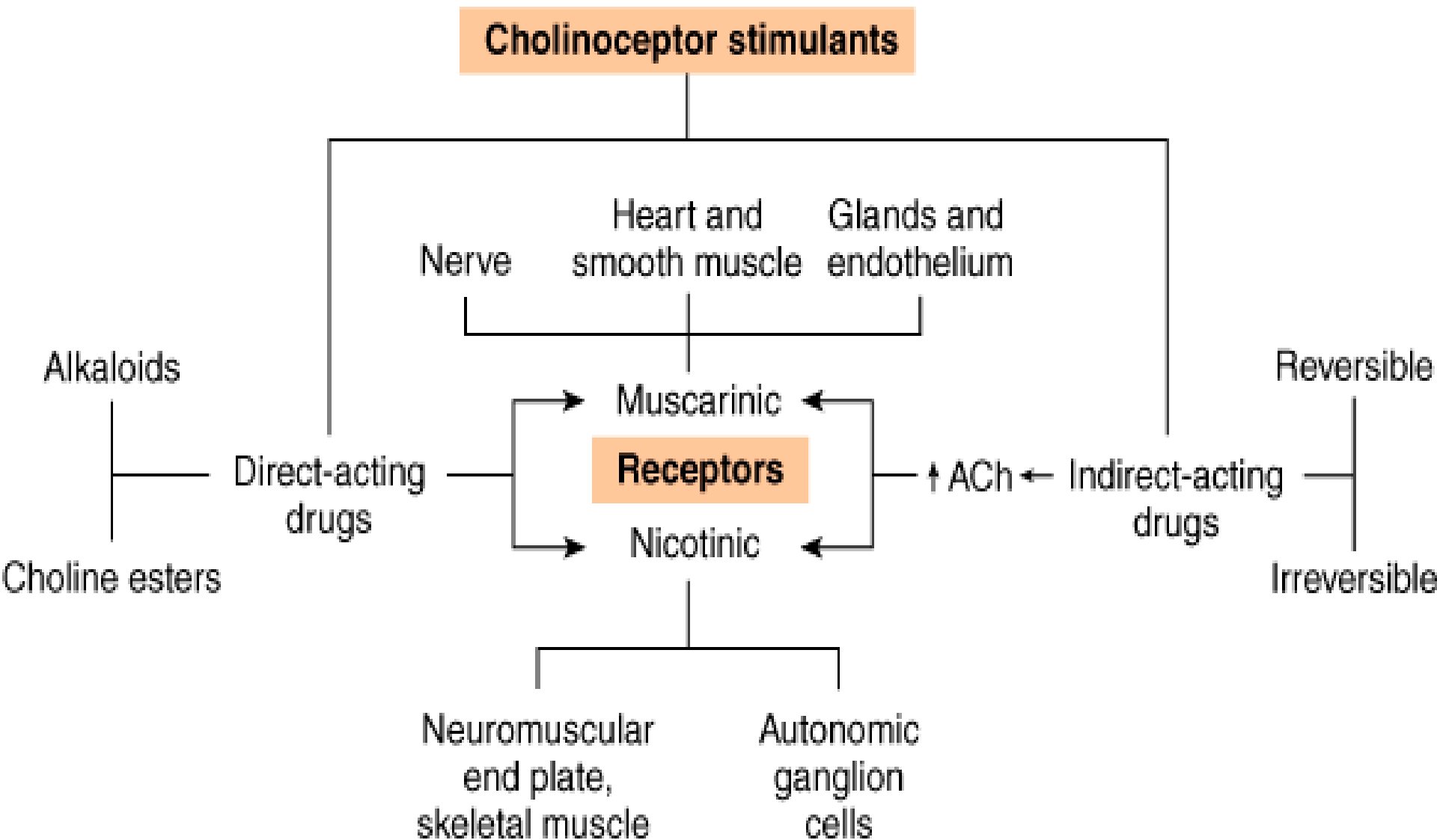
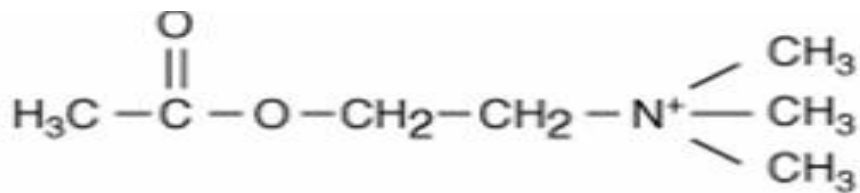


