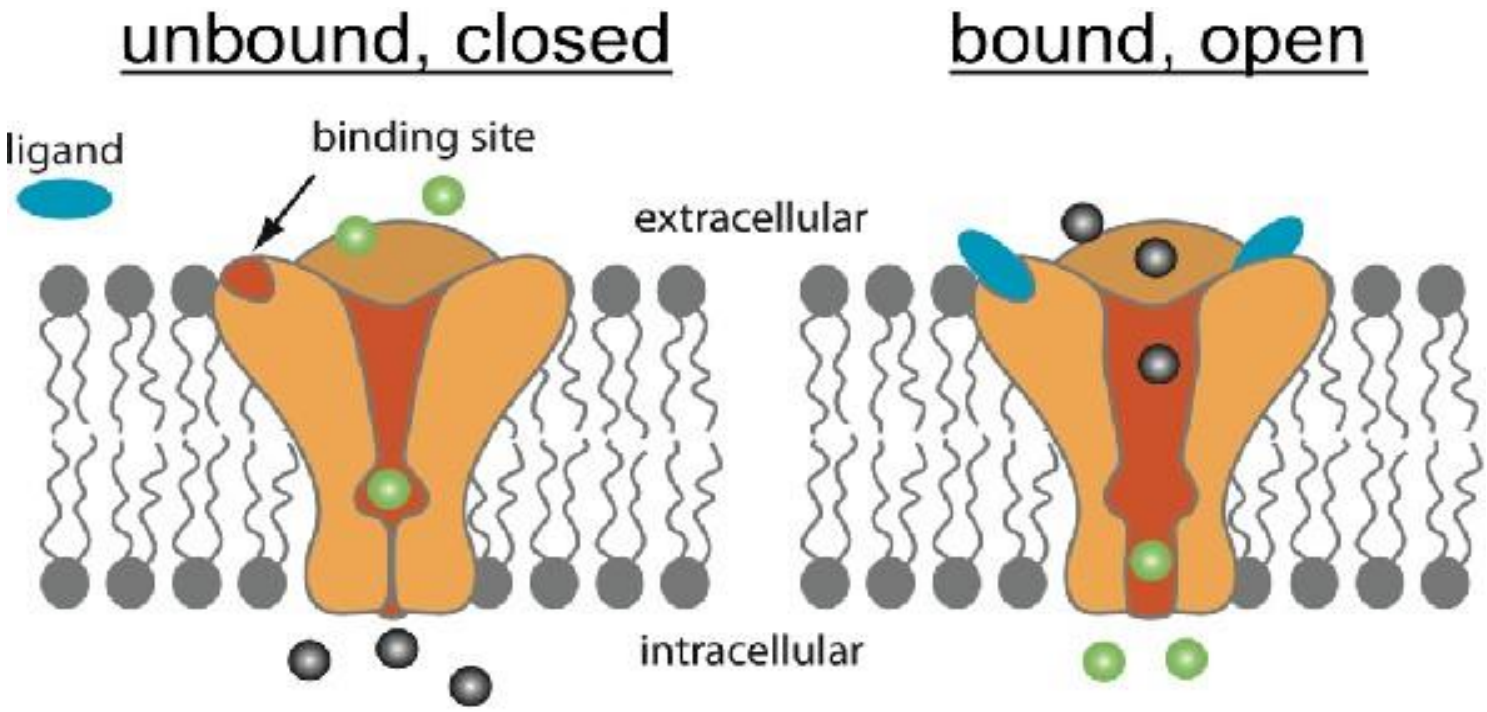
Adrenal medulla

Autonomic ganglia

Neuromascular junction


Nicotinic acetylcholine receptors
Nicotinic receptors are classified as N,G and M types.
N_N
N_G
N_M
CNS
Adrenal medulla
Autonomic ganglia
Skeletal muscle
CNS Excitation
Release of adrenaline
Ganglionic transmission
Skeletal muscle contraction
All nicotinic receptors are ionotropic receptors and fast acting

