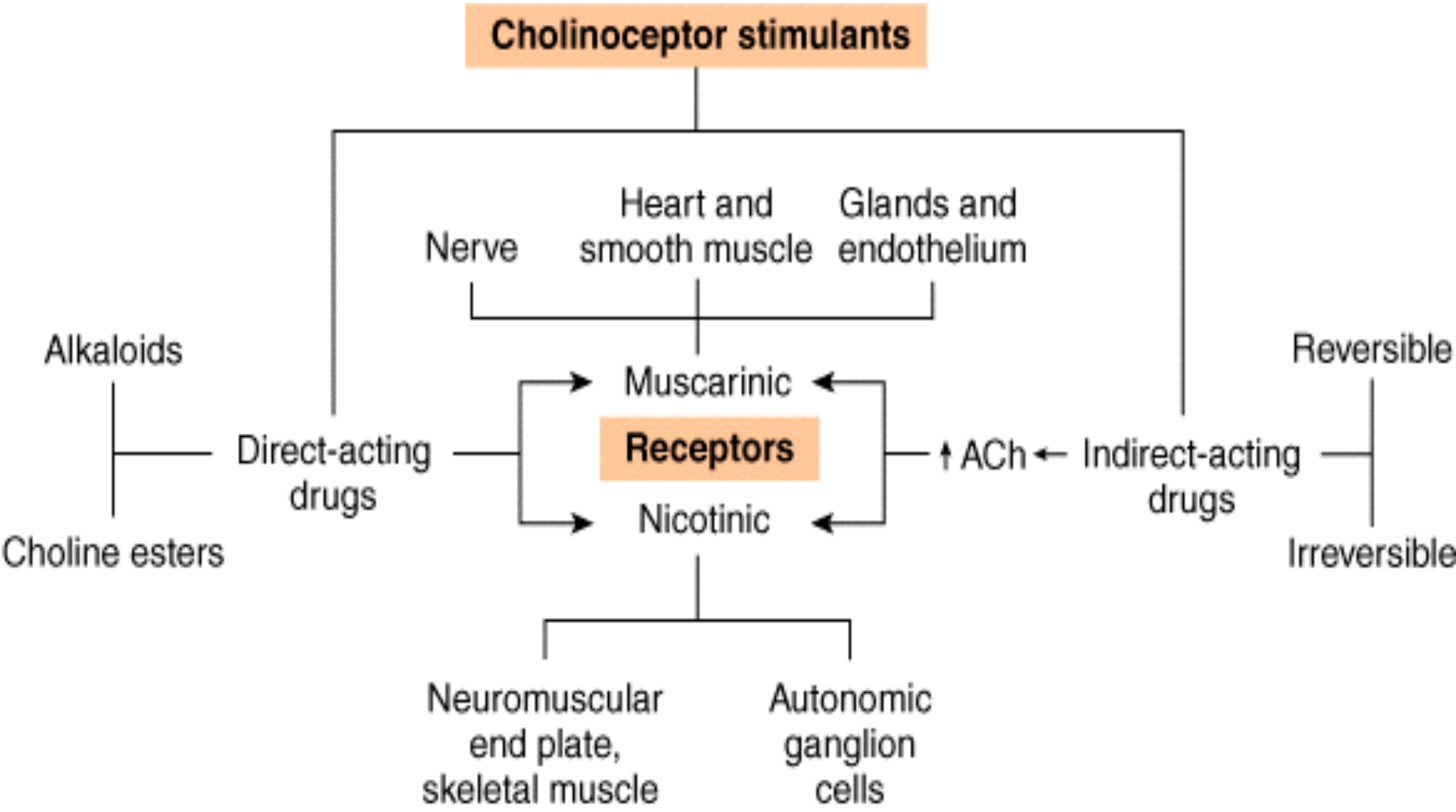
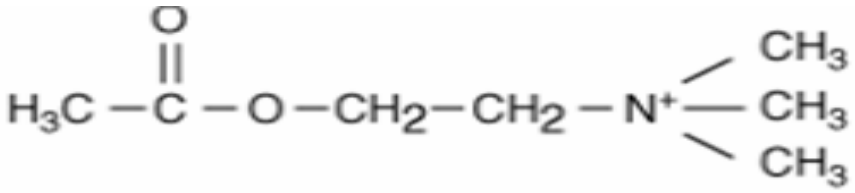
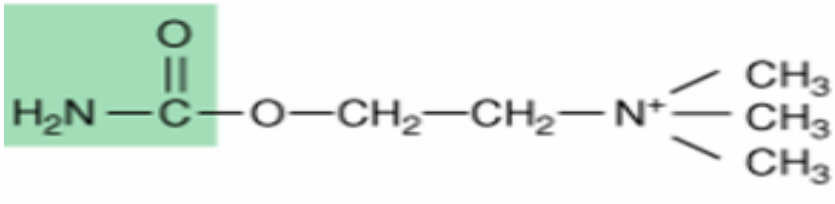
Cholinoceptor - Activating &Cholinesterase-Inhibiting Drugs -1



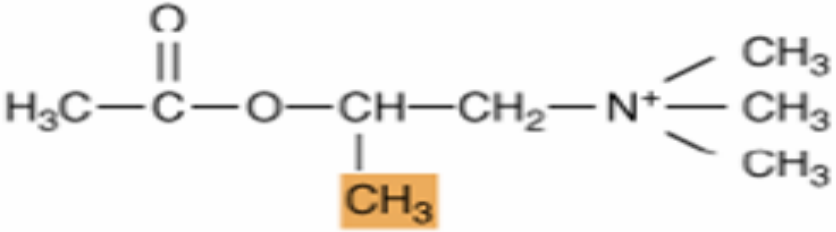
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com



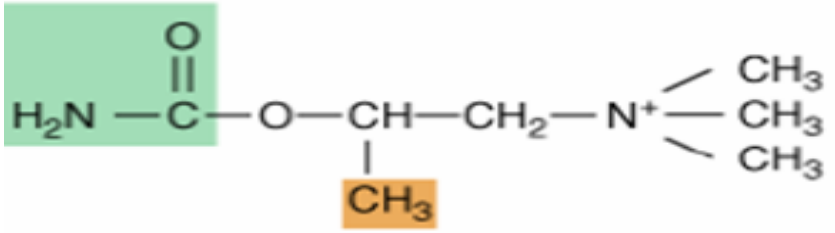
Acetylcholine



Carbachol
(carbamoylcholine)

