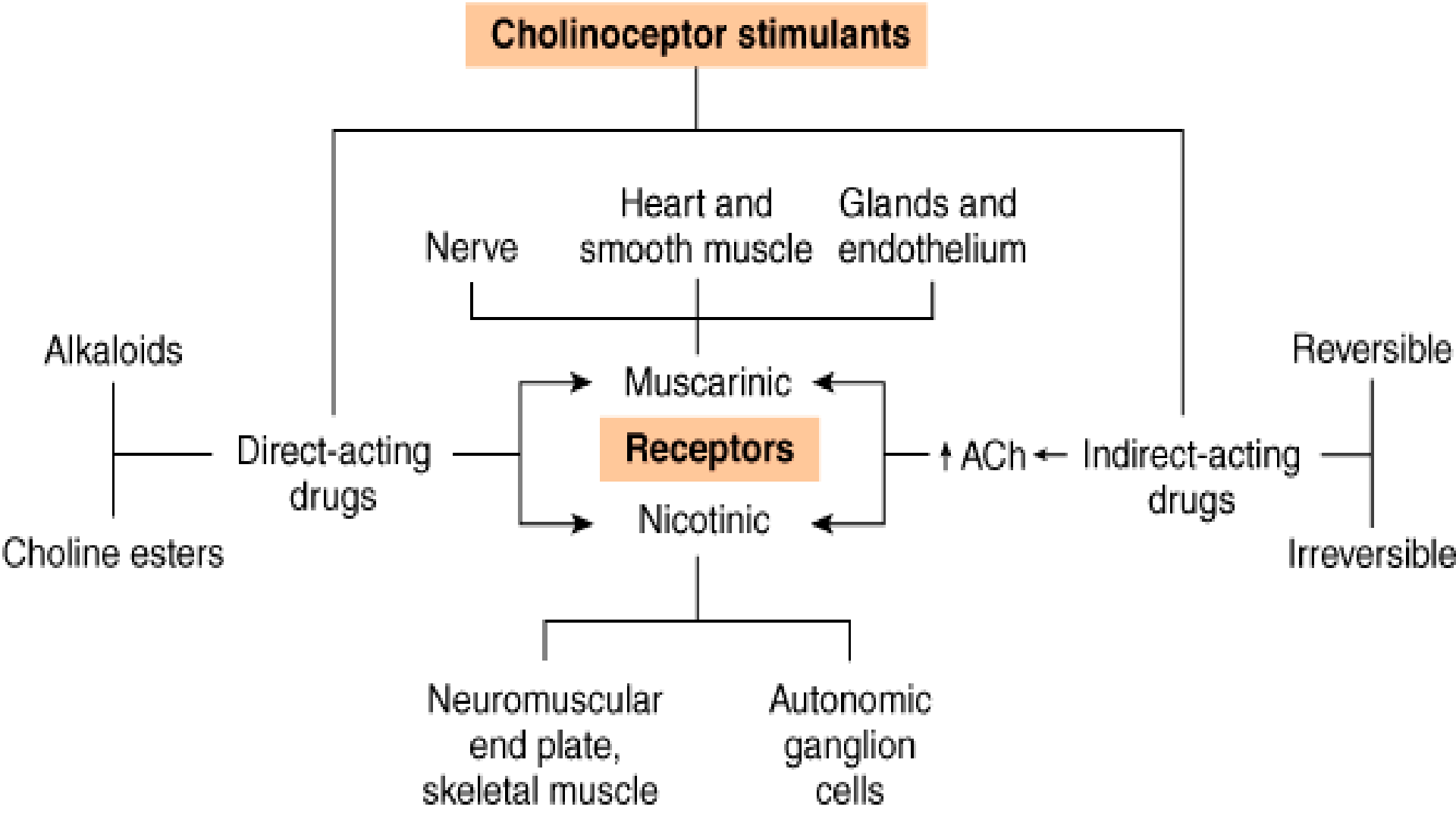
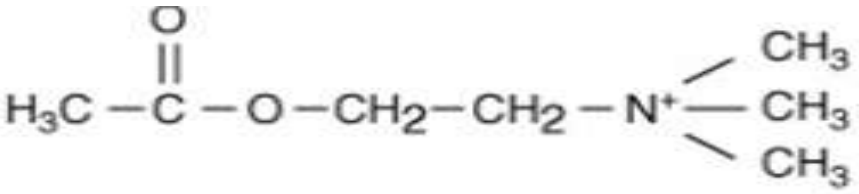
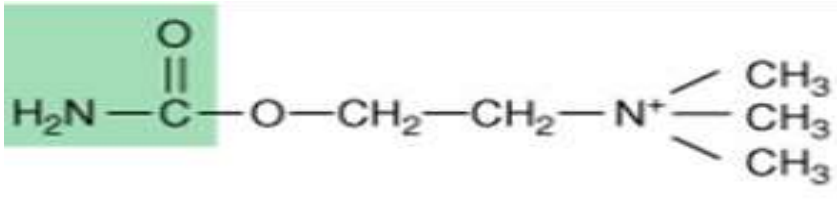
Cholinoceptor - Activating &Cholinesterase-Inhibiting Drugs



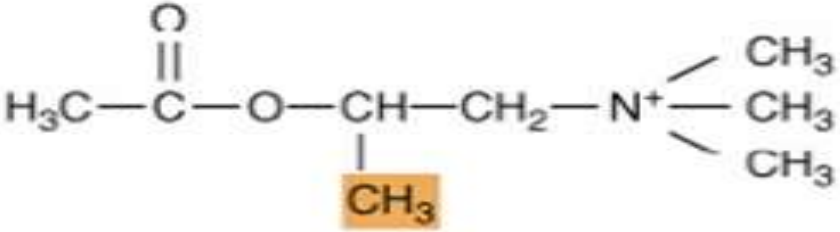
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com



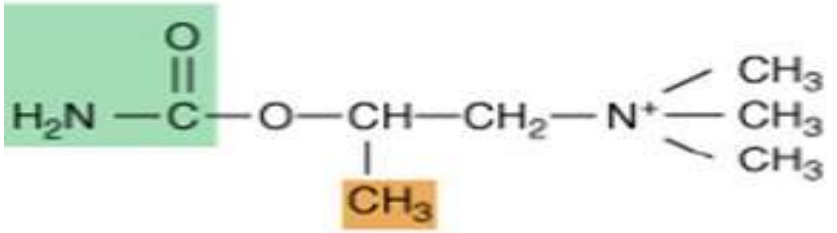
Acetylcholine



Carbachol
(carbamoylcholine)

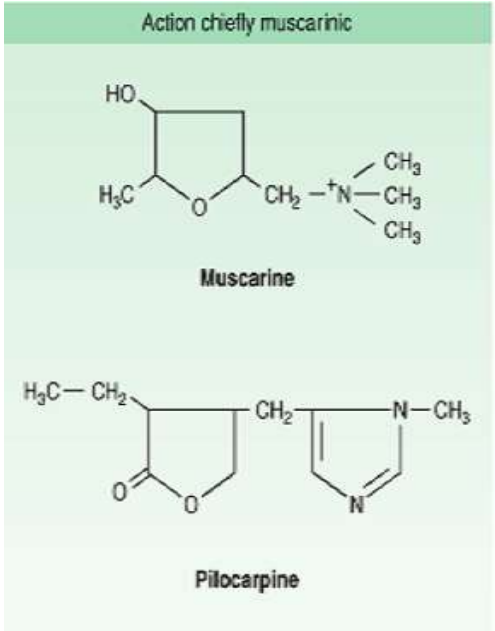


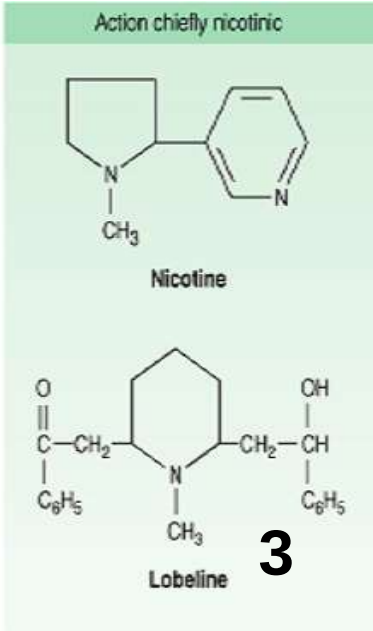
Methacholine
(acetyl-β-methylcholine)