# Cholinoceptor - Activating &Cholinesterase-Inhibiting Drugs

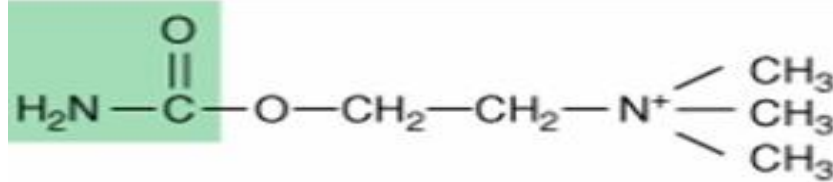


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>

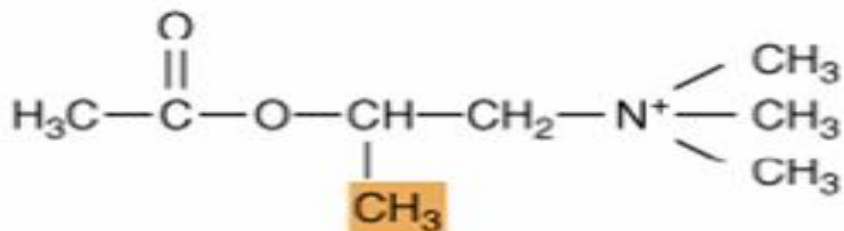
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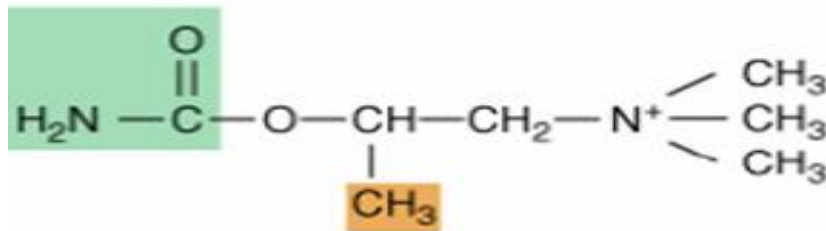
**Acetylcholine**