Ionotropic receptors



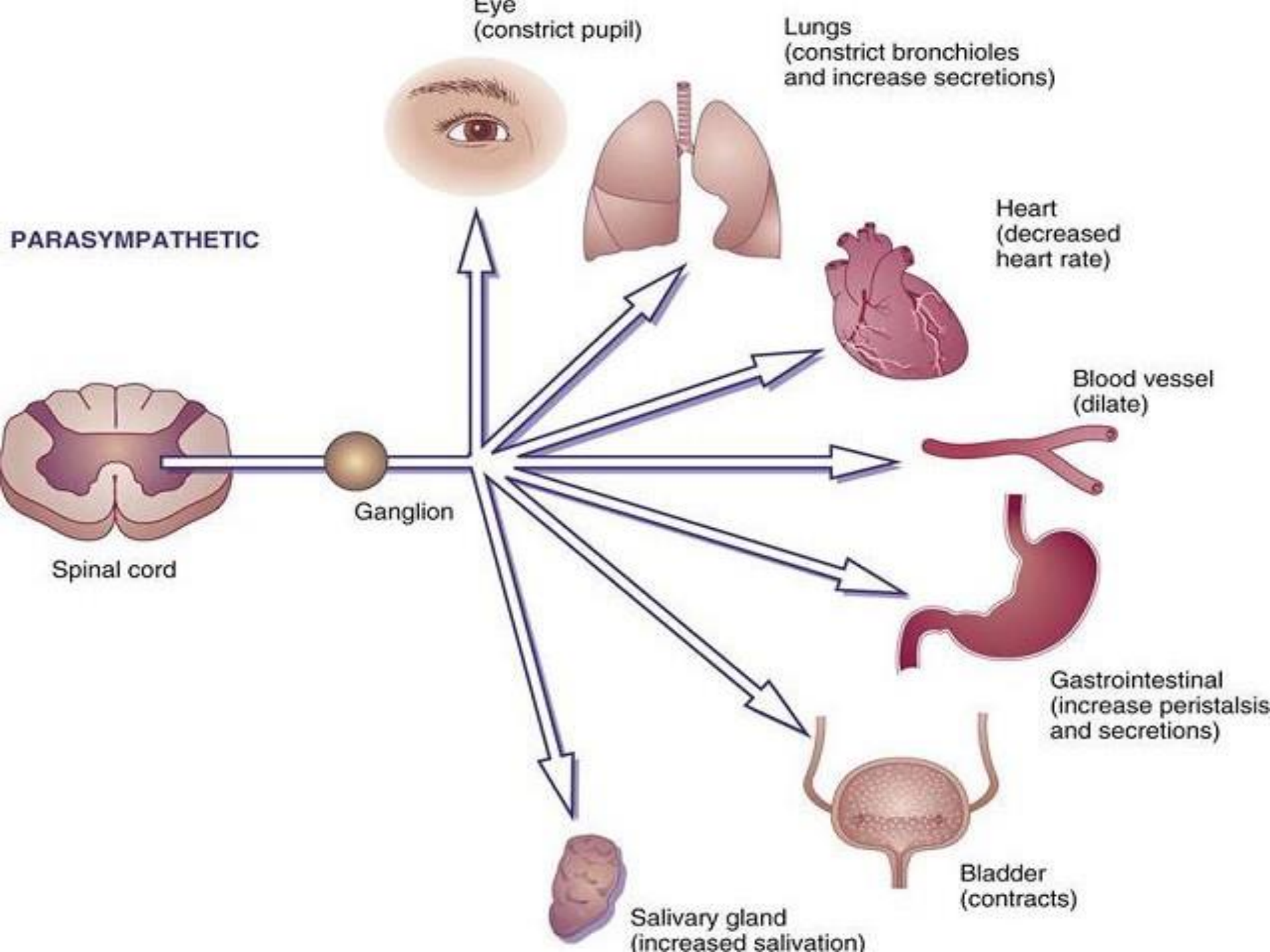
Ionotropic nicotinic receptors

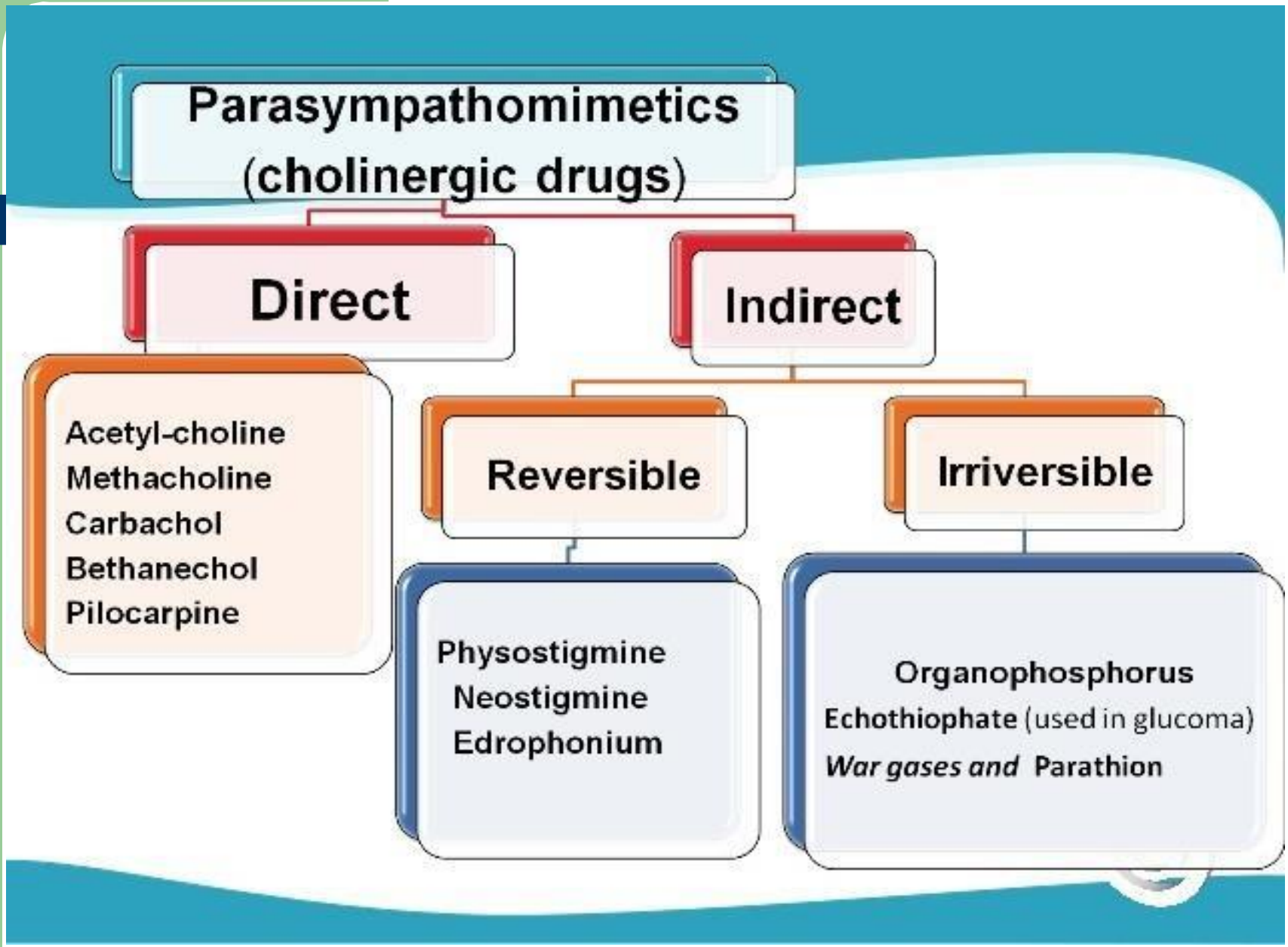
When nicotinic receptors are activated, sodium channels are opened leading to depolarization of membrane.

Parasympathomimetic agents

Drugs which mimic the effect of parasympathetic system.

Effects of parasympathetic system are shown on next slide.


Eye
(constrict pupil)
Lungs
(constrict bronchioles
and increase secretions)
PARASYMPATHETIC
Heart
(decreased
heart rate)
Blood vessel
(dilate)
Ganglion
Spinal cord
Gastrointestinal
(increase peristalsis
and secretions)
Bladder
(contracts)
Salivary gland
(increased salivation)

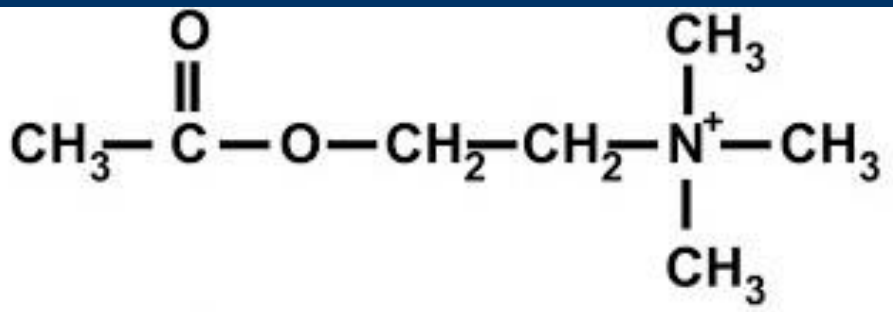

Parasympathomimetics
(cholinergic drugs)
Direct
Indirect
Acetyl-choline
Methacholine
Carbachol
Bethanechol
Pilocarpine
Reversible
Irriversible
Physostigmine
Neostigmine
Edrophonium
Organophosphorus
Echothiophate (used in glucoma)
War gases and Parathion

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.

Acetylcholine (prototype drug)



2-Acetoxy-*N*,*N*,*N*-trimethylethanaminium

Stimulates muscarinic and nicotinic receptors.

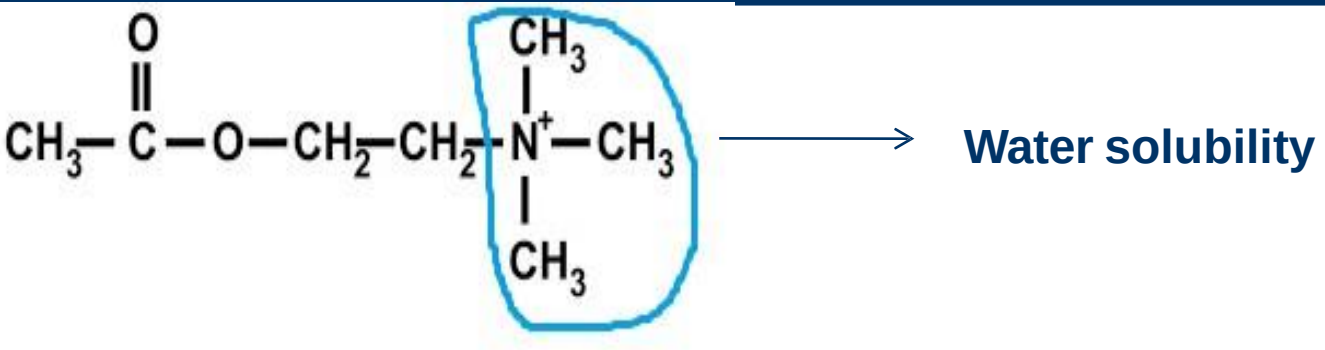
Stable in the solid crystalline form but undergoes rapid hydrolysis in aqueous solution.

- **Oral administration:**

rapid hydrolysis in the gastrointestinal tract.

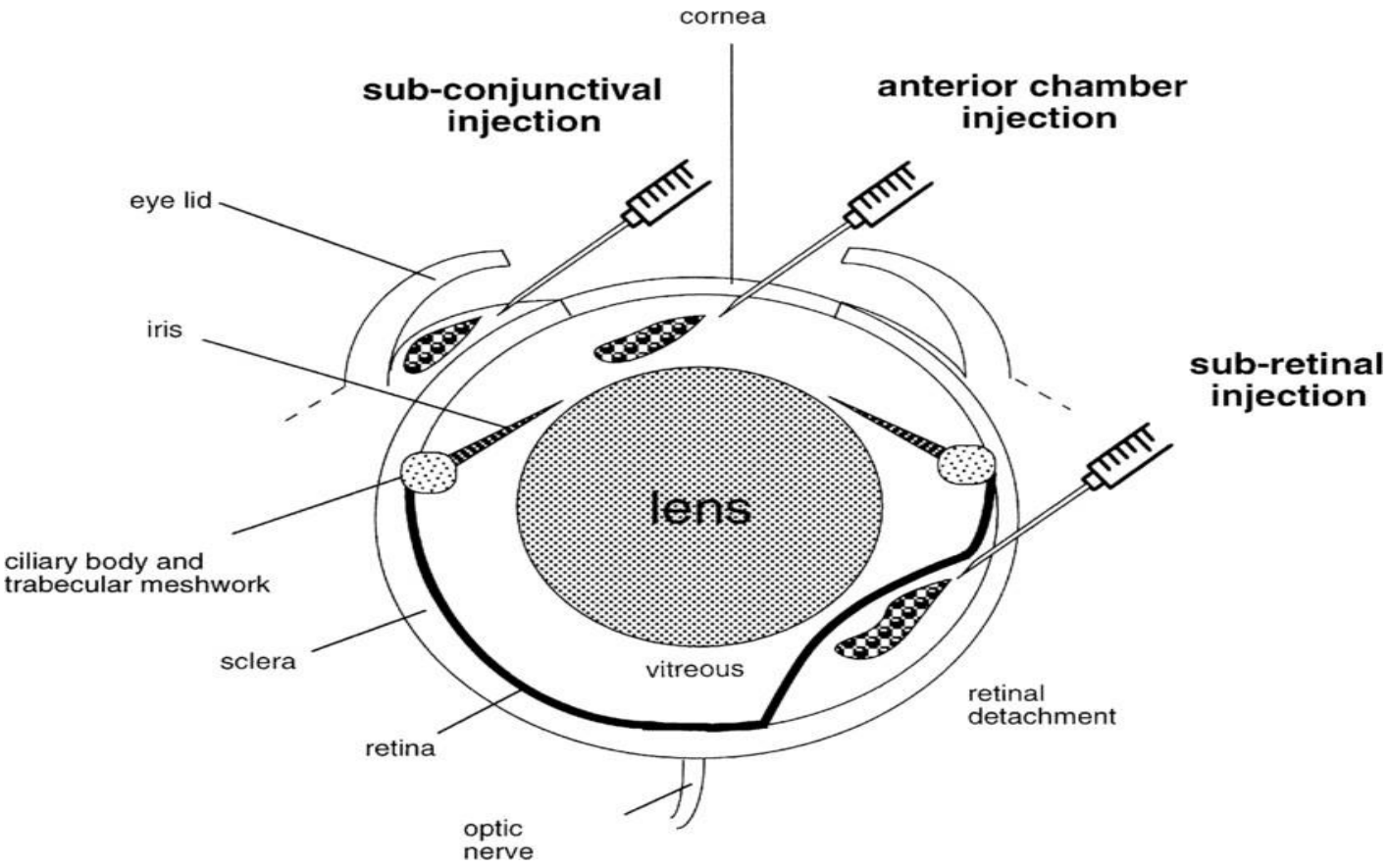
- **Parenterally:**

hydrolysis by butyrylcholinesterase (also known as pseudocholinesterase or plasma cholinesterase) in serum.