Bethanechol
(carbamoyl-β-methylcholine)

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

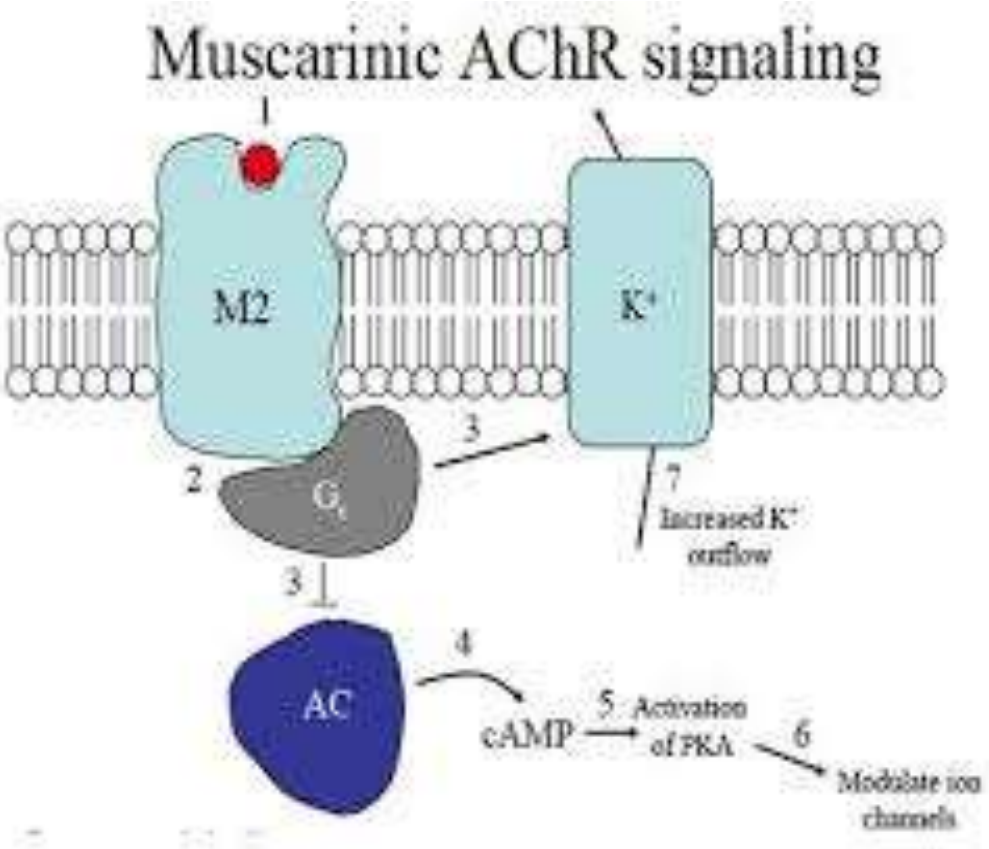




Mechanism of Action
Muscarinic transmission in the heart

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



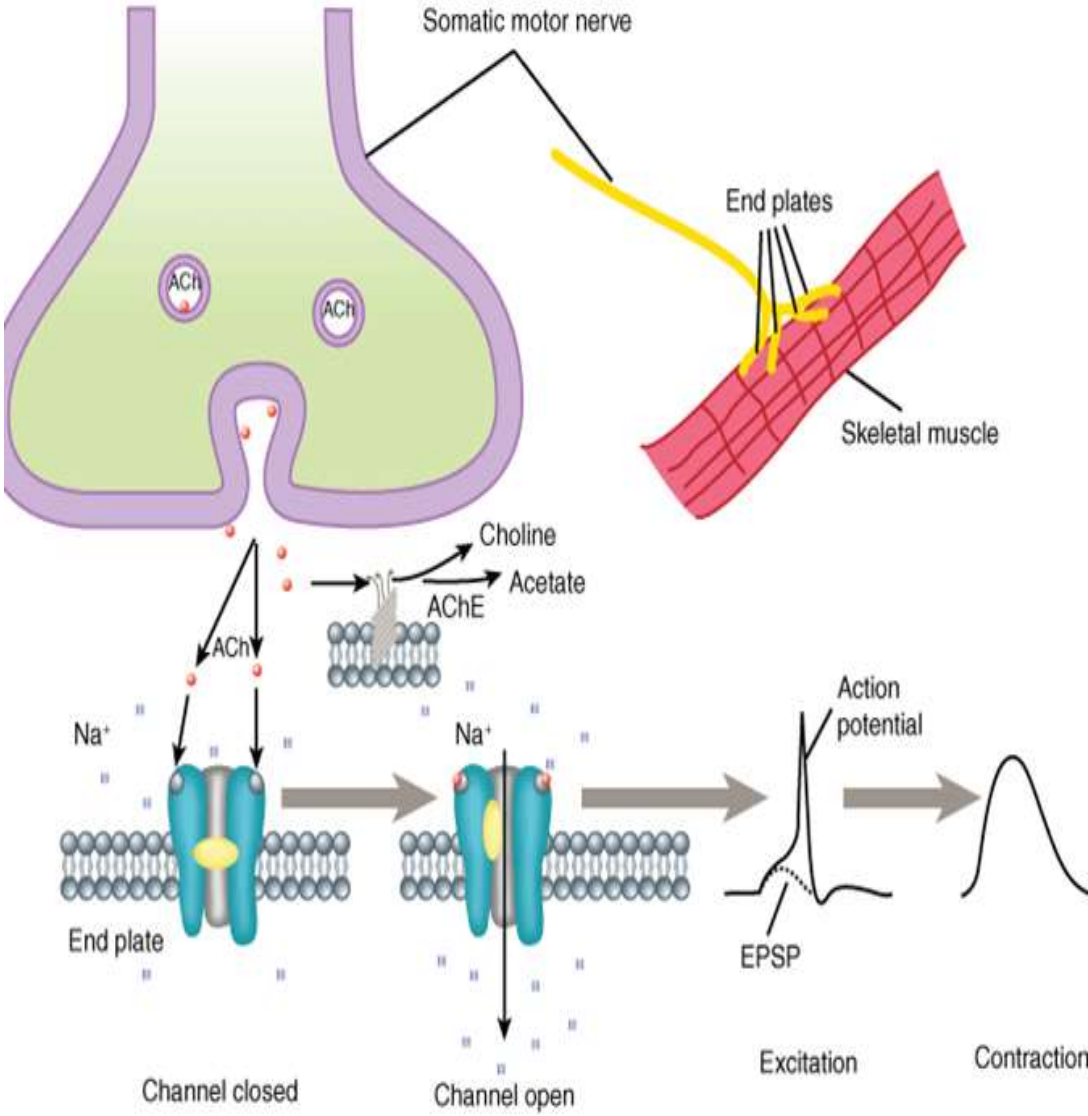
The phosphorylation of L-type Ca2+ channels is reduced.
M2R stimulates Gi protein↓→↓adenylyl cyclase→ ↓**cAMP** formation→↓HR &↓ force of contraction.