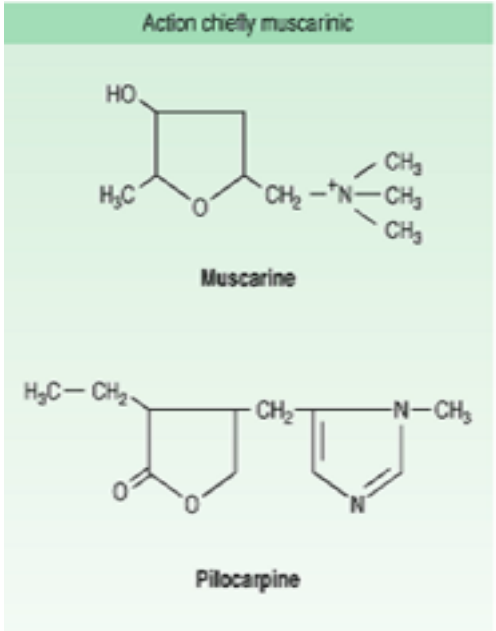


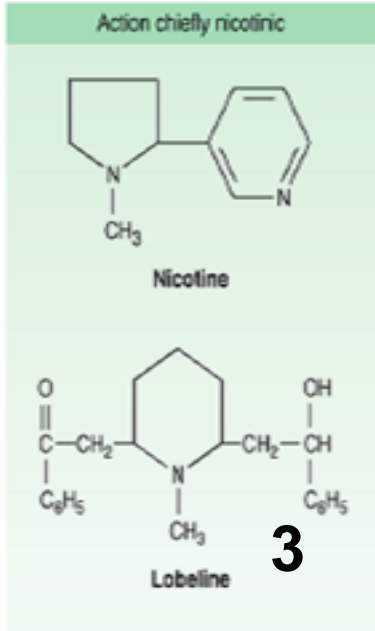
Methacholine
(acetyl-β-methylcholine)



Bethanechol
(carbamoyl-β-methylcholine)

Choline Ester	ACE	Muscarinic	Nicotinic
Acetylcholine	++++	+++	+++
Methacholine	+	++++	None
Carbachol	Negligible	++	+++
Bethanechol	Negligible	++	None

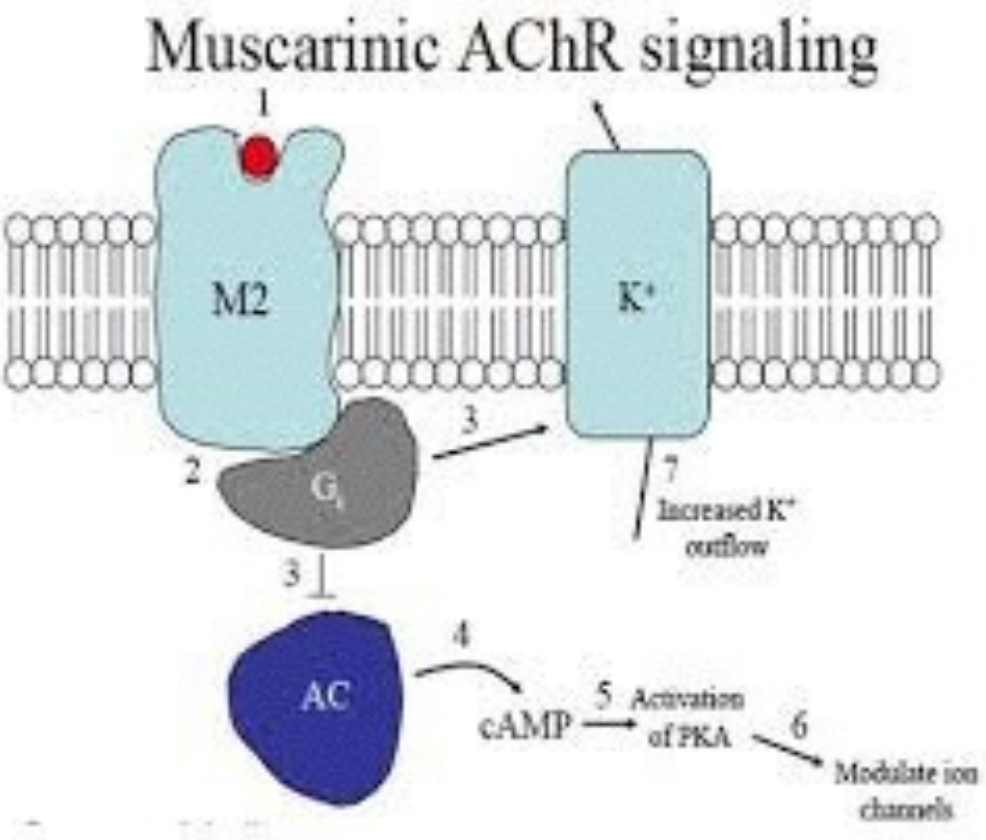




Mechanism of Action
Muscarinic transmission in the heart

Ach activates M2R linked via **Gi** protein to a **K+** channel Causing **hyperpolarization.**

Voltage-dependent opening of pacemaker Na+ channels is shifted to more negative Potentials



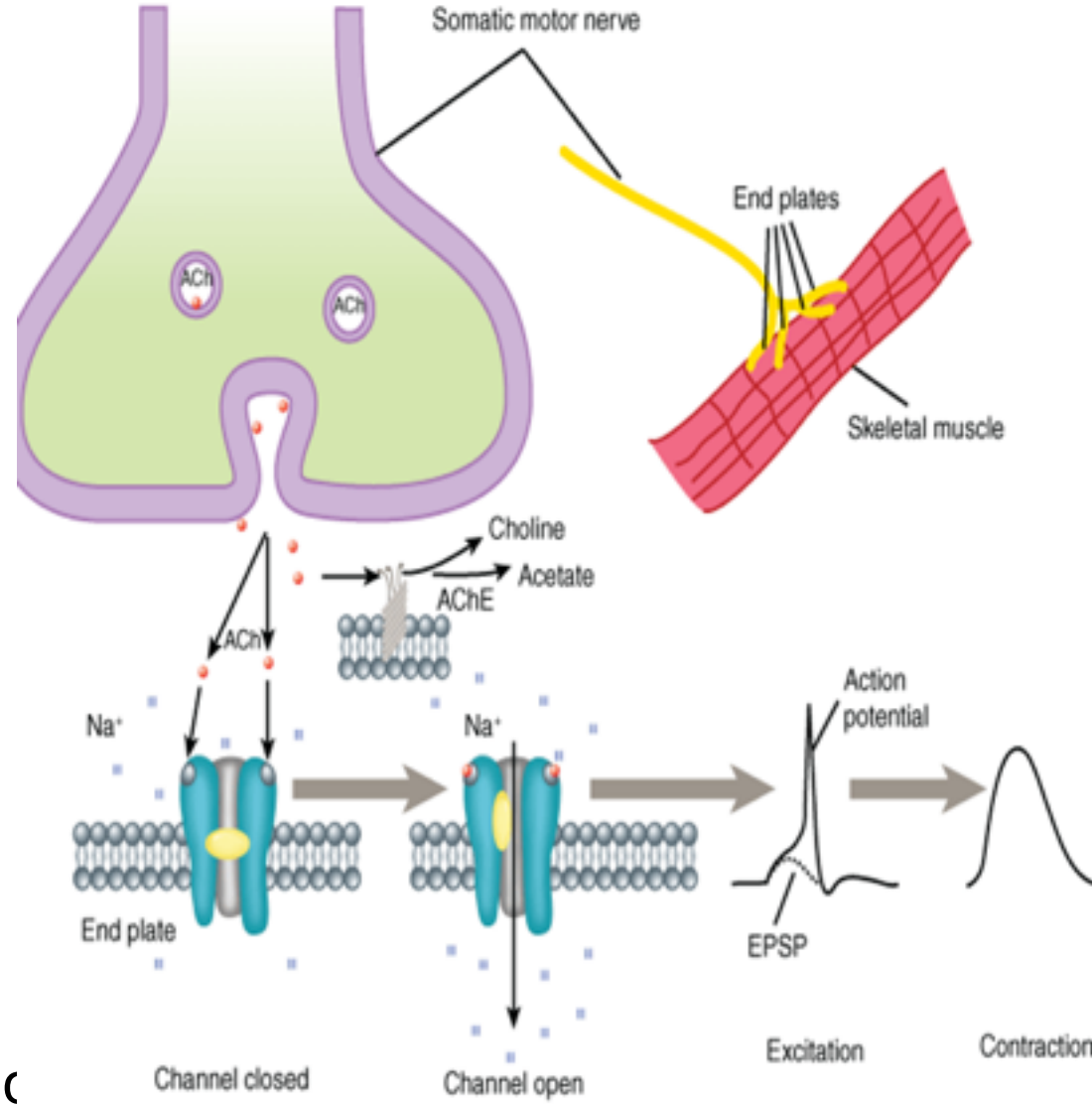
The phosphorylation of L-type Ca2+ channels is reduced.
M2R stimulates Gi protein↓→↓adenylyl cyclase→ ↓**cAMP** formation→↓HR &↓ force of contraction.