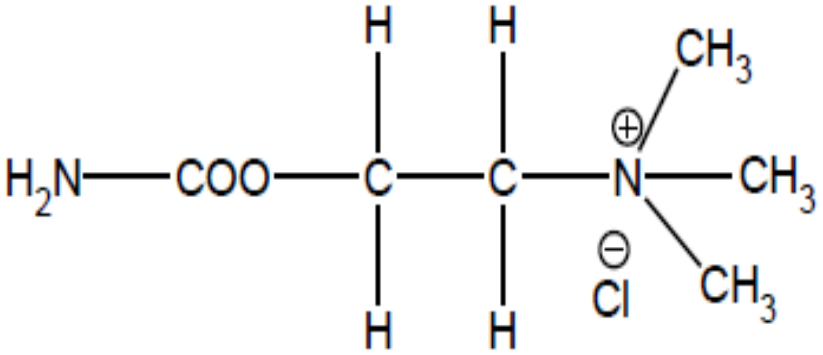


But quaternary ammonium salts are poorly absorbed across lipid membranes due to their high hydrophilic and ionic character.

- When used during ocular surgery to produce complete miosis within seconds acetylcholine must be directly instilled into the anterior chamber.


cornea
sub-conjunctival injection
anterior chamber injection
eye lid
iris
sub-retinal injection
lens
ciliary body and trabecular meshwork
sclera
vitreous
retinal detachment
retina
optic nerve

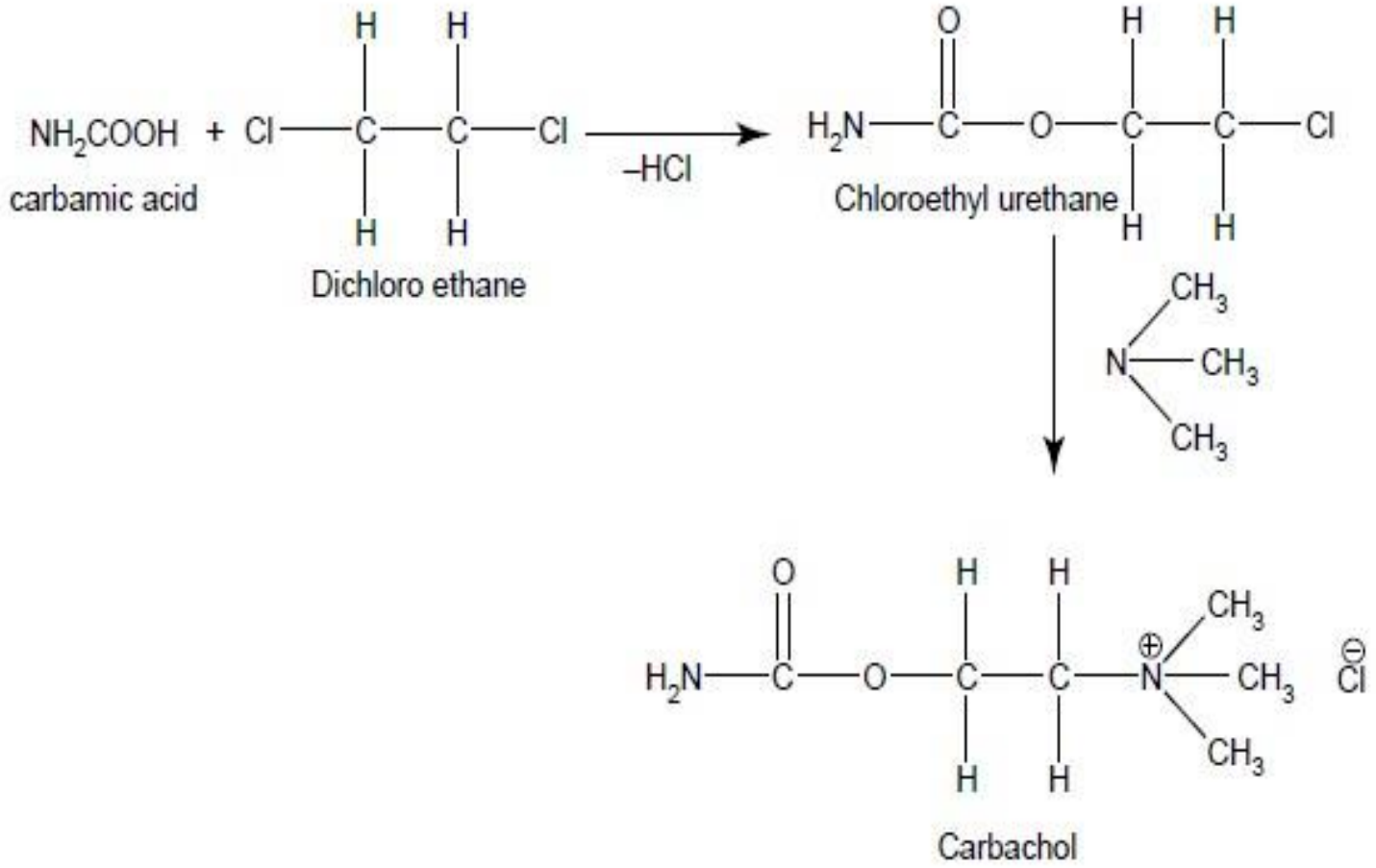
Carbachol

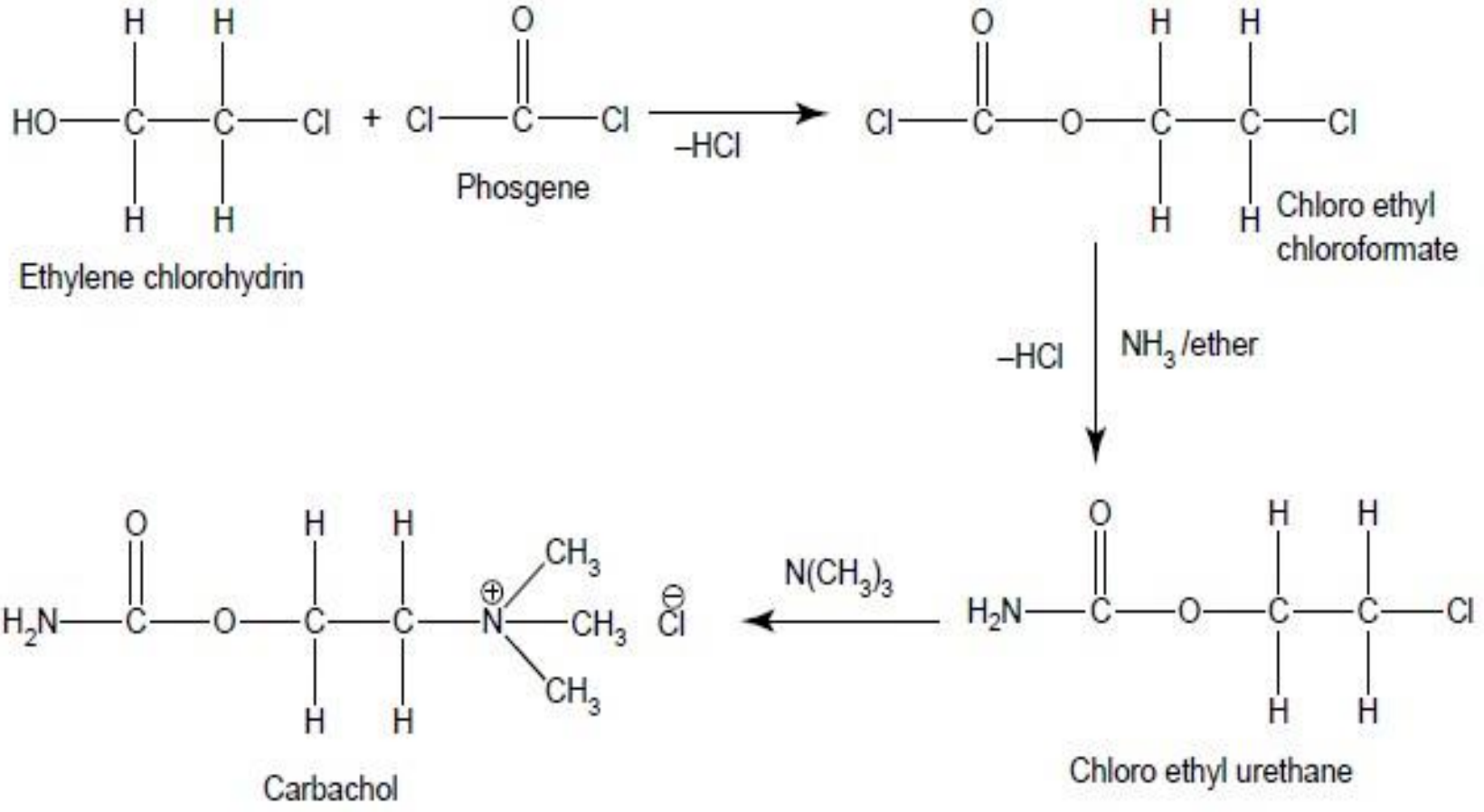


2-[(Aminocarbonyl)oxy]-*N*,*N*,*N* trimethylethanaminium chloride

- carbamate analog of acetylcholine
- exhibits affinity for both mAChRs and nAChRs.
- more resistant toward acid-, base-, or enzyme (AChE)-catalyzed hydrolysis than acetylcholine.
- also reported to exhibit weak anticholinesterase activity.