Nicotinic transmission at the neuromuscular junction.

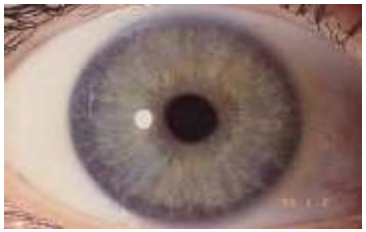
Ach interacts with subunits of the nicotinic receptor to open it, allowing Na+ to produce an excitatory postsynaptic potential (EPSP).

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

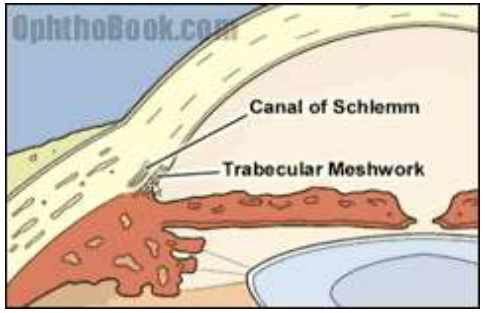
the extracellular Acetylcholinesterase(AChE) hydrolyzes Ach.



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 (bronchoconstriction)	Contraction
Bronchial glands	Stimulation

Gastrointestinal tract

Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation

Urinary bladder

Detrusor	Contraction	
Trigone and sphincter	Relaxation	voiding of urine

Glands

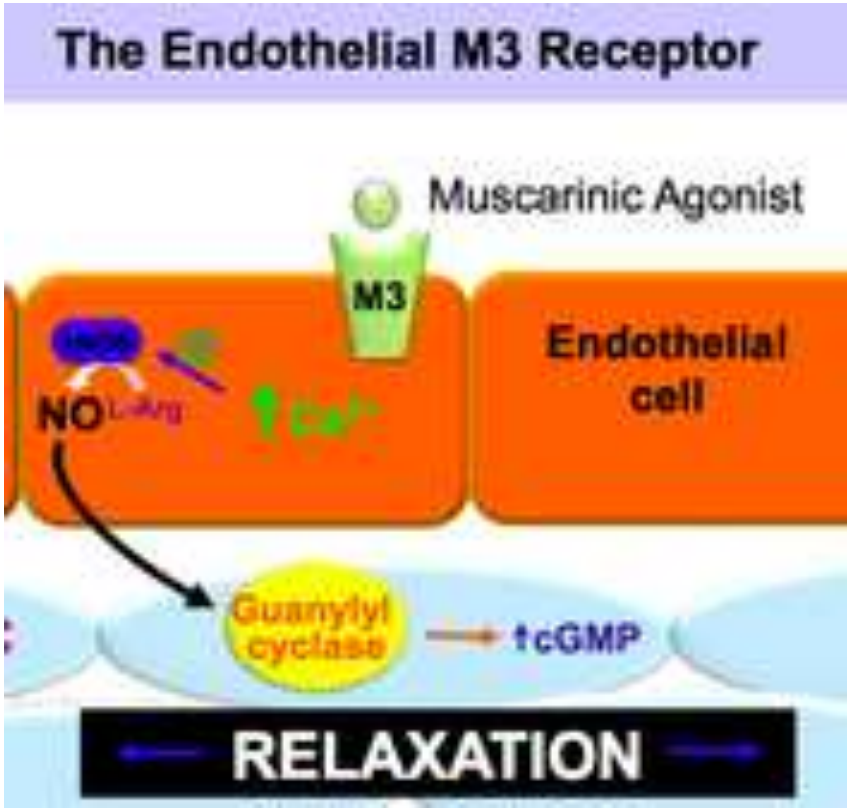
Sweat, salivary, lacrimal , nasopharyngeal	↑ Secretion

Organ System Effects

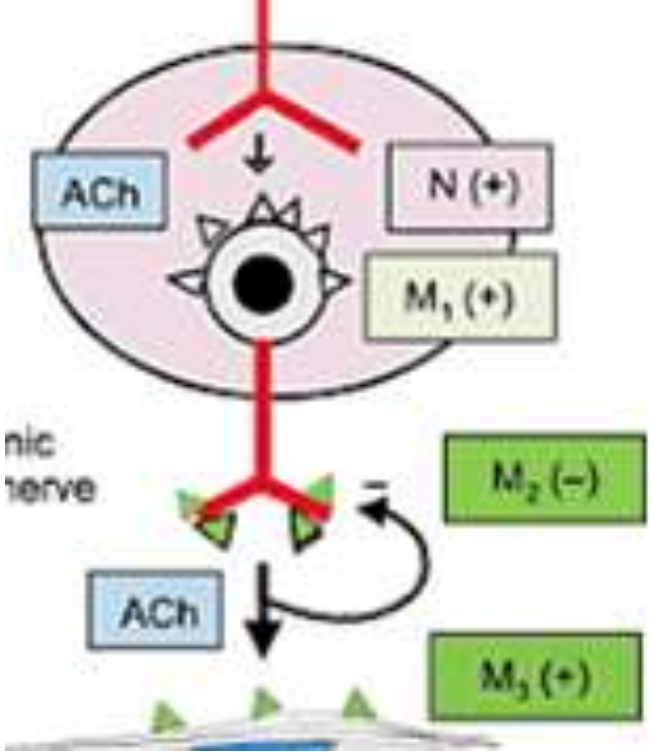
Cardiovascular System: M2

- 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.

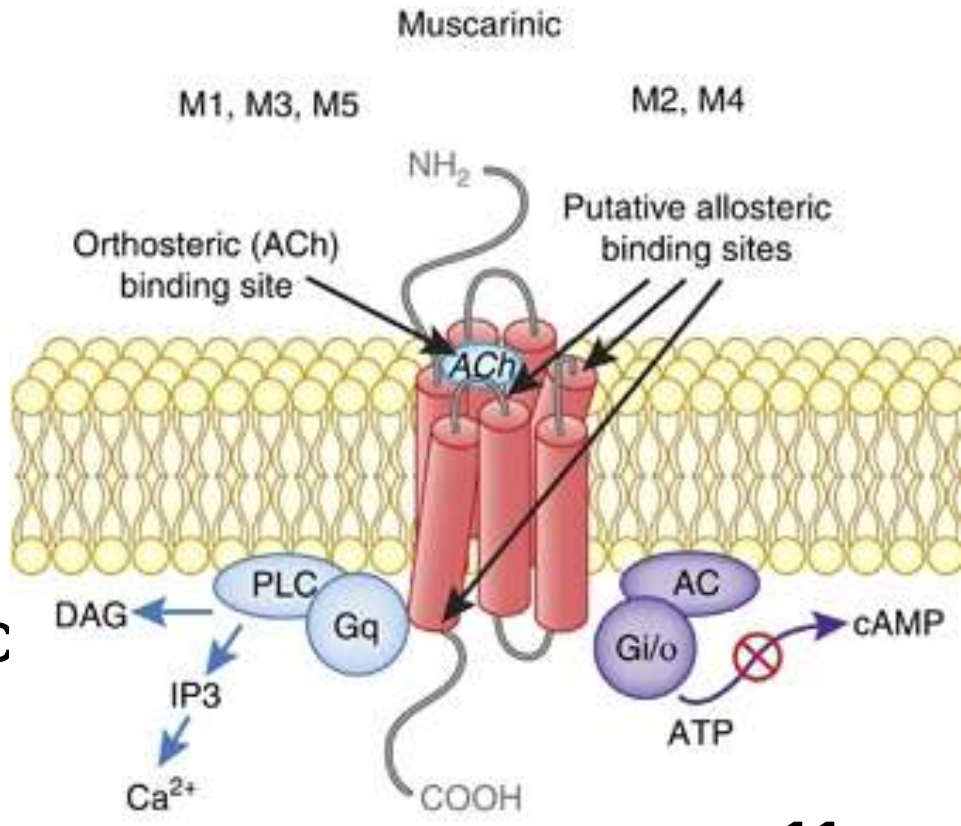
The longer-lasting hypertensive Effect is due to sympathetic ganglionic activation caused by activation of ganglionic **M1** receptors, which elicit slow excitatory postsynaptic potentials. This effect, like the hypotensive effect, can be blocked by atropine, an antimuscarinic drug.