Nicotinic transmission at the neuromuscular junction.

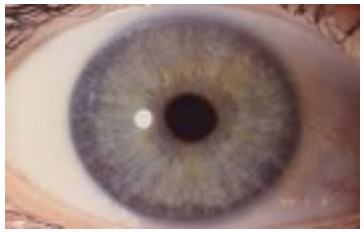
Ach interacts with subunits of the nicotinic receptor to open it, allowing Na+ to produce an excitatory postsynaptic potential (EPSP).

The EPSP depolarizes the muscle membrane, generating an action potential, and triggering contrac

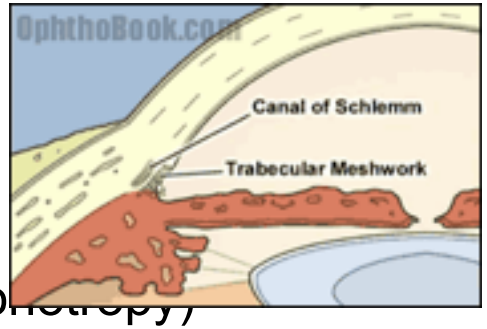
the extracellular Acetylcholinesterase(AChE) hydrolyzes Ach.



Effects of Direct-Acting Cholinoceptor Stimulants



Organ	**Response**
Eye	
Sphincter muscle of iris	Contraction (miosis).
Ciliary muscle	Contraction for near vision
	facilitation of aqueous humor outflow into the canal of Shlemm.



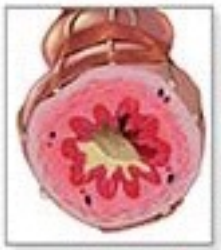
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy).
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period.
Ventricles	Small decrease in contractile strength

Blood vessels

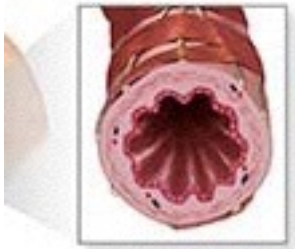
Arteries	Dilation via . **nitric oxide (NO)**
Veins	Dilation via . **nitric oxide (NO)**

Lung

Bronchial muscle	Contraction (bronch ı)
Bronchial glands	Stimulation



Asthmatic bronchiole



Normal bronchiole

Gastrointestinal tract

Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation

Urinary bladder

Detrusor	Contraction	
Trigone and sphincter	Relaxation	voiding of urine

Glands

Sweat, salivary, lacrimal , nasopharyngeal	↑ Secretion

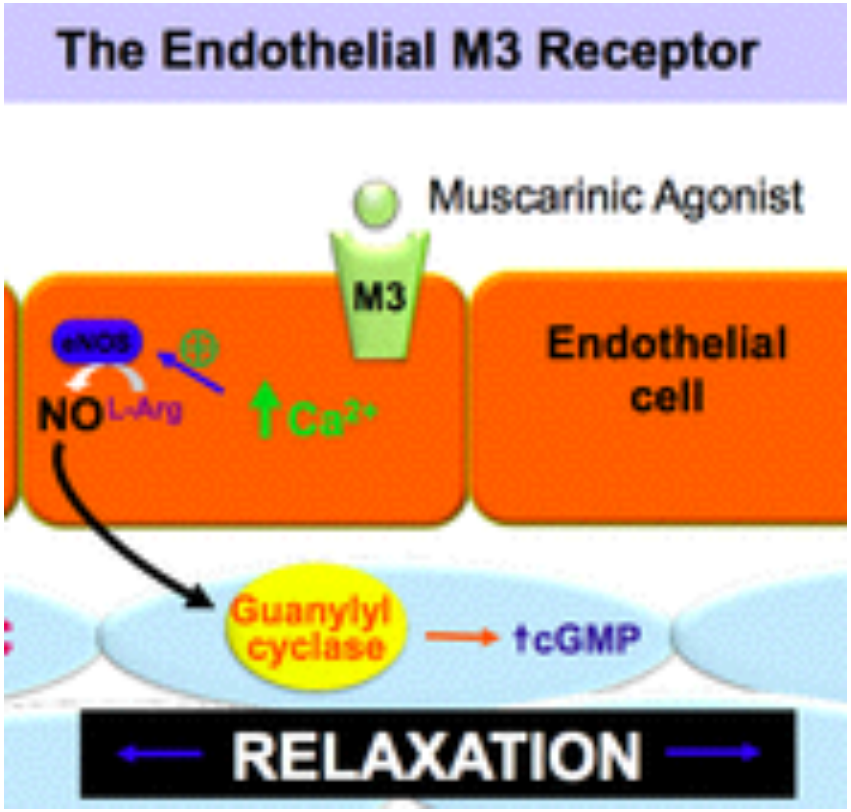
Organ System Effects

Cardiovascular System: M2

- IV infusions of low doses of **Ach** cause vasodilation, reduction in blood pressure, and a reflex increase in heart rate.
- Larger doses of a **Ach** produce bradycardia and decrease a AV node conduction velocity and hypotension.
- Decrease the contractility of atrial & ventricular cells.
- The direct slowing of sinoatrial rate & atrioventricular conduction is often opposed by reflex sympathetic discharge, elicited by the decrease in blood pressure.