**Carbachol  
(carbamoylcholine)**



**Methacholine  
(acetyl-β-methylcholine)**



**Bethanechol  
(carbamoyl-β-methylcholine)**

**Choline Ester    ACE    Muscarinic    Nicotinic**

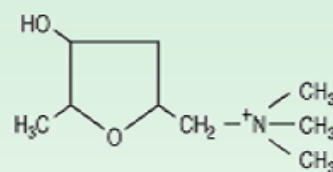
Acetylcholine    +++++    +++    +++

Methacholine    +    +++++    None

Carbachol    Negligible    ++    +++

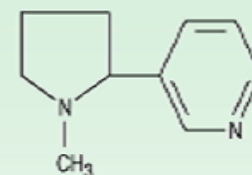
Bethanechol    Negligible    ++    None

Action chiefly muscarinic

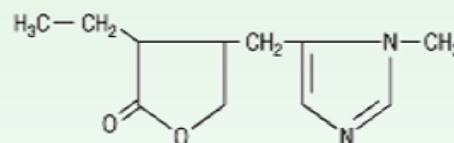


**Muscarine**

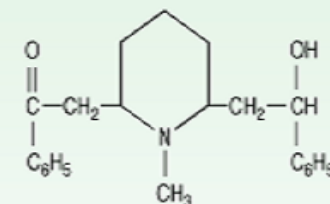
Action chiefly nicotinic



**Nicotine**



**Pilocarpine**

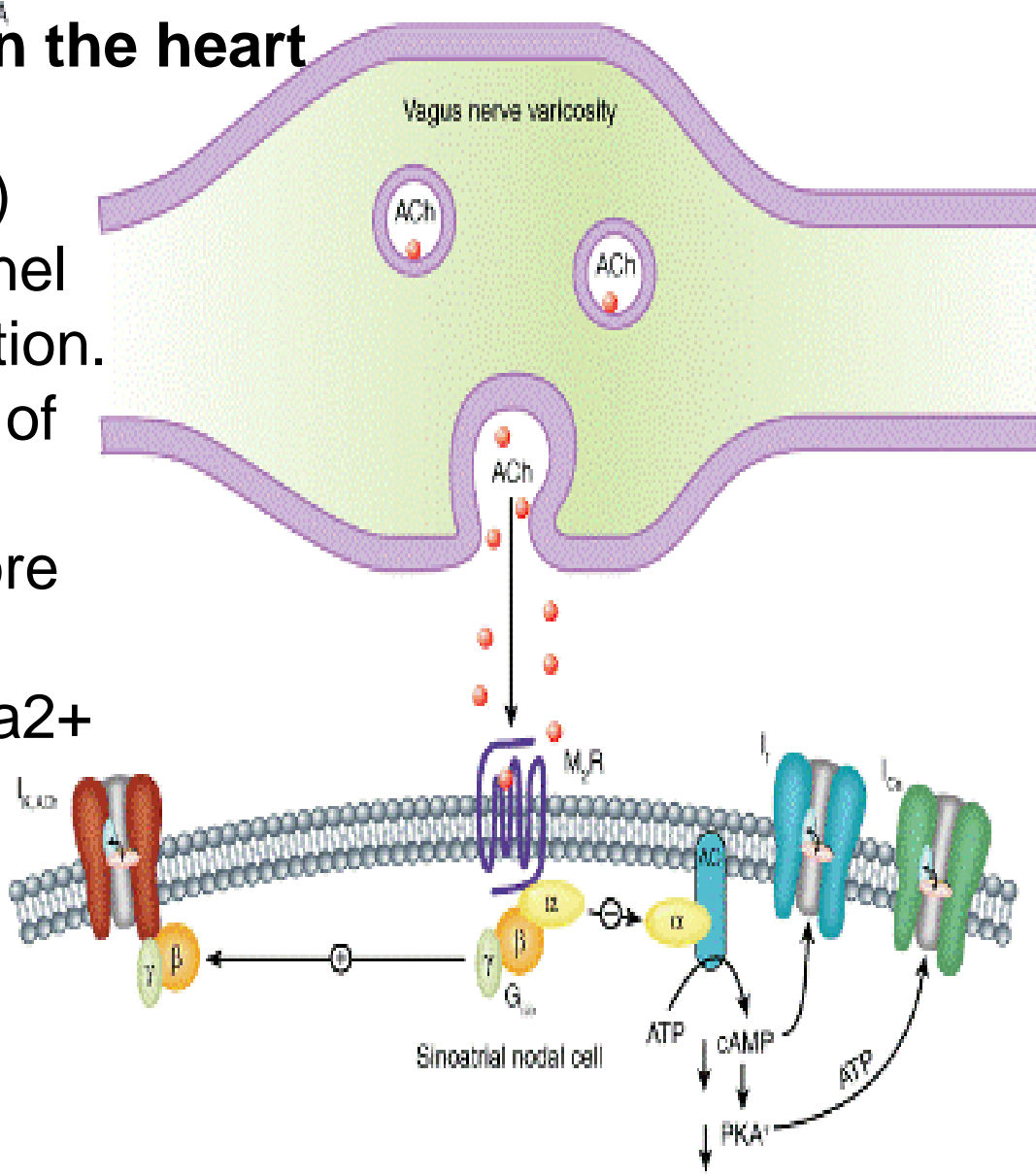


**Lobeline**

# Mechanism of Action

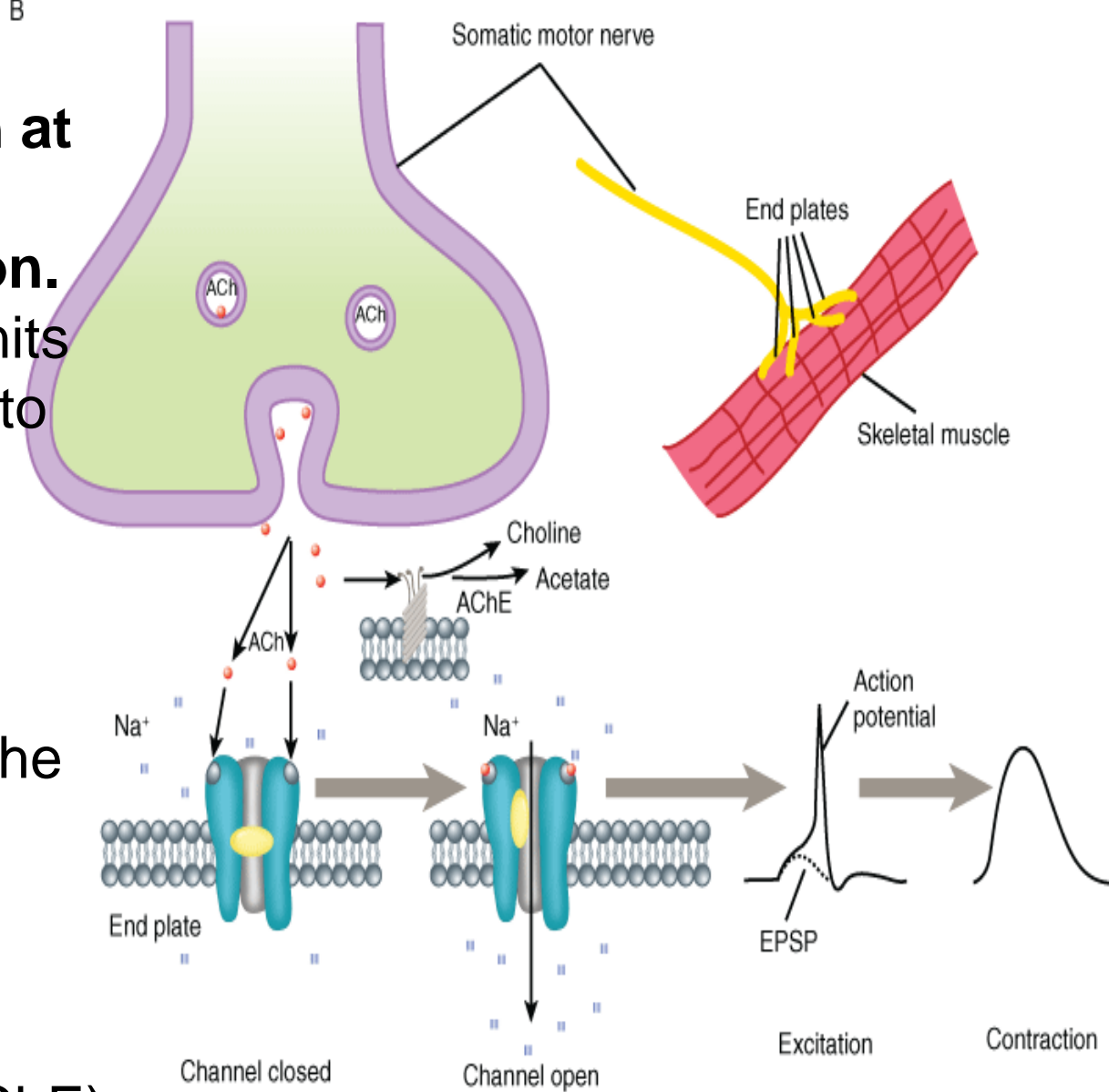
## Muscarinic transmission in the heart

ACh interacts with a muscarinic receptor (M2R) linked via Gi/o to a K<sup>+</sup> channel which causes hyperpolarization. Voltage-dependent opening of pacemaker sodium current channels (I<sub>f</sub>) is shifted to more negative potentials and the phosphorylation of L-type Ca<sup>2+</sup> channels (I<sub>Ca</sub>) is reduced



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

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# Nicotinic transmission at the skeletal neuromuscular junction.

ACh interacts with subunits of the nicotinic receptor to open it, allowing Na<sup>+</sup> to produce an excitatory postsynaptic potential (EPSP).