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

- 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:

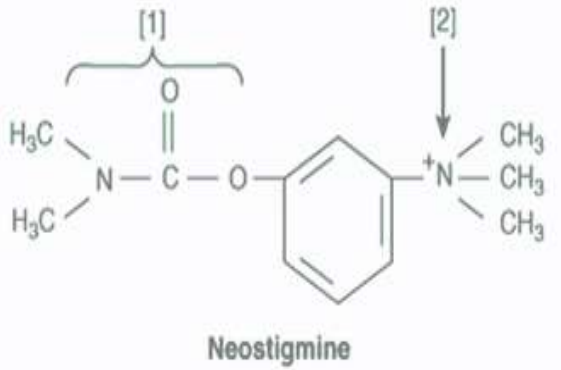
- Nicotinic applied directly causes contractile response varies from disorganized **fasciculations** to a strong contraction of the entire muscle.
- Nicotine also causes rapid development of **depolarization blockade**; transmission blockade persists even when the membrane has repolarized.
- This latter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

Indirect-Acting Cholinomimetics

Reversible Cholinesterase inhibitors.

Neostigmine

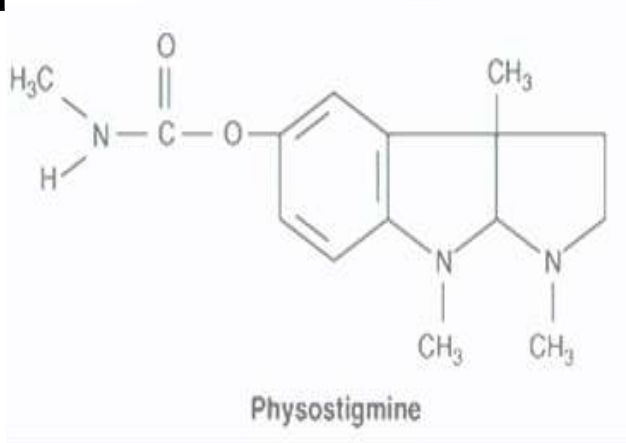
an ester composed of carbamic acid ([1]) and a phenol bearing a quaternary ammonium group([2]).



Neostigmine

Physostigmine

A naturally occurring carbamate, is a tertiary amine.