Synthesis

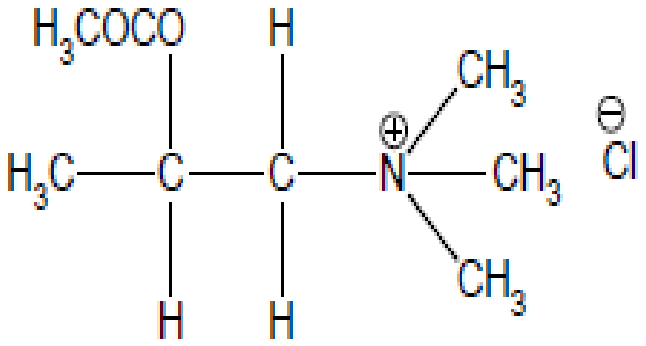

NH2COOH + Cl—C—C—Cl
carbamic acid
Dichloro ethane
–HCl
H2N—C(=O)—O—C—C—Cl
Chloroethyl urethane
N(CH3)3
H2N—C(=O)—O—C—C—N⊕(CH3)3 Cl⊖
Carbachol


Ethylene chlorohydrin
Phosgene
–HCl
Chloro ethyl chloroformate
–HCl
NH3 /ether
N(CH3)3
Chloro ethyl urethane
Carbachol

Use: treatment of glaucoma and for the induction of miosis in ocular surgery.

- available as an intraocular solution and an ophthalmic solution.

Methacholine



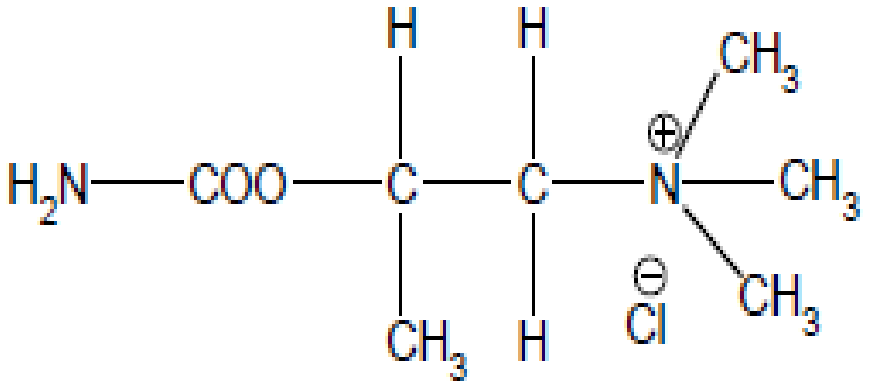
2-(Acetyloxy)-*N*,*N*,*N*-trimethylpropan-1-aminium

- selective muscarinic agonist with very little activity at nAChRs.

USES: via inhalation for the diagnosis of asthma.

Treat glaucoma

Bethanechol

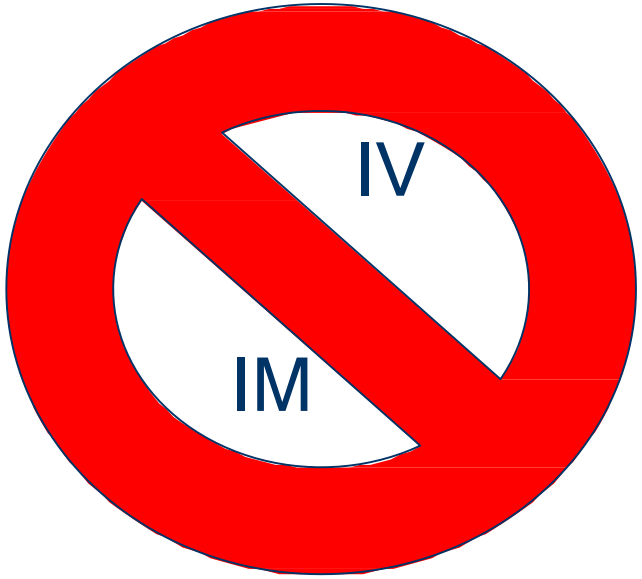


2-(Carbamoyloxy)-*N*,*N*,*N*-trimethylpropan-1-aminium

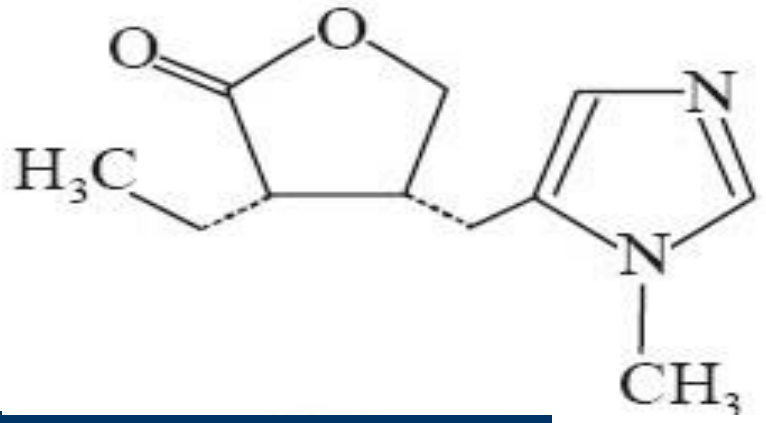
- carbamate analog of methacholine,
- selective for mAChRs and exhibits almost no affinity for nAChRs.

Used to treat postsurgical and postpartum urinary retention and abdominal distention.

It can be given subcutaneously.



Cholinergic crisis: over-stimulation at neuromuscular junction



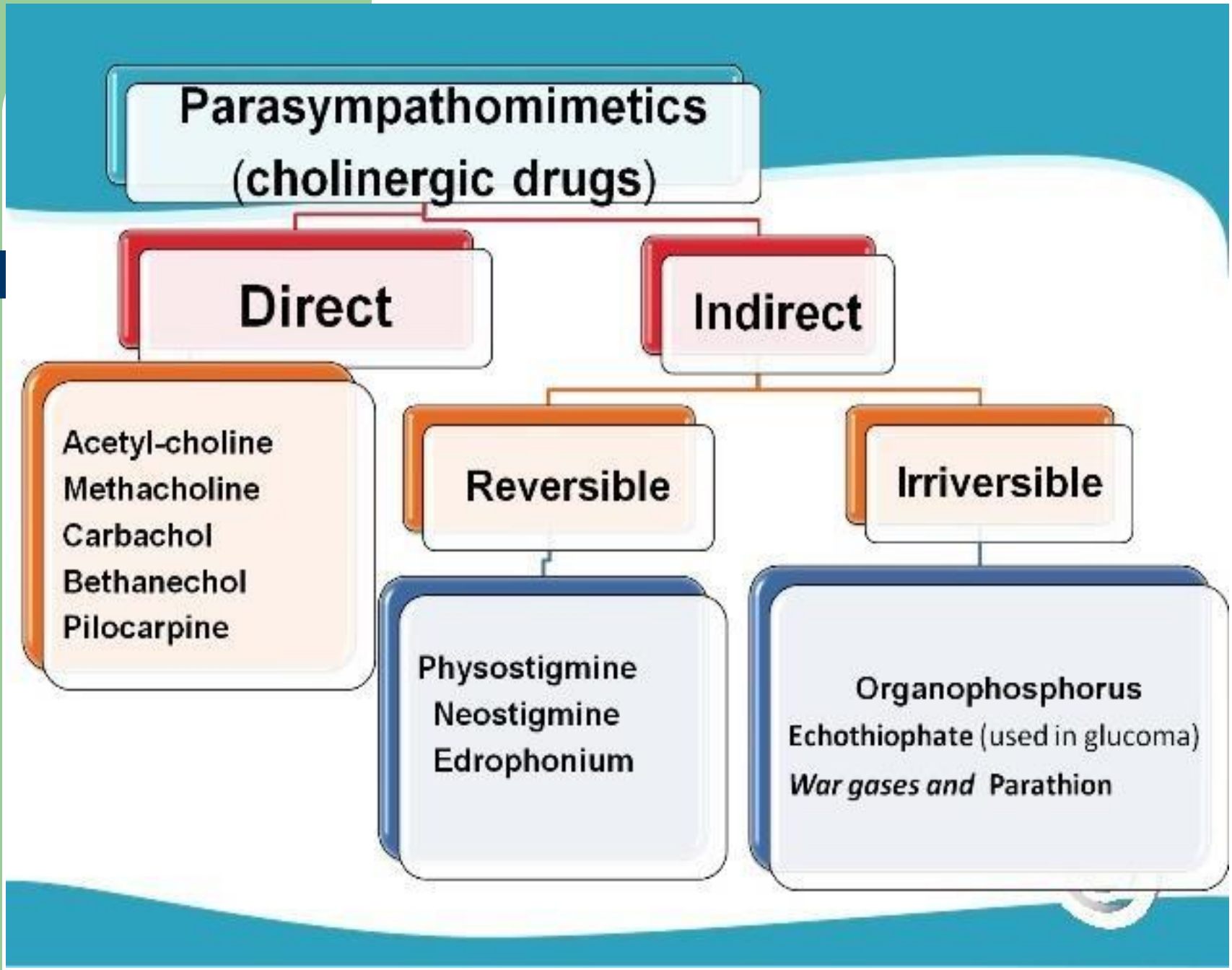
Pilocarpine

(3*S*,4*R*)-3-Ethyl-4-((1-methyl-1*H*-imidazol 5-yl)methyl) dihydrofuran-2(3*H*)-one

alkaloid obtained from *Pilocarpus jaborandi*

- muscarinic agonist with affinity for the M3 mAChR

- It penetrates the eye well and is the miotic of choice for open-angle glaucoma and to terminate acute angle closure attacks.
- It is also used for the treatment of xerostomia (dryness of the mouth) caused by radiation therapy of the head and neck, Sjögren syndrome, and mucositis following chemotherapy.