- IV injection of muscarinic agonists produces marked vasodilation.
- Muscarinic agonists release nitric oxide (NO), from the endothelial cells.
- The NO diffuses

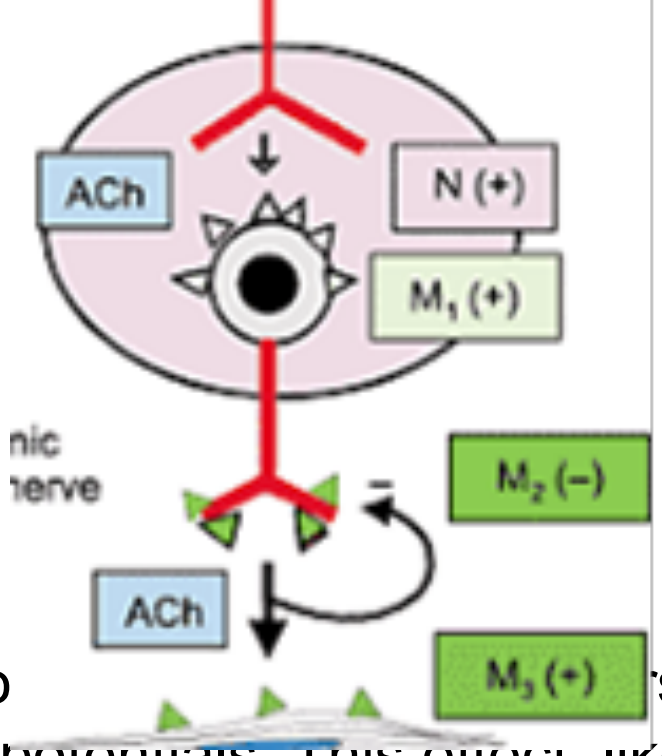
to adjacent vascular smooth muscle, where it activates guanylyl cyclase & increases cGMP, resulting in relaxation.



Pilocarpine

Natural alkaloid may produce hypertension after a brief initial hypotension.

The longer-lasting hypertensive Effect is due to sympathetic ganglionic activation caused by activation o's, which elicit slow excitatory postsynaptic potentials. This effect, like the hypotensive effect, can be blocked by atropine, an antimuscarinic drug.

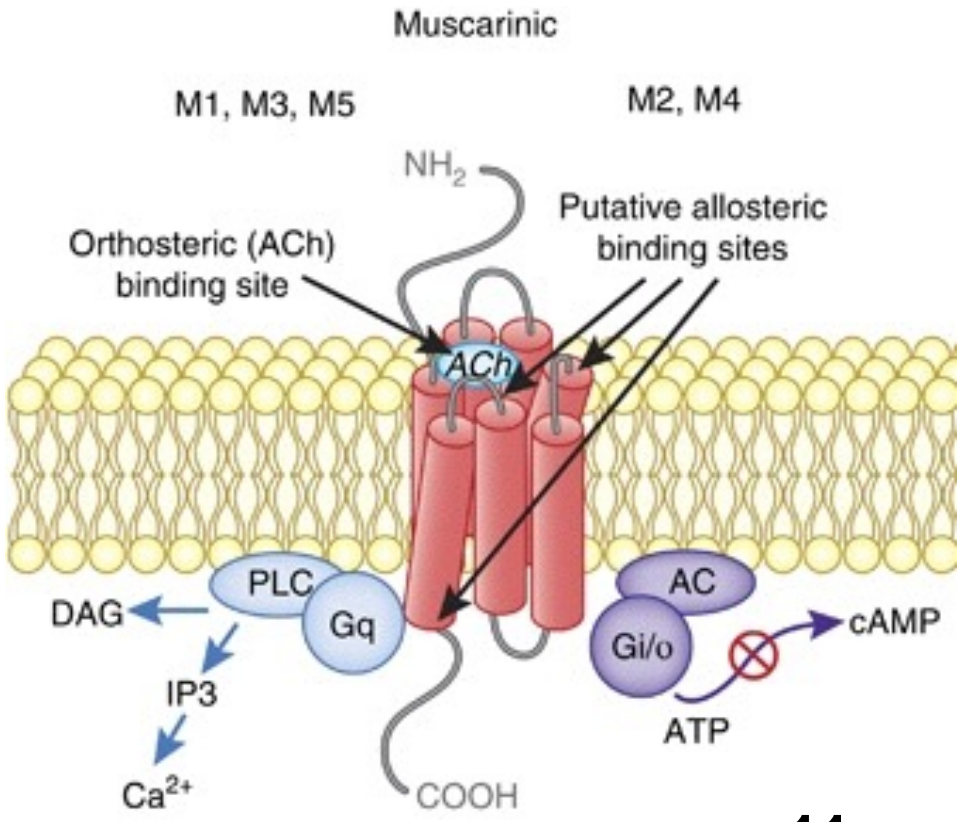


Respiratory System:

Bronchoconstriction and increase bronchial secretion.

Gastrointestinal Tract:

- increases the secretory and motor activity of the gut.
- The salivary and gastric glands are strongly stimulated.
- Peristaltic activity is increased and most sphincters are relaxed.
- The **M3** receptor is required for direct activation of smooth muscle contraction, whereas the **M2** receptor reduces **cAMP** formation & relaxation caused by sympathomimetic drugs.



Genitourinary Tract :

- Stimulate the detrusor muscle and relax the trigone and sphincter muscles of the bladder, thus promoting voiding.
- The function of M2 and M3 receptors in the urinary bladder is the same as in intestinal smooth muscle.
- The human uterus is not sensitive to muscarinic agonists.

Miscellaneous Secretory Glands

- Muscarinic agonists stimulate secretion of sweat, lacrimal, and nasopharyngeal glands

Central Nervous System:

The CNS contains both muscarinic and nicotinic receptors, the brain is richer in muscarinic sites and the spinal cord contains more nicotinic sites.

Pilocarpine is used to induce chronic epilepsy in rats, to examine different treatments (M1 effect).

Presynaptic nicotinic receptors regulate the release of several neurotransmitters.

In high concentrations, **nicotine** induces tremor, emesis, and stimulation of the respiratory center. At still higher levels, nicotine causes convulsions & fatal coma.

Autonomic ganglia:

CVS

- CVS In the CVS, the effects of nicotine are chiefly **sympathomimetic**.
- Nicotine causes hypertension, tachycardia which may alternate with a bradycardia mediated by vagal discharge.

GIT and urinary tracts:

- The effects are **parasympathomimetic**:

  nausea, vomiting, diarrhea, and voiding of urine.
- Prolonged exposure may result in depolarizing blockade of the ganglia.

Neuromuscular Junction:

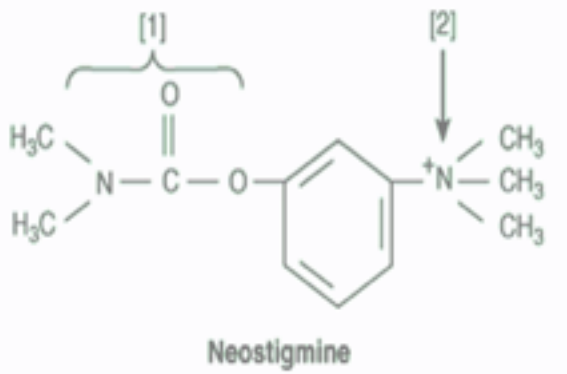
- Nicotinic applied directly causes contractile response varies from disorganized **fasciculations** to a strong contraction of the entire muscle.
- Nicotine also causes rapid development of **depolarization blockade**; transmission blockade persists even when the membrane has repolarized.
- This latter phase of block is manifested as flaccid paralysis of skeletal muscle.