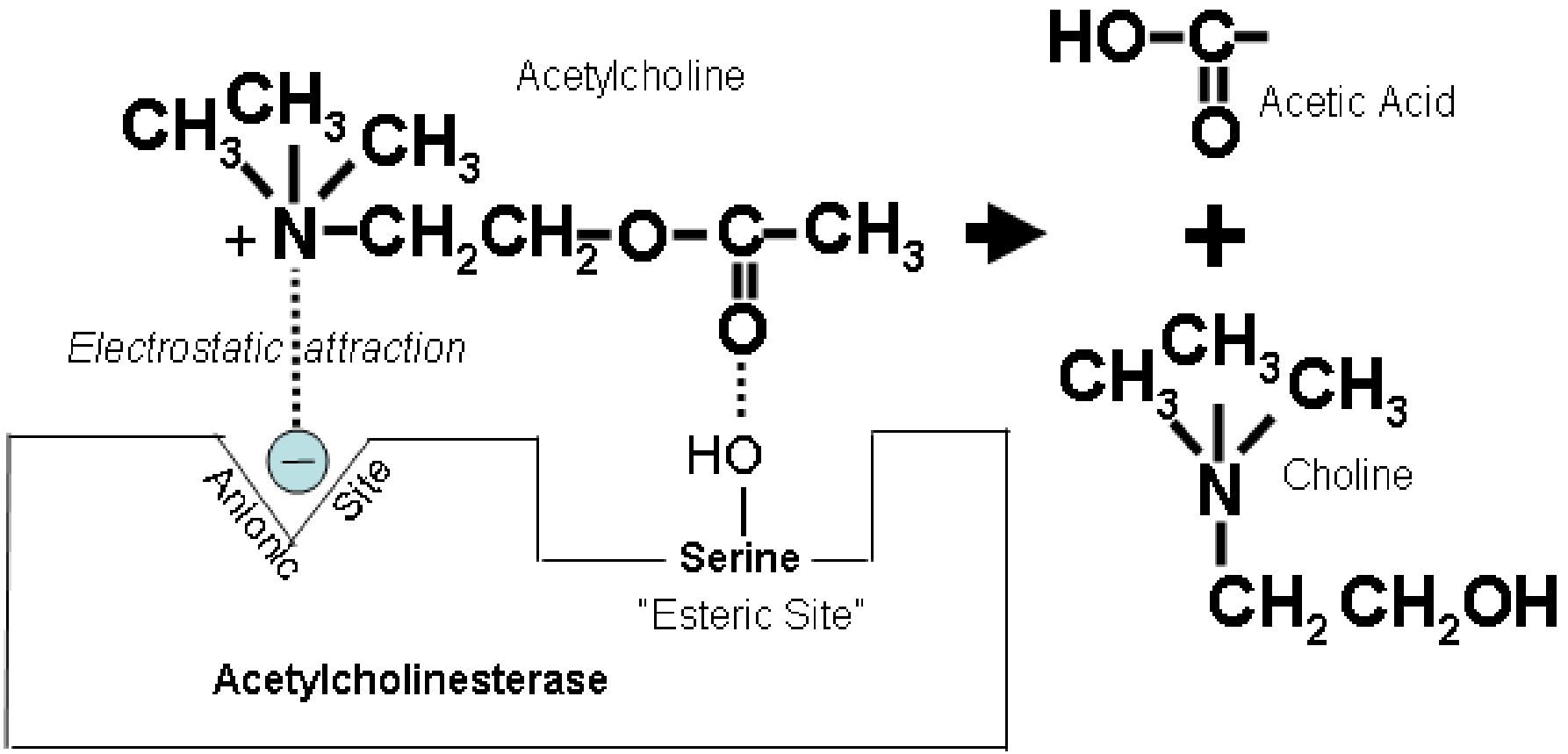


Physostigmine

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

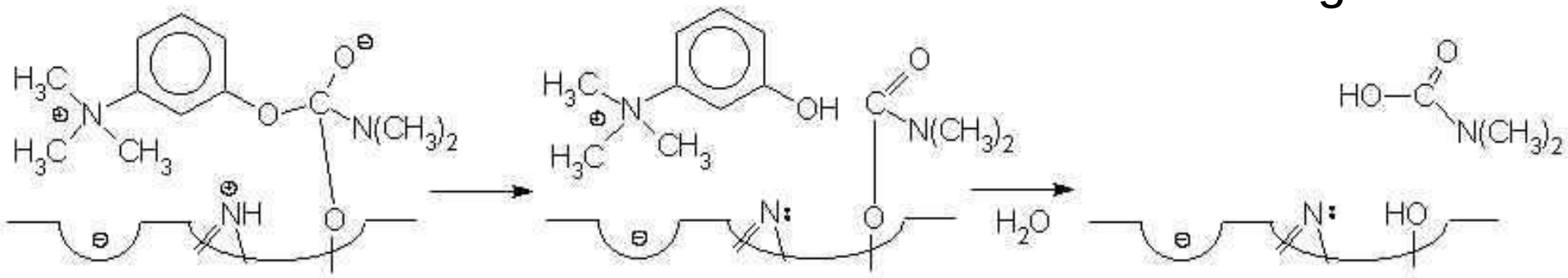
Edrophonium

Metabolism of Acetylcholine



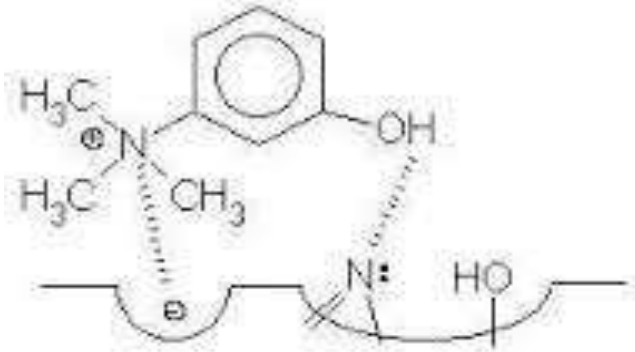
The positively charged nitrogen in the acetylcholine molecule is attracted to the ionic site on acetylcholinesterase, and hydrolysis is catalyzed at the esteric site to form choline and acetic acid.

Neostigmine



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

Edrophonium

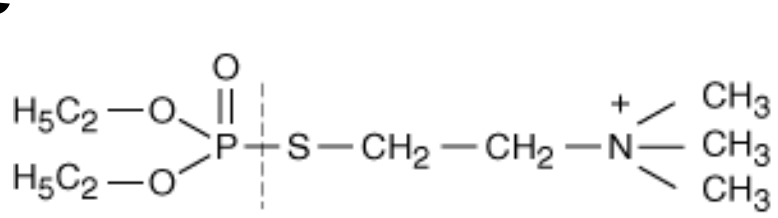


Enzyme-Inhibitor Complex

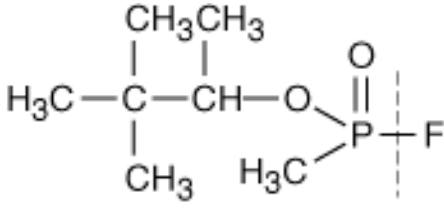
Stabilized by an ionic bond at the anionic site and through weak hydrogen bonding at the esteratic site.

Irreversible cholinesterase inhibitors. organophosphate

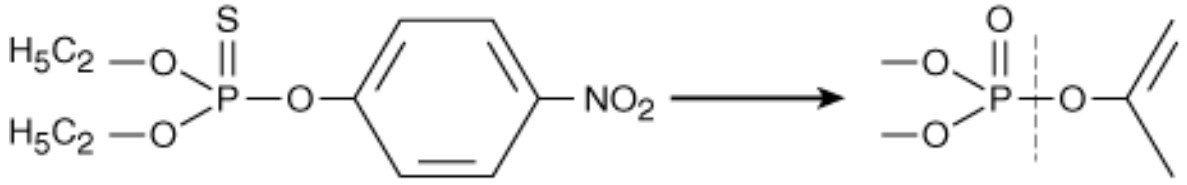
The dashed lines indicate the bond that is hydrolyzed in binding to the enzyme.
The shaded ester bonds in malathion represent the points of detoxification of the molecule in mammals and birds.