Parasympathomimetics
(cholinergic drugs)
Direct
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Irriversible
Physostigmine
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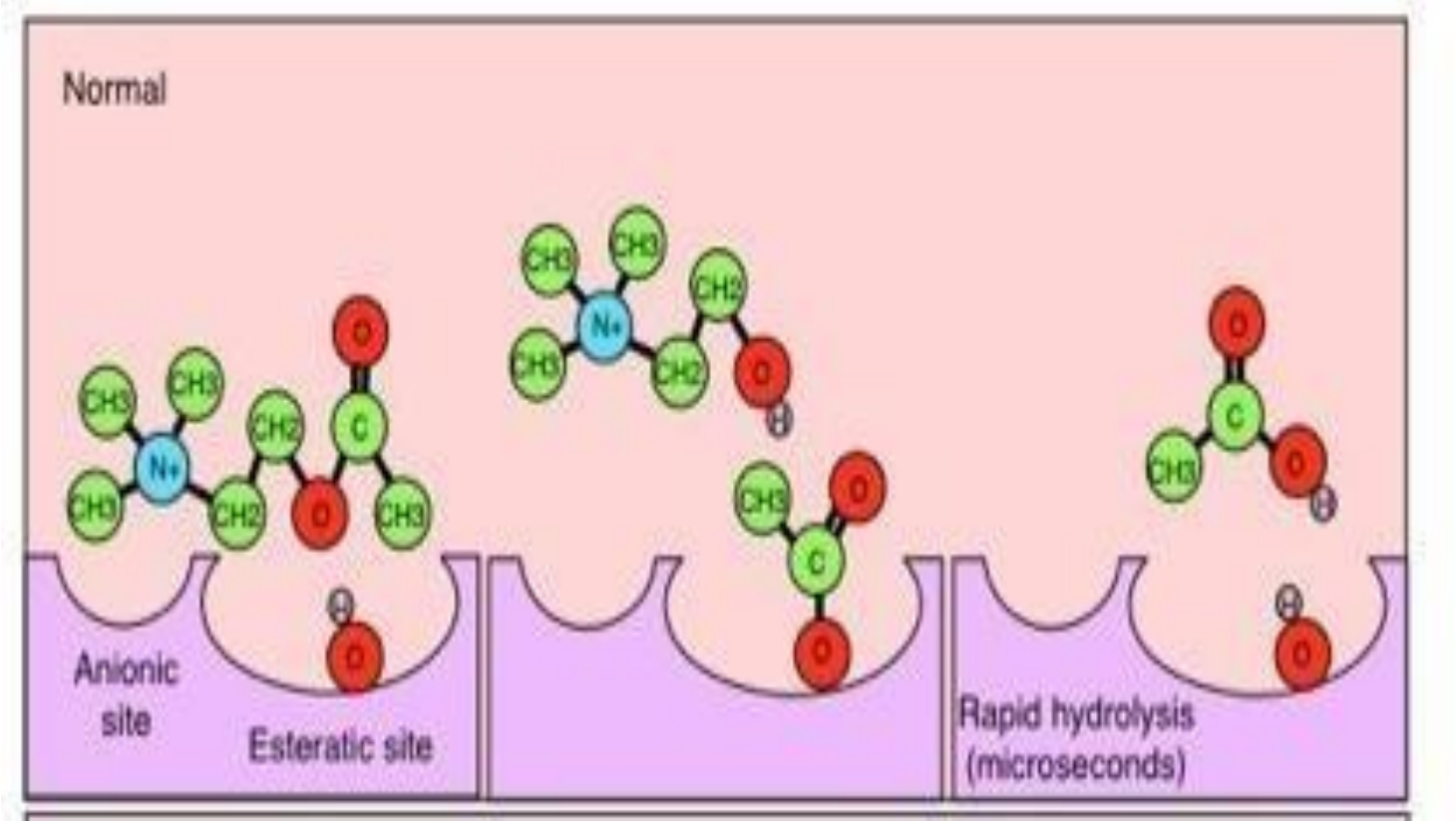
Edrophonium
Organophosphorus
Echothiophate (used in glucoma)
War gases and Parathion

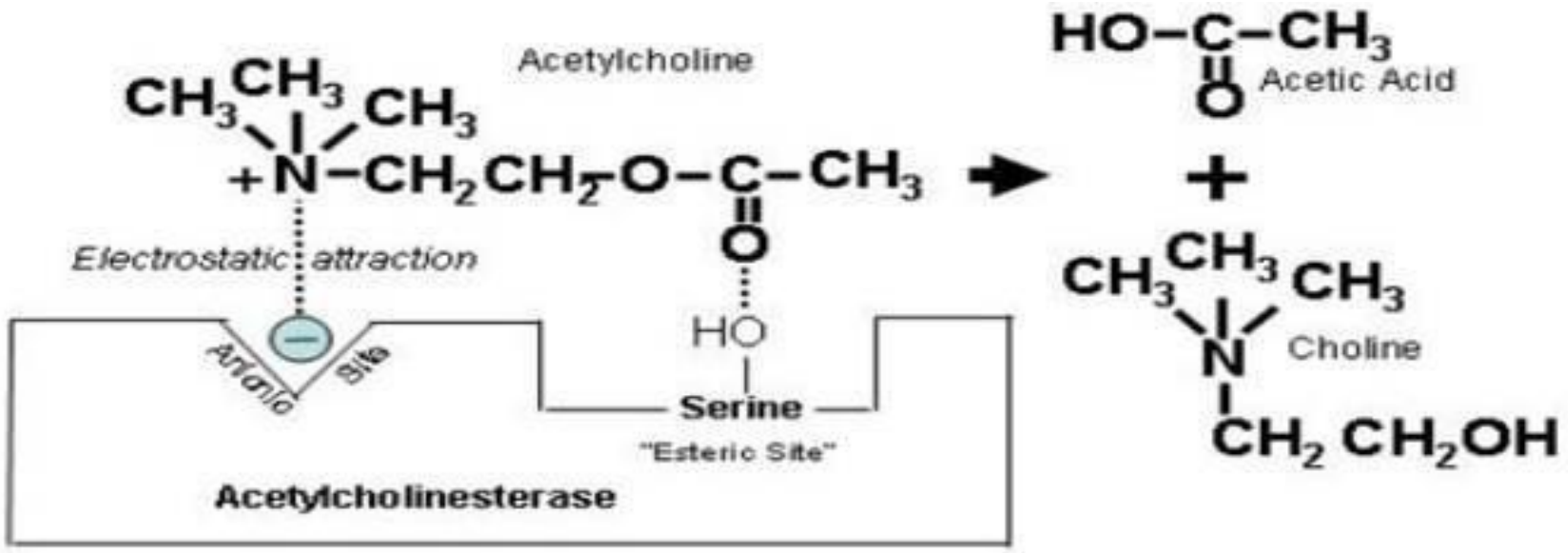
Acetylcholinesterase

AChE is a hydrolase that hydrolyzes choline esters.

high catalytic activity—each molecule of AChE degrades about 25,000 molecules of ACh per second, The active site of AChE comprises 2 subsites—the anionic site and the esteratic subsite.


Normal
Anionic site
Esteratic site
Rapid hydrolysis (microseconds)

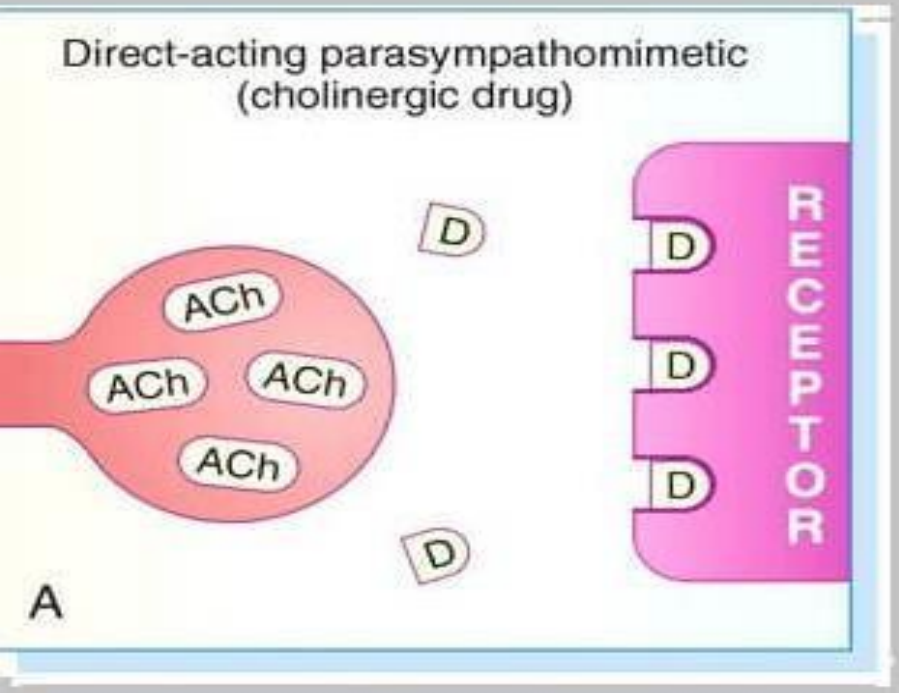
Action of acetylcholine is teminated by enzymatic hydroysis by acetylcholinesterase.