Indirect-Acting Cholinomimetics

Reversible Cholinesterase inhibitors.

Neostigmine

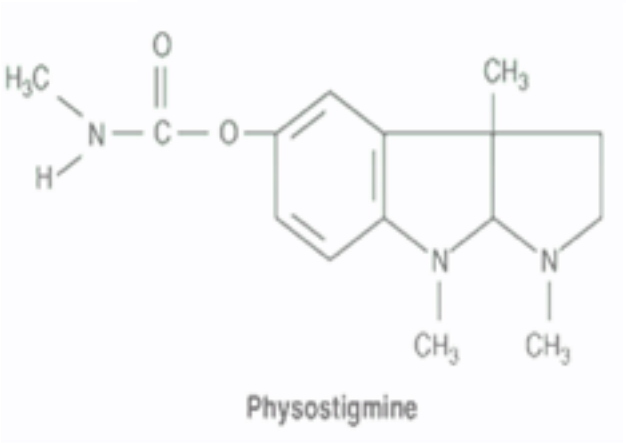
an ester composed of carbamic acid ([1]) and a phenol bearing a quaternary ammonium group([2]).



Neostigmine

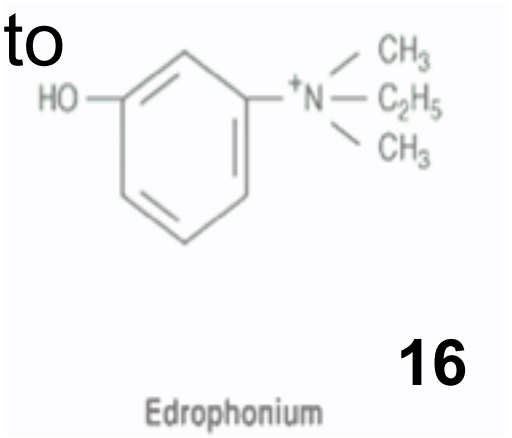
Physostigmine

A naturally occurring carbamate, is a tertiary amine.



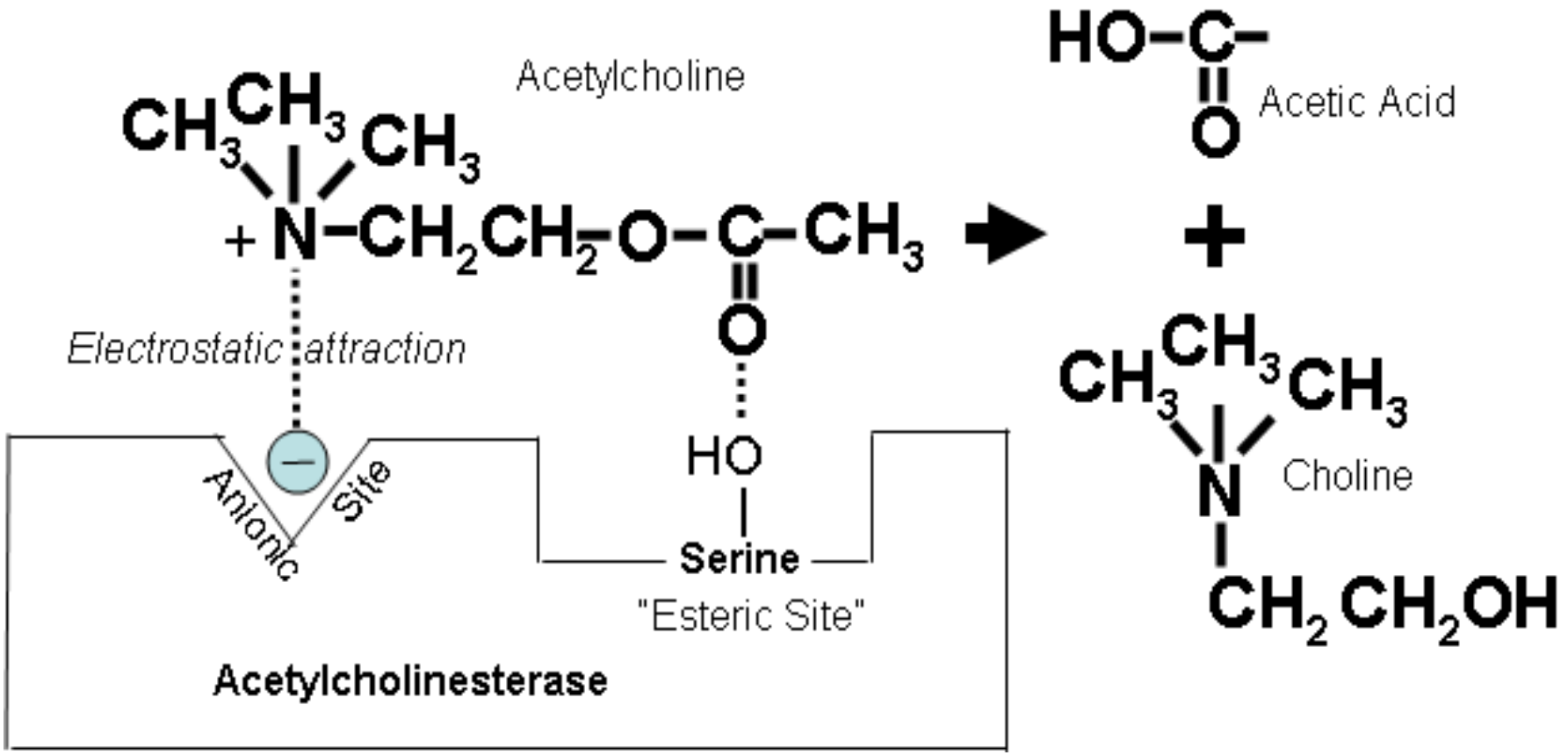
Physostigmine

Edrophonium is not an ester but binds to the active site of the enzyme.



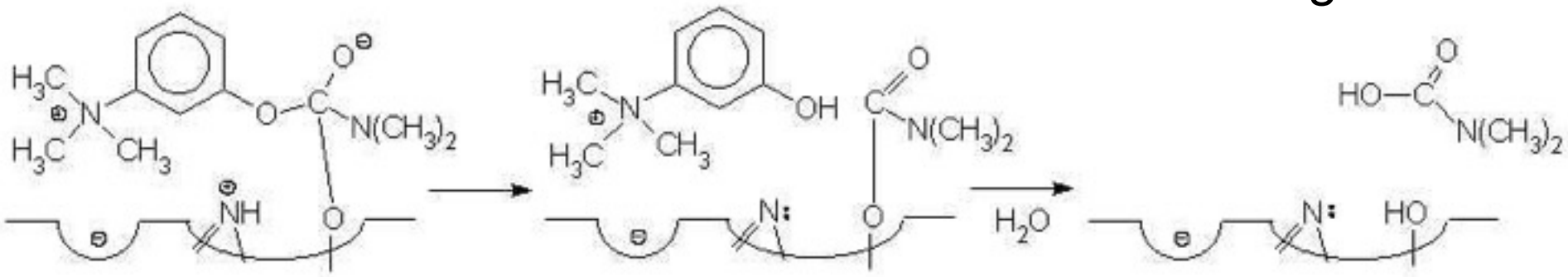
Edrophonium

Metabolism of Acetylcholine



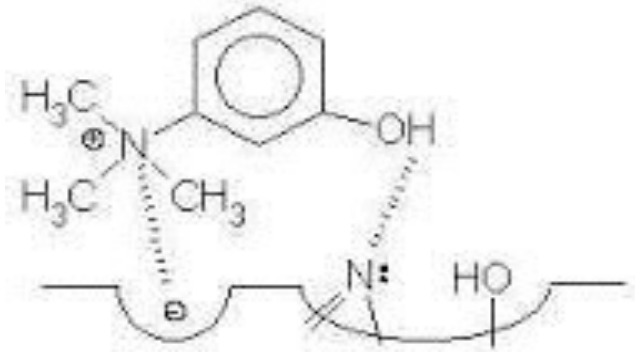
The positively charged nitrogen in the acetylcholine molecule is attracted to the ionic site on acetylcholinesterase, and hydrolysis is catalyzed at the esteric site to form choline and acetic acid.