Echothiophate

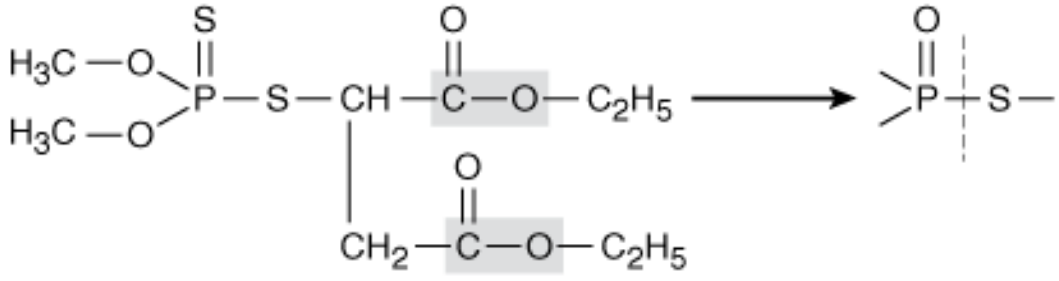


Soman



Parathion

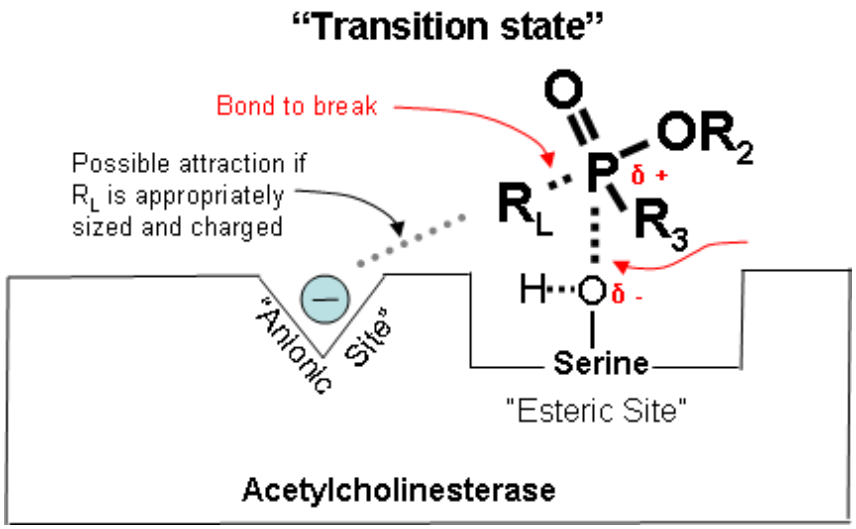
Paraoxon

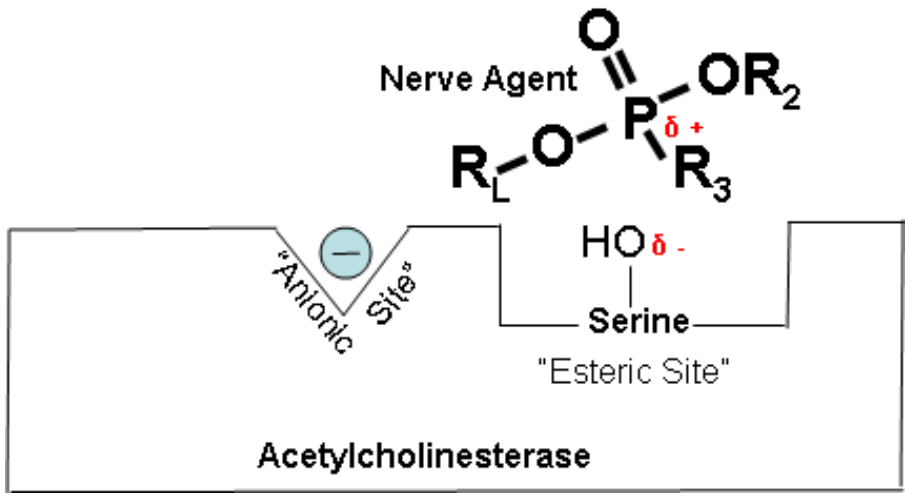


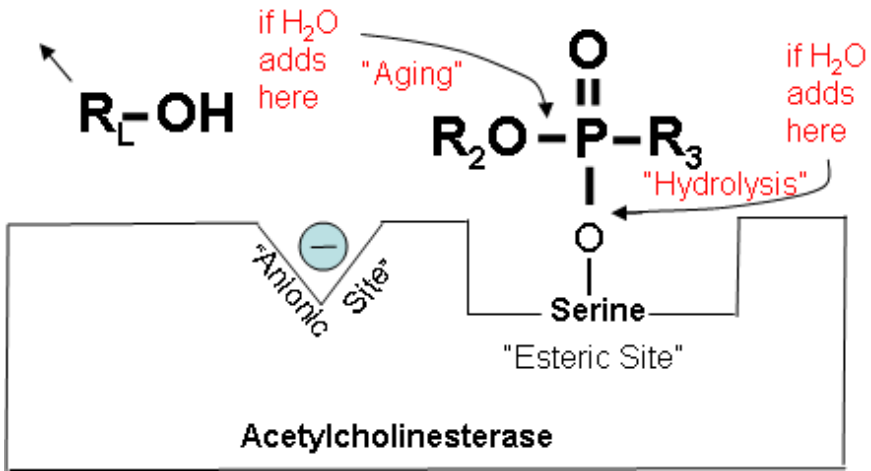
Malathion

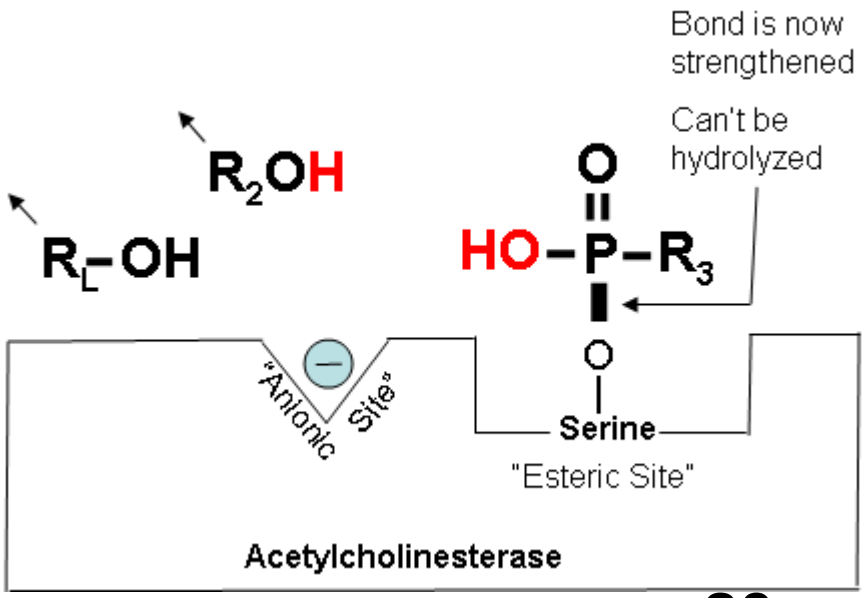
Malaoxon

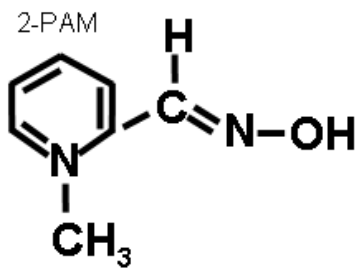
a cholinesterase inhibitor attaches to the serine hydroxyl group on ACh.E. This prevents acetylcholine from interacting with the cholinesterase enzyme and being broken down.