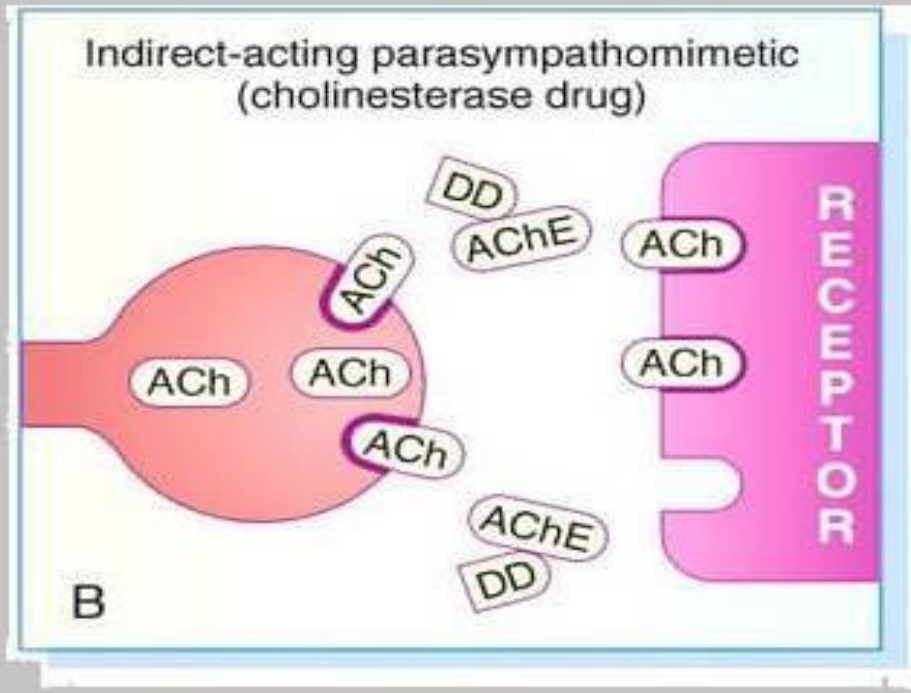


Indirectly acting agents have primary effect on the active site of this enzyme.

Indirectly acting agents

Direct and indirect parasympathomimetic drugs





1. **Reversible:**

The amine or ammonium AChE inhibitors react reversibly with enzymes. They reversibly acylate the esteratic serine hydroxyl.

Duration: few weeks to months.

Eg: Physostigmine, Neostigmine, Pyridostigmine, Edrophonium chloride, tacrine, Ambenonium chloride,

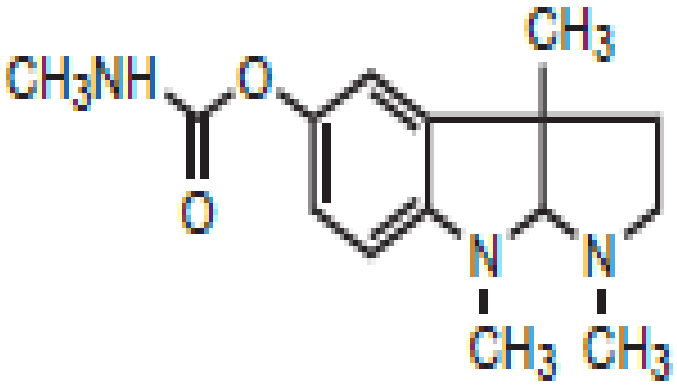
2. Irreversible:

Organophosphate type AChE inhibitors form an irreversible firm bond with enzymes (esteratic site)

Duration of action: few weeks to month

Eg: Isofluorphate, Echothiophate iodide, Parathione, Malathion.

Physostigmine



(3a*S*,8a*R*)-1,3a,8-Trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl methylcarbamate

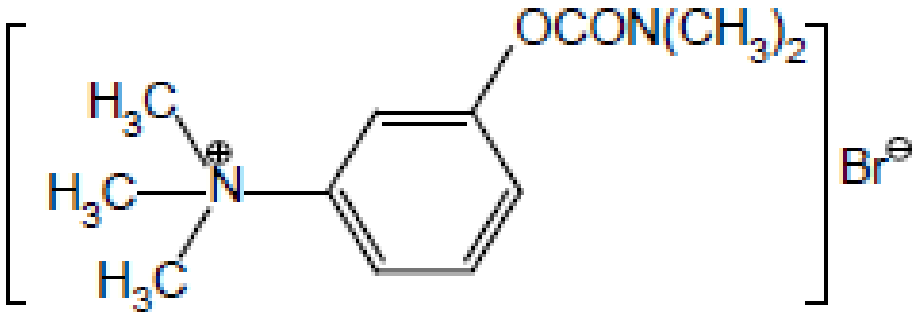
- an alkaloid obtained from seeds of the Calabar bean (*Physostigma venenosum)*

- *Oldest anticholiesterase agent.*

USES

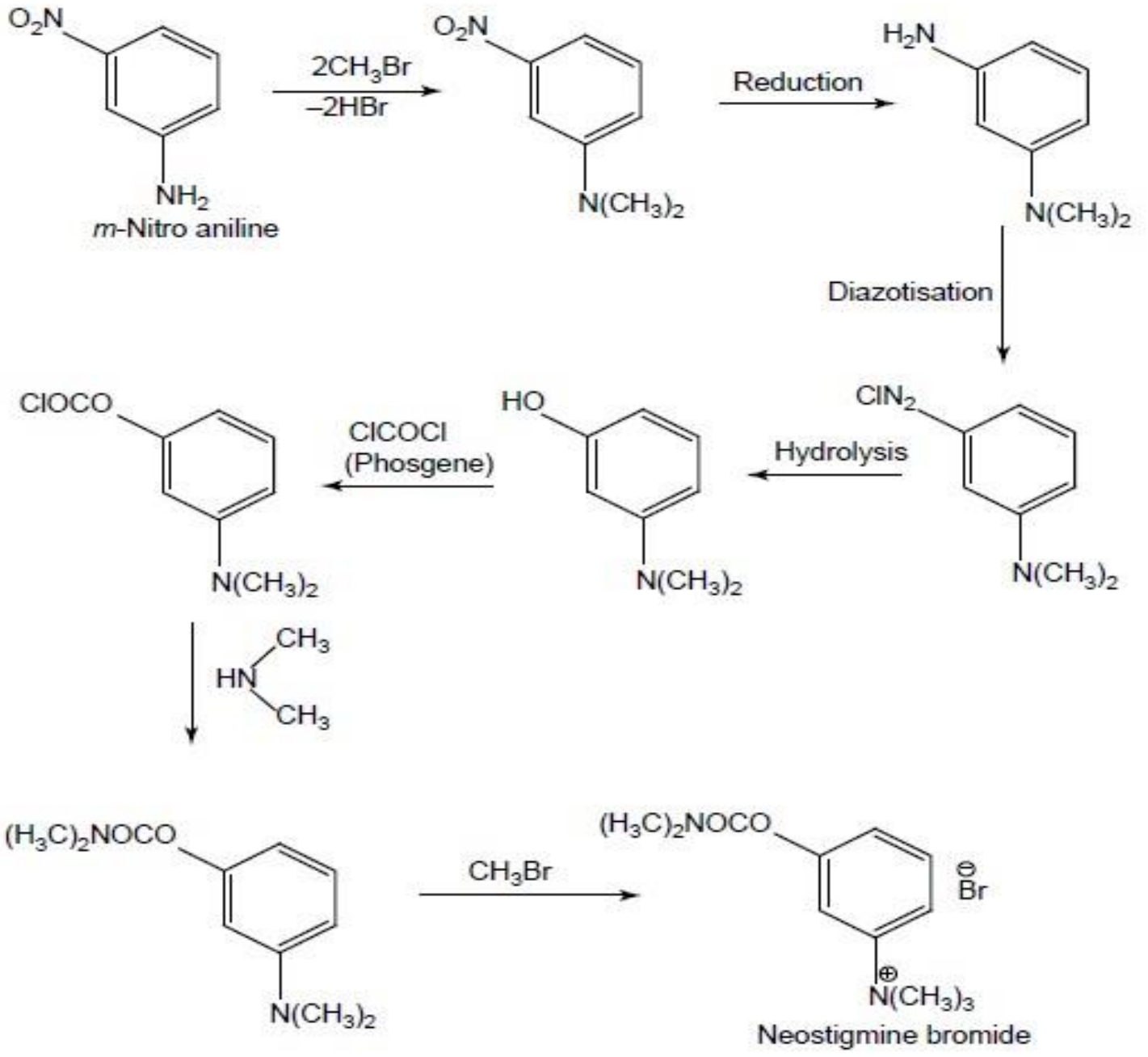
- Treatment of glaucoma.
- It can penetrate blood brain barrier and is used to antagonize toxic effect of antimuscarinic drugs, tricyclic antidepressants, H1 antihistamines and benzodiazepines.
- Also used in treatment of alzheimer's disease.