Neostigmine



Stabilized by an ionic bond at the anionic site and a hydrolyzable covalent bond at the esteratic site, e.g.,

Edrophonium



Enzyme-Inhibitor Complex

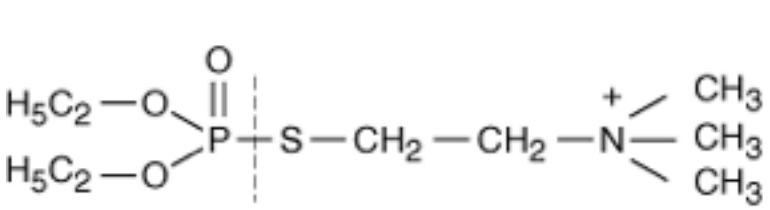
Stabilized by an ionic bond at the anionic site and through weak hydrogen bonding at the esteratic site.

Irreversible cholinesterase inhibitors. organophosphate

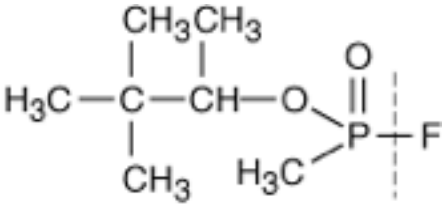
Structures of some organophosphate cholinesterase inhibitors.

The dashed lines indicate the bond that is hydrolyzed in binding to the enzyme

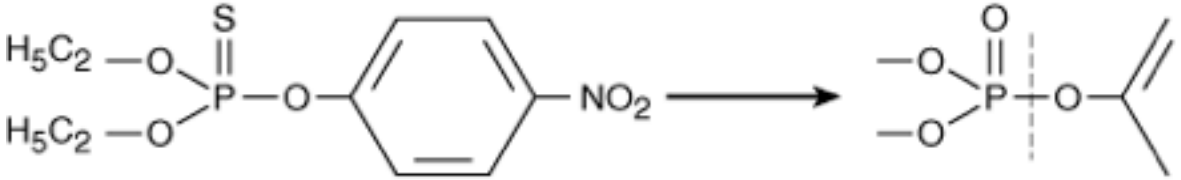
The shaded ester bonds in malathion represent the points of detoxification of the molecule in mammals and birds.