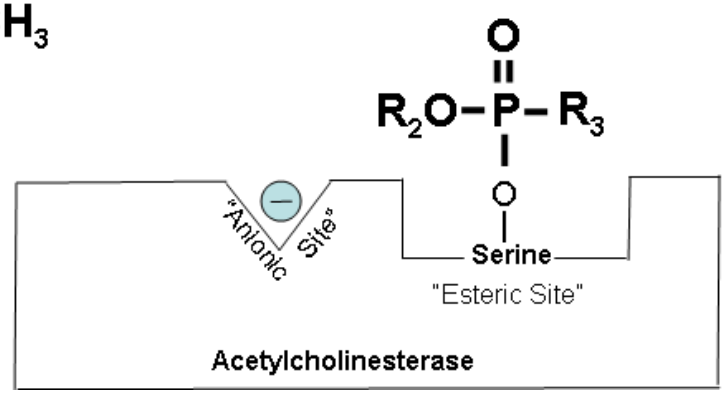


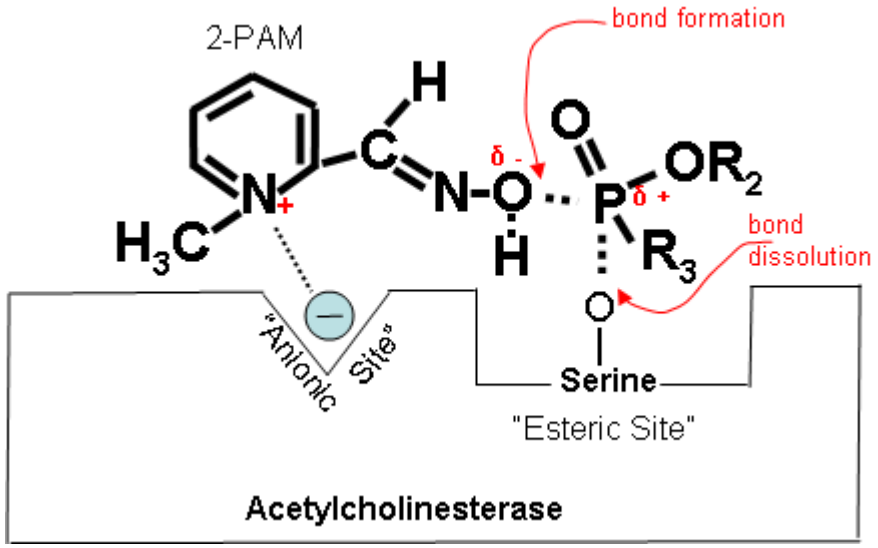




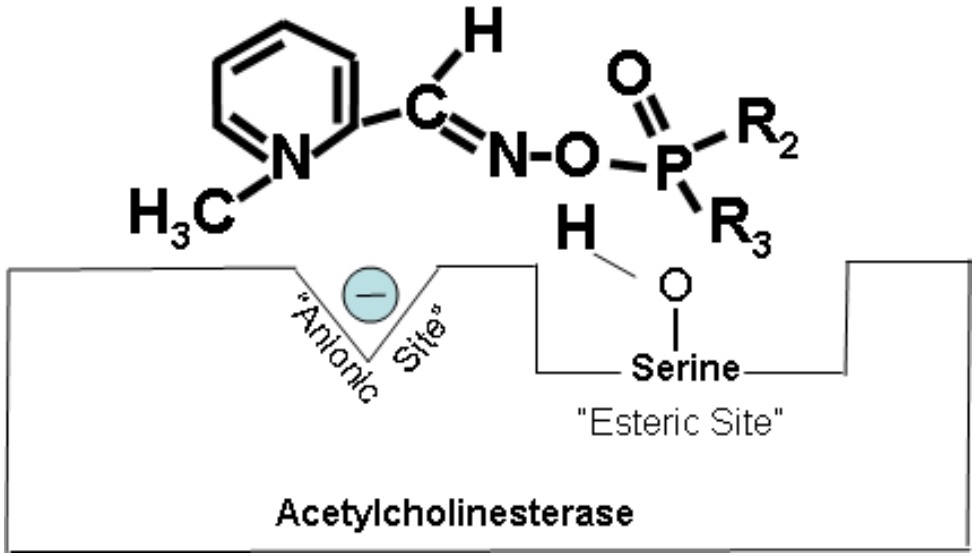


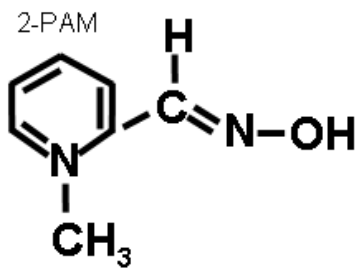


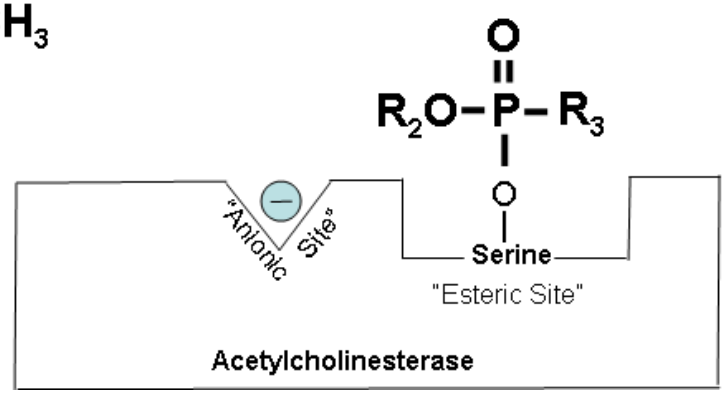


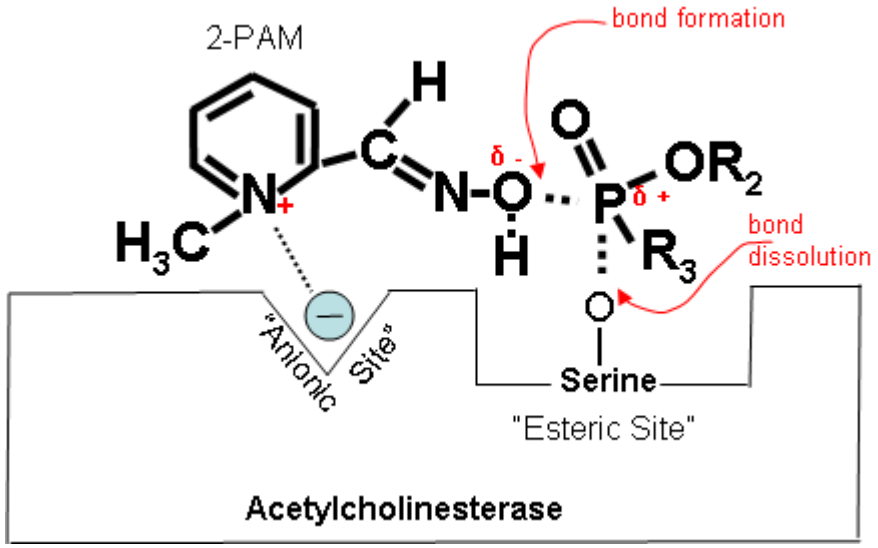


"Regenerated cholinesterase"









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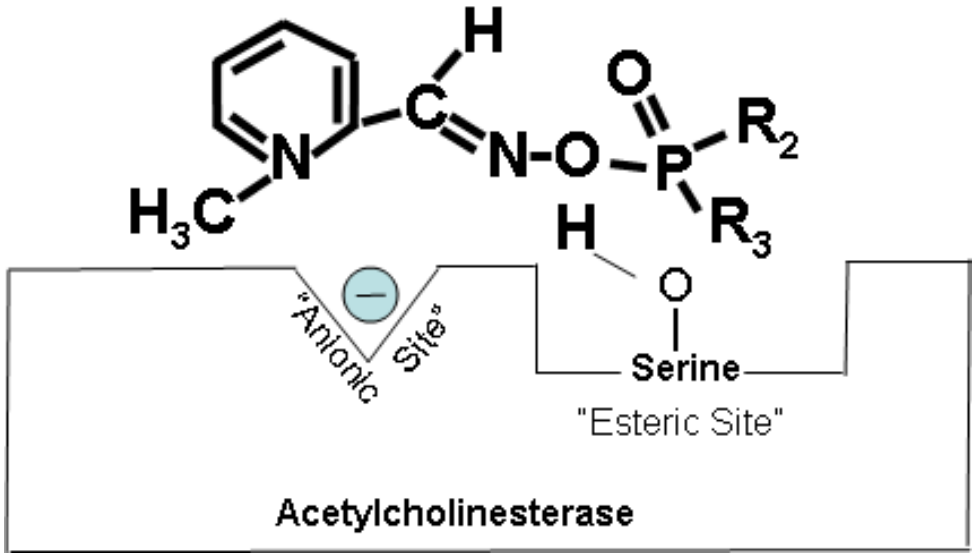

Absorption, Distribution, and Metabolism

- **Quaternary carbamates** are relatively insoluble in lipids due to their positive charge, so absorption is poor and distribution into the CNS is negligible.
- Thus, much larger doses are required for oral administration than for parenteral injection.

- **Physostigmine** 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

Mechanism of Action

- **increase** the concentration of endogenous **acetylcholine** at cholinoceptors.
- **Edrophonium** is a quaternary alcohols, bind **electrostatically and by hydrogen bonds** to the active site, thus preventing access of acetylcholine.
- The enzyme-inhibitor complex does not involve a covalent bond and is short-lived (on the order of 2–10 minutes).

- Carbamate esters, e.g., **neostigmine** and **physostigmine**. undergo a two-step hydrolysis sequence similler to acetylcholine.

- The covalent bond of the *carbamoylated* enzyme is more resistant to the second (hydration) process, and this step is correspondingly prolonged (**30 minutes to 6 hours**).

- The organophosphates. undergo initial binding and hydrolysis by the enzyme, resulting in a ***phosphorylated* active site**.

The covalent phosphorus-enzyme bond is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours).

After the initial binding-hydrolysis step, the phosphorylated enzyme complex may undergo a process called **aging.**

Aging involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor and further strengthens the phosphorus-enzyme bond.

Aging occurs within 10 minutes with the chemical warfare agent, soman, and in 48 hours with the agent, VX.

- **Pralidoxime** If given before aging has occurred, is able to break the phosphorus-enzyme bond and can be used as **"cholinesterase regenerator"** drugs for organophosphate insecticide poisoning.

Organ System Effects

Central Nervous System

- In **low concentrations**, the lipid-soluble cholinesterase inhibitors cause a subjective alerting response.
- **In higher concentrations**, they cause generalized **convulsions**, which may be followed by coma and respiratory arrest.

Eye, Respiratory Tract, GIT, Urinary Tract

The effects are qualitatively similar to the effects of the direct-acting cholinomimetics.

Cardiovascular System

Mimic the effects of vagal nerve activation on the heart.

Negative **chronotropic, dromotropic**, and **inotropic** effects and cardiac output falls.

The fall in cardiac output is due to bradycardia, decreased atrial contractility, and some reduction in ventricular contractility.

The latter effect occurs as a result of prejunctional inhibition of NE release.

Minimal effects by direct action on vascular smooth muscle because most vascular beds lack cholinergic innervations.

The *net* cardiovascular effects of moderate doses of cholinesterase inhibitors consist of:

modest bradycardia

a fall in cardiac output

an increased vascular resistance (**sympathetic ganglion stimulation**) that result in a rise in blood pressure.

Neuromuscular Junction

- Low concentrations prolong and intensify the actions of Ach.

  This increases the strength of contraction, especially in muscles weakened by curare-like neuromuscular blockers or by myasthenia gravis.

- At higher concentrations fibrillation of muscle fibers. **Antidromic firing** (nerve impulses in a direction opposite to normal) of the motor neuron may also occur, resulting in fasciculations that involve an entire motor unit.