Neostigmine

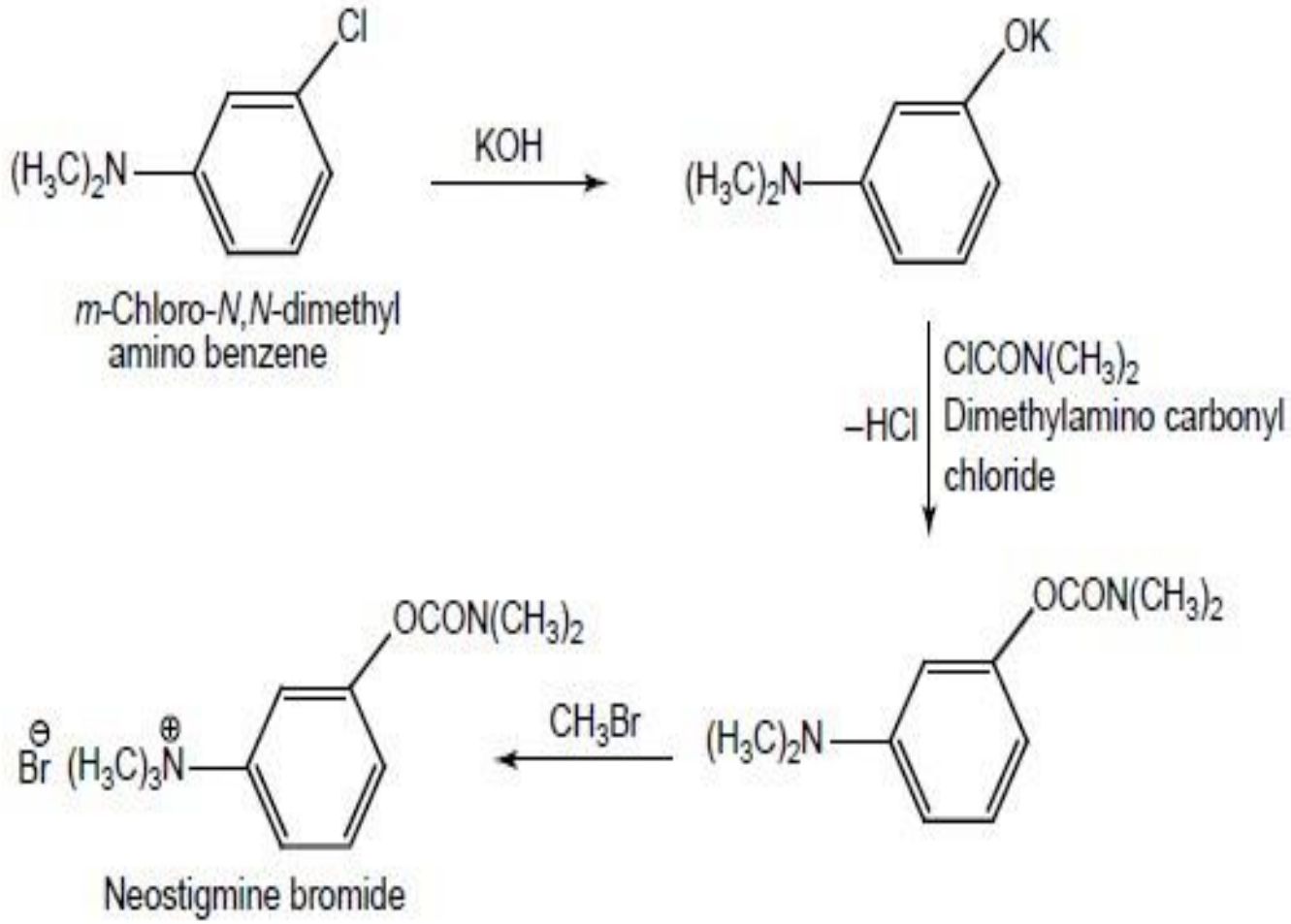


3-{[(Dimethylamino)carbonyl]oxy}-*N*,*N*,*N*-trimethylbenzenaminium

Route I. From: Meta nitro aniline



Route II. From: *m*-Chloro-*N*,*N*-dimethyl amino benzene

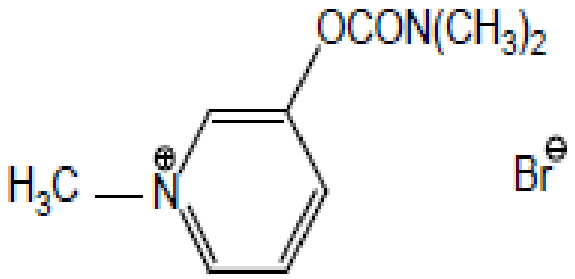


Uses:

- prophylaxis of postoperative abdominal distension and urinary retention, myasthenia gravis
- reversal of neuromuscular blockade.

Myasthenia gravis (**MG**) is a long-term neuromuscular disease that leads to varying degrees of skeletal muscle weakness. The most commonly affected muscles are those of the eyes, face, and swallowing. It can result in double vision, drooping eyelids, trouble talking, and trouble walking. Onset can be sudden.

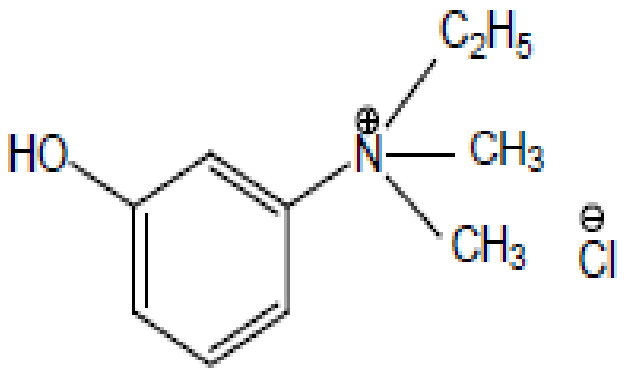
Pyridostigmine



3-[(dimethylcarbamoyl)oxy]-1-methylpyridinium

- It is used in the treatment of myasthenia gravis and it antagonizes the effects of neuromuscular blocking (NMB) agents.
- orally effective and, compared to neostigmine, has a longer duration of action and a lower incidence of side effects. Thus, it is a better choice for oral therapy of myasthenia gravis.

Edrophonium chloride

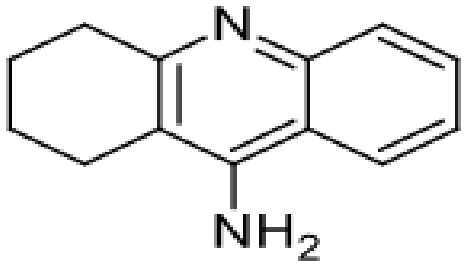


N-Ethyl-3-hydroxy-*N*,*N* dimethylbenzenaminium

On parenteral administration, edrophonium has a more rapid onset and shorter duration of action than neostigmine, pyridostigmine, or ambenonium.

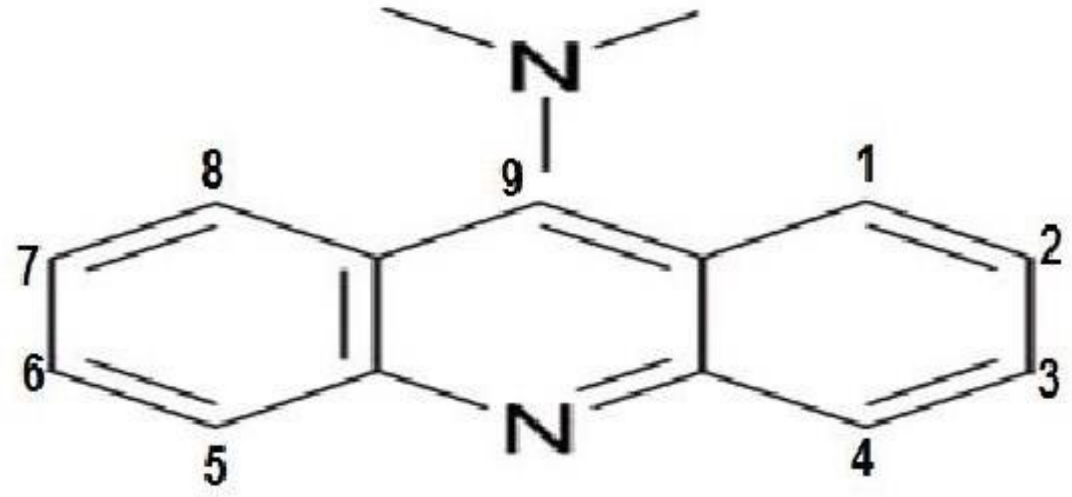
- It is used as an antiarrhythmic drug in paroxysmal atrial tachycardia.
- Diagnosis of myasthenia gravis.
- Administered intramuscularly to rapidly reverse the effects of nondepolarizing neuromuscular blocking agents like *d-tubocurarine and gallamine.*

Tacrine hydrochloride



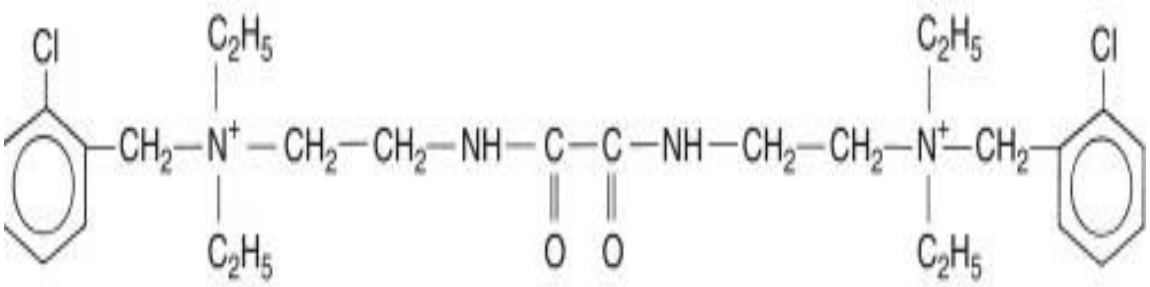
1,2,3,4-Tetrahydroacridin-9-amine

- Aminoacridine synthesized in the 1930s
- nonclassical cholinesterase inhibitor that binds to both AChE and butyrylcholinesterase