Echothiophate

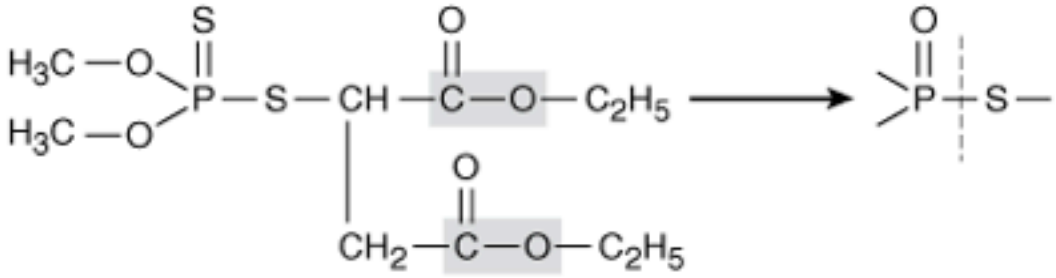


Soman



Parathion

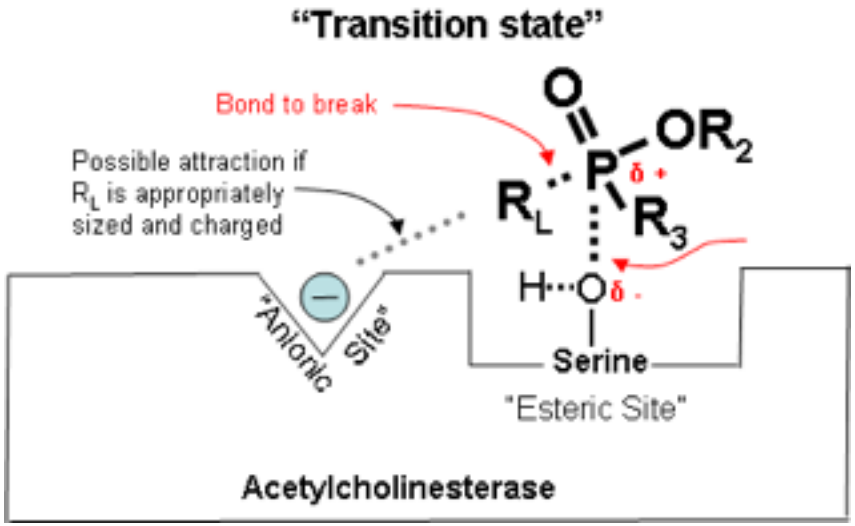
Paraoxon

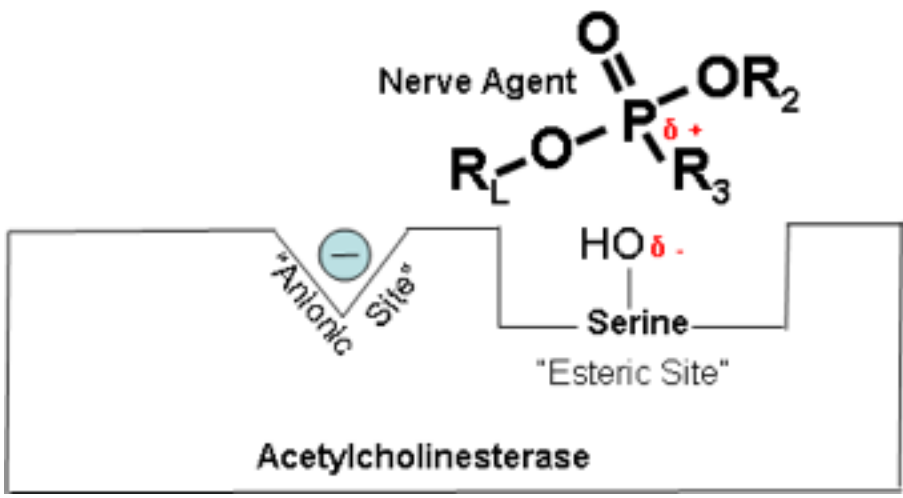


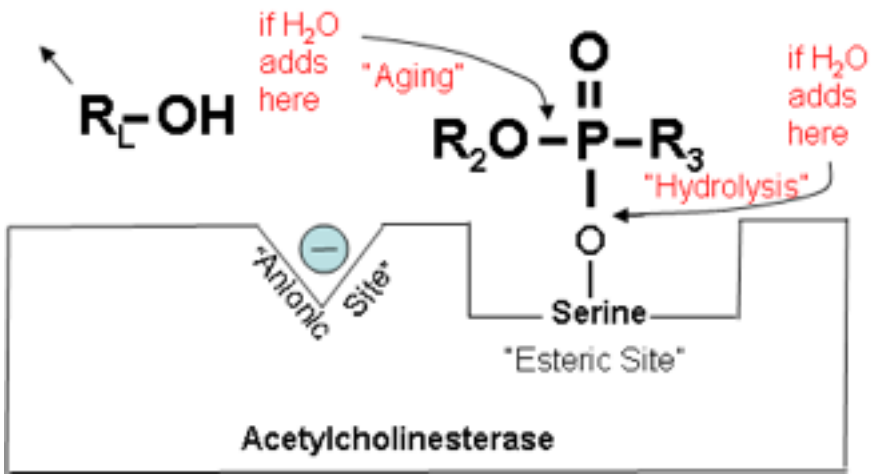
Malathion

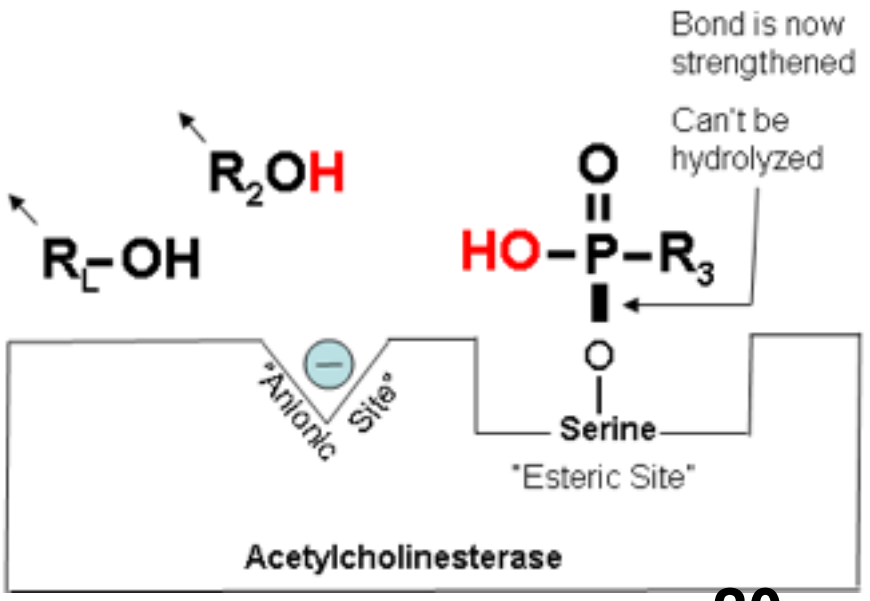
Malaoxon

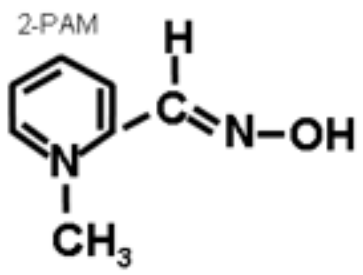
a cholinesterase inhibitor attaches to the serine hydroxyl group on ACh.E. This prevents acetylcholine from interacting with the cholinesterase enzyme and being broken down.