- With marked inhibition of acetylcholinesterase, **depolarizing neuromuscular blockade** occurs followed by a phase of **nondepolarizing blockade** as seen with **succinylcholine** (a depolarising neuromuscular blocker).

- Some quaternary carbamate cholinesterase inhibitors, e.g., **neostigmine**, have an additional *direct* nicotinic agonist effect at the neuromuscular junction.
- This may contribute to the effectiveness of these agents as therapy for myasthenia.

Clinical Uses

The Eye

- **Glaucoma** was treated with pilocarpine, methacholine, carbachol or ChEIs; physostigmine, demecarium, echothiophate, isoflurophate).
- These drugs have been replaced by **topical -β-blockers** and **prostaglandin** derivatives.
- **Acute angle-closure glaucoma** is a medical emergency that usually requires **surgery.**
- Initial therapy consists of a combination of a direct muscarinic agonist and a cholinesterase inhibitor (e.g., pilocarpine plus physostigmine).

GI and Urinary Tracts

Clinic. Uses cont.

- **Postoperative ileus** (atony or paralysis of the stomach or bowel following surgical manipulation) and **congenital megacolon**.

- **Urinary retention** postoperatively or postpartum or secondary to spinal cord injury or disease (neurogenic bladder).

- **Bethanechol** and **Neostigmine** are the most widely used,
- Must be **No mechanical obstruction** to outflow before using the cholinomimetic agents.

- **Pilocarpine**

Used to increase salivary secretion.

- **Cevimeline**

  A new direct-acting muscarinic agonist used for the treatment of dry mouth associated with Sjögren's syndrome (a systemic autoimmune disease) and that caused by radiation damage of the salivary glands.

Neuromuscular Junction

Myasthenia gravis is an autoimmune disease affecting skeletal muscle neuromuscular junctions.

The antibodies **reduce nicotinic receptor function**.

Frequent findings are ptosis, diplopia, difficulty in speaking, swallowing, and extremity weakness.

Severe disease may affect all the muscles, including those necessary for respiration.

- The disease resembles the neuromuscular paralysis produced by *d*-tubocurarine.
- Patients with myasthenia are very sensitive to the action of **neuromuscular blockers** and other drugs that interfere with neuromuscular transmission, e.g., aminoglycoside antibiotics.
- Patients with **ocular myasthenia** may be treated with cholinesterase inhibitors alone.
- Patients having more widespread muscle weakness are also treated with **immunosuppressant** drugs .

Clinic. Uses cont.

Edrophonium is used as a **diagnostic test** for myasthenia.

- A 2 mg dose is injected IV. If the patient has myasthenia gravis, an improvement in muscle strength that lasts 5 minutes can be observed.
- Edrophonium is also used to assess the adequacy of treatment with the longer-acting cholinesterase inhibitors in patients with myasthenia gravis.
- Clinical situations in which severe myasthenia (**myasthenic crisis**) must be distinguished from excessive drug therapy (**cholinergic crisis**).

Clinic. Uses cont.

- Long-term therapy is usually accomplished with **pyridostigmine**; **neostigmine** or **ambenonium**.

- Muscarinic effects is controlled by **atropine**. Tolerance to the muscarinic effects develops, so atropine treatment is not required.

- Neuromuscular blockade is frequently produced as an adjunct to **surgical anesthesia**. After surgery, **neostigmine** and **edrophonium** are the drugs of choice used to **reverse this pharmacologic paralysis promptly**.

Central Nervous System

- **Tacrine** is an anticholinesterase used for the treatment of mild to moderate **Alzheimer's disease**.

  Tacrine's efficacy is modest, and hepatic toxicity is significant.
- **Donepezil**, is newer, more selective used in treatment of **Alzheimer's** patients.
- Given once daily because of its long half-life, and it lacks the hepatotoxic effect of tacrine.

Toxicity

- Varies markedly depending on their **absorption**, access to the CNS, and metabolism.
- **Direct-Acting Muscarinic Stimulants**
- **Pilocarpine** and the **choline esters** over dosage cause:

  nausea, vomiting, diarrhea, urinary urgency, salivation, sweating, cutaneous vasodilation, and bronchial constriction.

- The effects are all blocked competitively by **atropine**

Certain mushrooms

contain muscarinic alkaloids.

(*Amanita muscaria,* the first source of muscarine, contains very low concentrations of the alkaloid.)

Ingestion of these mushrooms causes typical signs of muscarinic excess within 15–30 minutes.

Treatment is with **atropine**, 1–2 mg parenterally.

Direct-Acting Nicotinic Stimulants

Acute Toxicity

- The **fatal dose** of nicotine is 40 mg, or 1 drop of the pure liquid.

  This is the amount of nicotine in two regular cigarettes.

Fortunately, most of the nicotine in cigarettes is destroyed by burning or escapes via the "side stream" smoke.

- Ingestion of nicotine insecticides or of tobacco by infants and children is usually followed by vomiting, limiting the amount of the alkaloid absorbed.

Toxic effects of a large dose of nicotine are:

(1) central stimulant actions, which cause convulsions and may progress to coma and respiratory arrest;

(2) skeletal muscle end plate depolarization, which may lead to depolarization blockade and respiratory paralysis.

(3) hypertension and cardiac arrhythmias.

Treatment of acute poisoning is symptom-directed.

- Muscarinic excess resulting from parasympathetic ganglion stimulation can be controlled with **atropine.**

- Central stimulation is treated with anticonvulsants such as **diazepam**. Neuromuscular blockade is not responsive to treatment and requires mechanical respiration.

- Fortunately, nicotine is metabolized and excreted relatively rapidly. Patients who survive the first 4 hours usually recover completely if hypoxia and brain damage have not occurred.

Chronic Nicotine Toxicity

- Nicotine contributes to the increased risk of **vascular disease and sudden coronary death associated with smoking**.
- Also, the high incidence of **ulcer recurrences** in smokers.
- **Replacement therapy with nicotine** in the form of gum, transdermal patch, nasal spray, or inhaler are used to help patients stop smoking.

Varenicline

- Has **partial agonist action at central nicotinic receptors (**α4β2 and α6β2**)**

- It stimulates basal mesolimbic dopamine release to approximately 50% of the maximal effect of nicotine.
- It prevents the stimulant effect of nicotine at presynaptic nicotinic receptors that cause release of dopamine.
- its use is limited by nausea and insomnia and also by exacerbation of psychiatric illnesses, including anxiety and depression.

Cholinesterase Inhibitors

- The major source of intoxications is **pesticide**.
- **pesticides** can cause symptoms which persist for days.
- chemical warfare agents (**soman, sarin, VX**) induce effects rapidly.

. M**iosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea**.

CNS involvement (**cognitive disturbances, convulsions, and coma**) usually follows rapidly, accompanied by peripheral nicotinic effects, especially depolarizing neuromuscular blockade.

Therapy always includes:

(**1**) maintenance of vital signs—respiration in particular may be impaired.

(**2**) decontamination to prevent further absorption.

(**3**) atropine parenterally in large doses, given as often as required to control muscarinic excess.

Therapy often also includes treatment with pralidoxime, and benzodiazepines for seizures.

- **Preventive therapy for cholinesterase inhibitors warfare agents**
- Personnel are given **autoinjection syringes containing pyridostigmine and atropine**.

- **Chronic exposure** to certain organophosphate compounds causes **delayed neuropathy associated with demyelination of axons**.
- The effects are not caused by cholinesterase inhibition but rather by neuropathy target esterase (NTE) inhibition whose symptoms (weakness of upper and lower extremities, unsteady gait) appear 1–2 weeks after exposure.

- **Another nerve toxicity called intermediate syndrome** occurs 1–4 days after exposure to organophosphate insecticides.
- This syndrome is also characterized by muscle weakness.