N
8
9
1
7
2
6
3
N
5
4

- its use is limited due to hepatotoxicity and development of safer AChEIs.
- Was prototypical drug for treatment of alzheimer’s disease.
- Use discontinued since 2013

Ambenonium chloride,

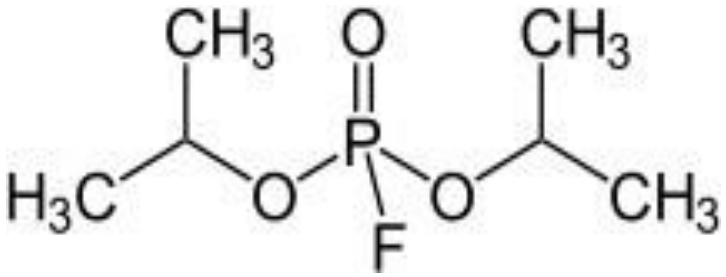


Ambenonium

2,2'-[(1,2-Dioxoethane-1,2-diyl)diimino]*bis*[*N*-(2-chlorobenzyl)-*N*,*N*-diethylethanaminium]

- Reversible inhibition of acetylcholinesterase
- Management of myaesthenia gravis.
- Withdrawn from the market in the United States in 2010

Isoflurophate/Isofluorophate

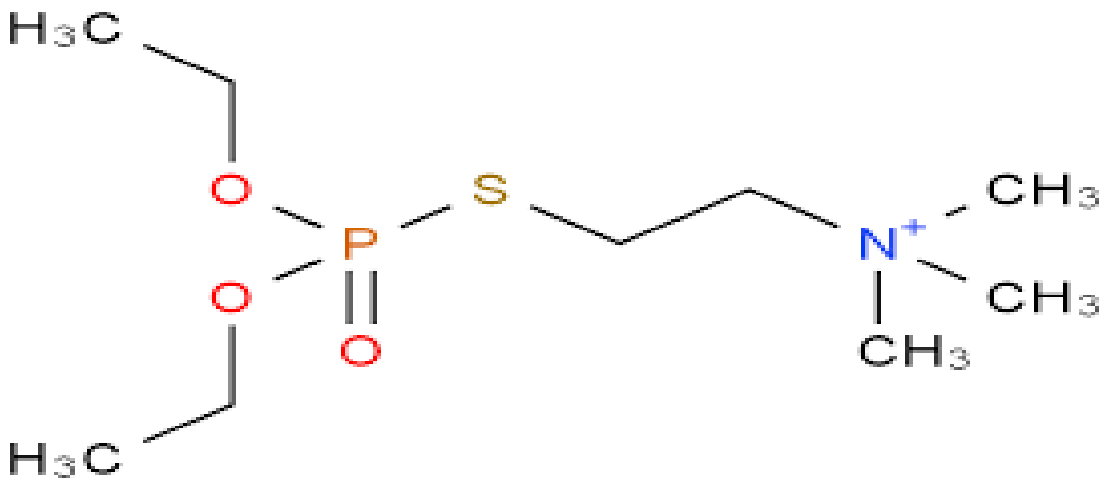


bis(propan-2-yl) fluorophosphonate

Used as miotic agent.

Potent neurotoxin

Echothiophate Iodide (Phospholine Iodide)



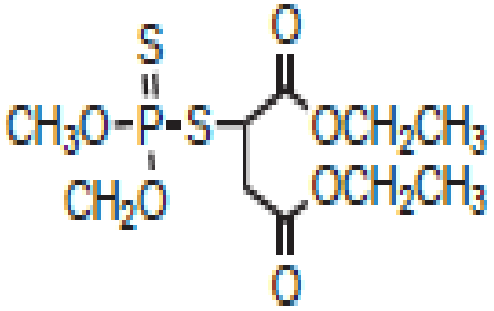
2-(Diethoxyphosphorylsulfanyl)ethyl-*N*,*N*,*N*-trimethylazanium iodide

- Treatment of glaucoma and strabismus (cross eye).

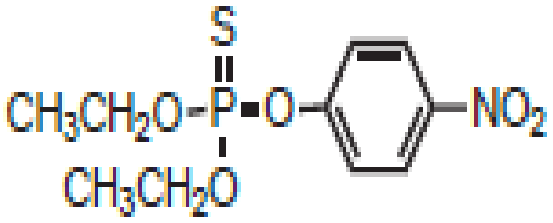
Insecticidal AChEIs

- AChEI insecticides is beneficial to agricultural production throughout the world.

Extremely lipophilic, another physicochemical property common to these compounds is a high vapor pressure.



Malathion



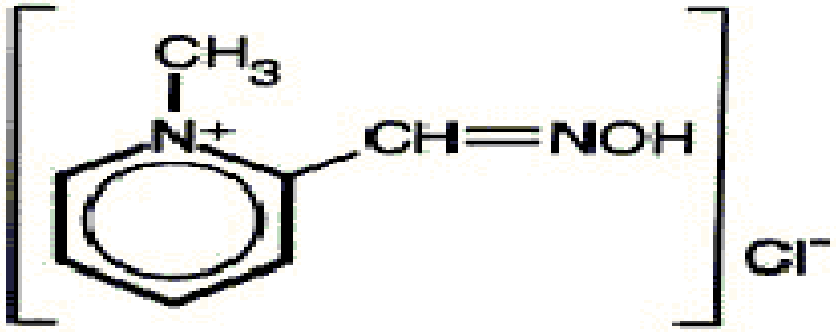
Parathion

- **Malathion** is a dithiophosphate ester that has found use both as an aerial insecticide and clinically as a mitocide for topical treatment of lice infestations of the hair and scalp.
- **Parthione** : Highly toxic

Choliesterase reactivator

- Drugs used to reverse the inactivation of cholinesterase caused by organophosphates or sulphonates.
- These are used as antidotes against organophosphates or sulphonates.
- Examples: **Pralidoxime**, obidoxime, isonitrozine.

Pralidoxime chloride



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

Pralidoxime is typically used in cases of organophosphate poisoning.

Mechanism of action

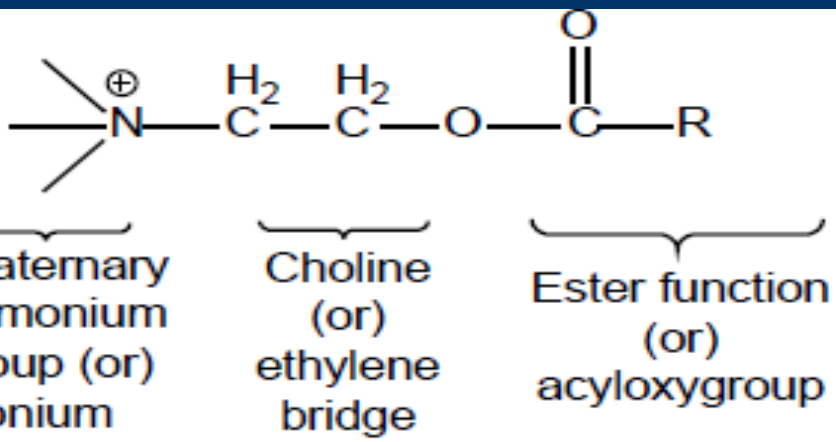
- Organophosphates bind to the hydroxy component (the esteric site) of the active site of the acetylcholinesterase enzyme, thereby blocking its activity.
- Pralidoxime binds to the other half (the unblocked, anionic site) of the active site and then displaces the phosphate from the serine residue.
- The conjoined poison / antidote then unbinds from the site, and thus regenerates the fully functional enzyme.

- Uses: antidote for organophosphorus compounds like parathion and related pesticides poison.

SAR

- 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.


O
⊕
N
H2
C
H2
C
O
C
R
Quaternary ammonium group (or) onium
Choline (or) ethylene bridge
Ester function (or) acyloxygroup

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.

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.

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 β-substitution leads to reduction of nicotinic activity to greater extent.
- Replacement of ester group with ether or ketone produces chemically stable and potent compounds.

- Students, next topic is anticholinergic drugs.
- So lets have a glance at difference between the cholinergics and anticholinerics….it will be easier for you to study….

Cholinergic actions	Anticholinergic actions
Eye 1. Contraction of circular muscle of iris (miosis) 2. Contraction of ciliary muscles for near vision	1. Mydriasis 2. Cycloplegia relaxation of ciliary muscles
Heart bradycardia (↓ heart rate)	Tachycardia (↑ heart rate)
Urinary bladder Contraction of muscles Relaxation of sphincter	Relaxation of muscles contraction of sphincter

Cholinergic drugs	Anticholinergic drugs
Exocrine glands Increase of sweat, saliva, lacrimal, bronchial, intestinal secretions	Decrease all secretion
GIT ↑ peristalsis ↑ secretion relaxation of sphincter	↓ peristalsis ↓ secretion Contraction of sphincter
Lung 1. Bronchoconstriction 2. ↑ bronchial secretion	1. Bronchodilatation 2. Decrease secretion