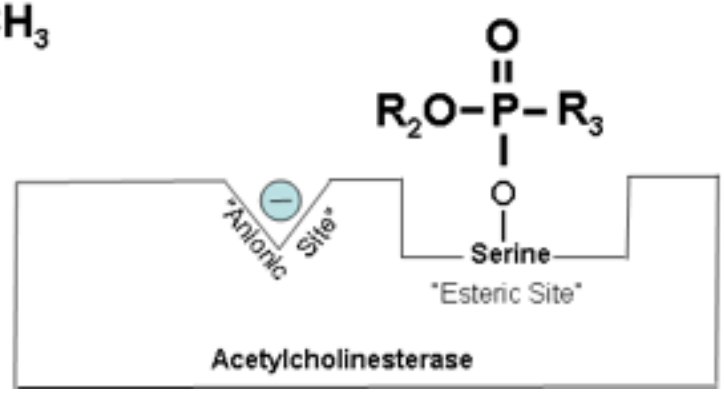


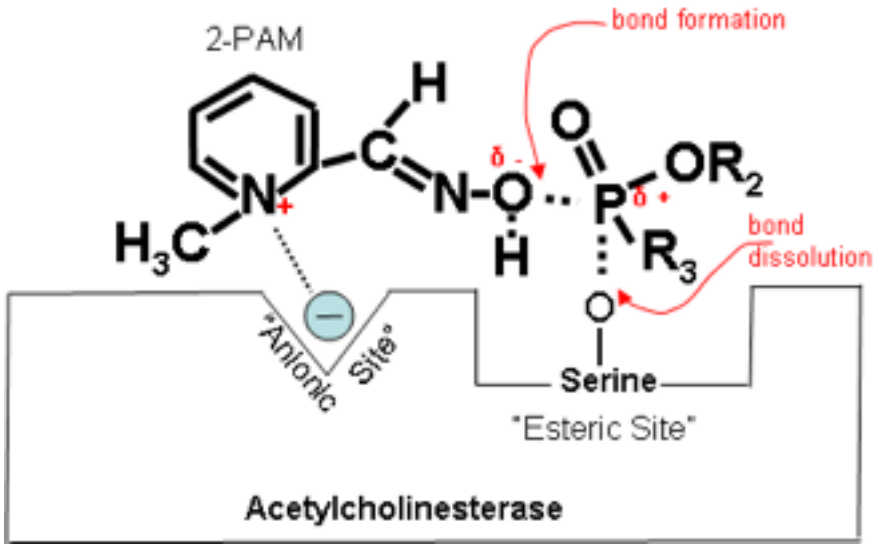




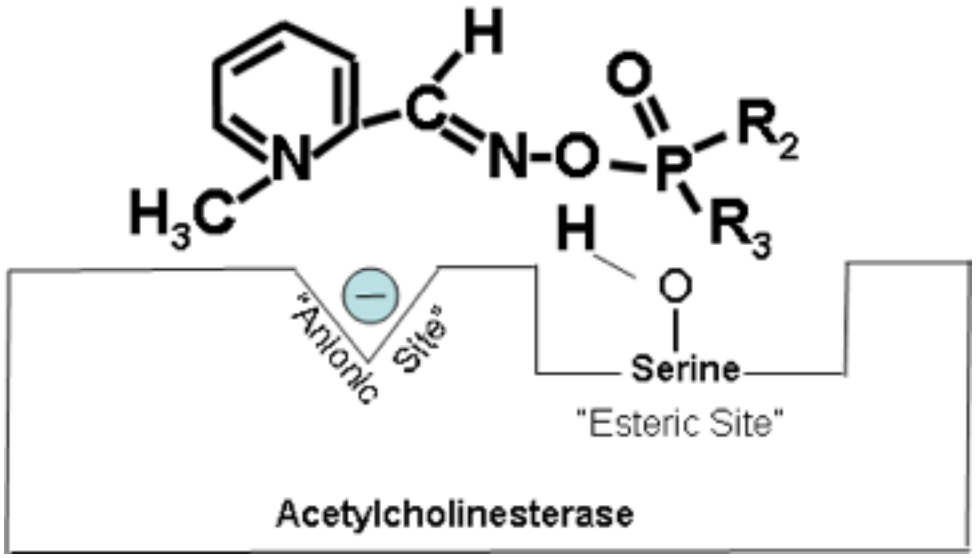


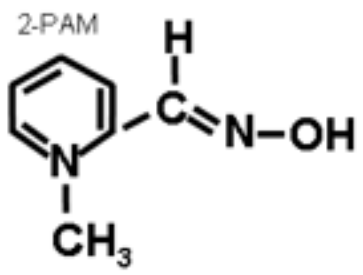


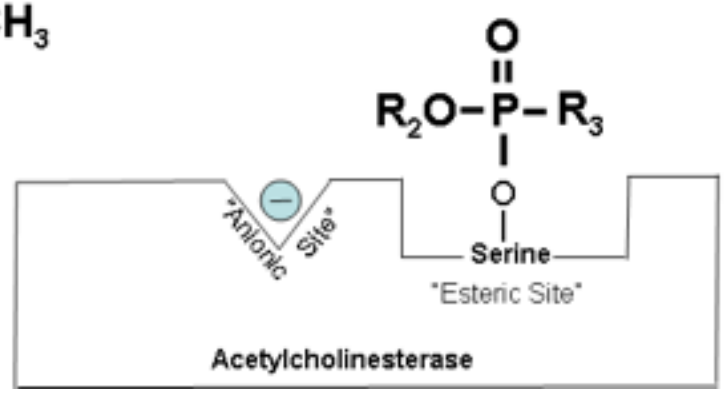


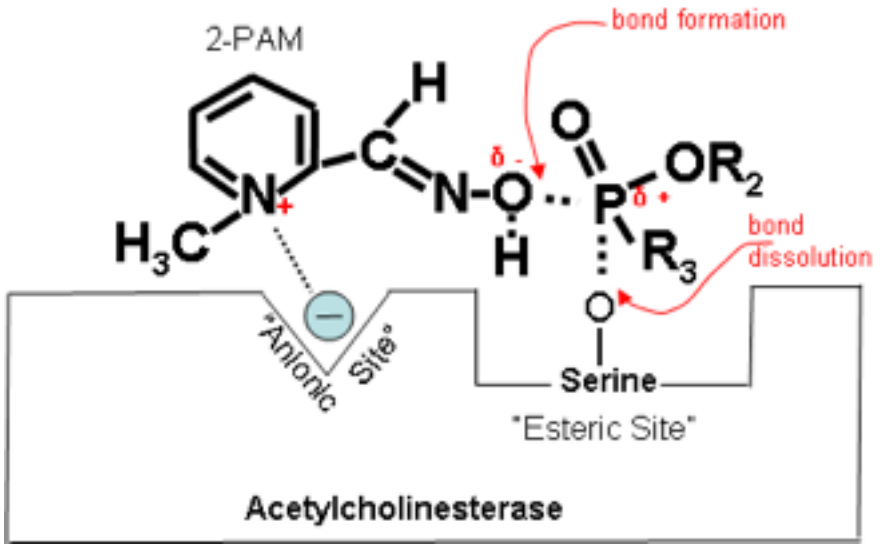


"Regenerated cholinesterase"









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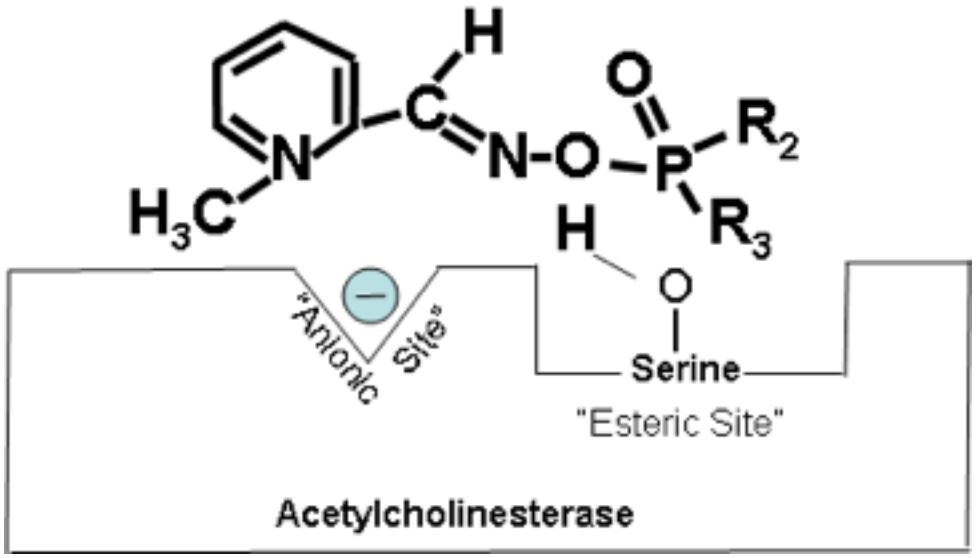

Absorption, Distribution, and Metabolism

- Absorption of the **quaternary carbamates** from the conjunctiva, skin, and lungs is **poor**, since their permanent charge renders them relatively insoluble in lipids.
- Thus, much larger doses are required for oral administration than for parenteral injection.

- Distribution into the CNS is negligible. **Physostigmine**, in contrast, is well absorbed from all sites and can be used topically in the eye.
- It is distributed into the CNS and is more toxic than the more polar quaternary carbamates.

- The carbamates metabolized by nonspecific esterases and by cholinesterase.
- The **duration** of their effect is determined chiefly by the stability of the inhibitor-enzyme complex , not by metabolism or excretion.

- The organophosphates are **well absorbed** from the skin, lung, gut, and conjunctiva—thereby making them dangerous to humans and highly effective as insecticides.
- Parathion, malathion, must be activated in the body by conversion to the oxygen analogs

Therapeutic Uses and Durations of Action of Cholinesterase Inhibitors

	Uses	Approximate Duration of Action
Alcohols		
• Edrophonium	Myasthenia gravis, ileus,	5–15 minutes
Carbamates and related agents		
• Neostigmine	Myasthenia gravis, ileus	0.5–2 hours
• Pyridostigmine	Myasthenia gravis	3–6 hours
• Physostigmine	Glaucoma	0.5–2 hours
• Ambenonium	Myasthenia gravis	4–8 hours
• Demecarium	Glaucoma	4–6 hours
Organophosphates		
• Echothiophate	Glaucoma	100 hours