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

Acetylcholinesterase (AChE) in the extracellular Matrix hydrolyzes ACh.

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# Effects of Direct-Acting Cholinoceptor Stimulants

<b>Organ</b>	<b>Response</b>
<b>Eye</b>	
• Sphincter muscle of iris	Contraction (miosis).
• Ciliary muscle	Contraction for near vision facilitation of aqueous humor outflow into the canal of Shlemm.
<b>Heart</b>	
• Sinoatrial node	Decrease in rate (negative chronotropy)
• Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period.
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period.
Ventricles	Small decrease in contractile strength

## Blood vessels

Arteries	Dilation (via EDRF).
Veins	Dilation (via EDRF).

**EDRF, endothelium-derived relaxing factor. nitric oxide (NO)**

- **Lung**

Bronchial muscle	Contraction (bronchoconstriction)
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 minimally effective doses of **Ach** cause **vasodilation**, reduction in blood pressure, often accompanied by 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 and ventricular cells.
- The direct slowing of sinoatrial rate and 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 and increases cGMP, resulting in relaxation.
- **Pilocarpine (Natural alkaloid)** may produce hypertension after a brief initial hypotensive response. The longer-lasting hypertensive effect is due to **sympathetic ganglionic activation** caused by activation of ganglionic **M1** receptors, which elicit slow excitatory (depolarizing) postsynaptic potentials.
- This effect, like the hypotensive effect, can be blocked by atropine, an antimuscarinic drug.

- **Respiratory System:**

- Bronchoconstriction due to contraction of the smooth muscle of the bronchial tree.
- Increases bronchial secretion.

- **Gastrointestinal Tract:**

- increases the secretory and motor activity of the gut. The **salivary and gastric glands are strongly stimulated**; the pancreas and small intestinal glands are stimulated less so.
- **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 and relaxation caused by sympathomimetic drugs.

- **Genitourinary Tract :**
- Muscarinic agonists 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 appears to be 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).

**oxotremorine** produces tremor, hypothermia, and antinociception (increased tolerance for pain ) M2.

Animals lacking M3 receptors had reduced appetite and diminished body fat mass

Presynaptic nicotinic receptors allow Ach & nicotine to 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.

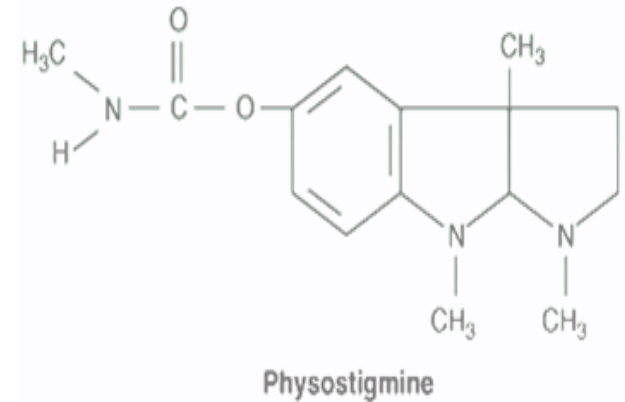
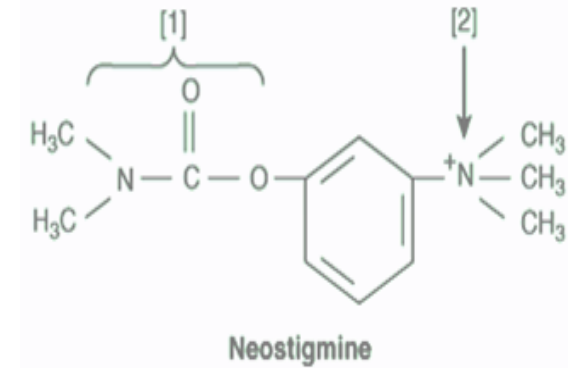
- **Autonomic ganglia:**
- In the CVS, the effects of nicotine are chiefly **sympathomimetic**.
- Nicotine causes hypertension, tachycardia which may alternate with a bradycardia mediated by vagal discharge.
- **GIT and urinary tracts:**
- The effects are **parasympathomimetic**: nausea, vomiting, diarrhea, and voiding of urine are commonly observed. 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

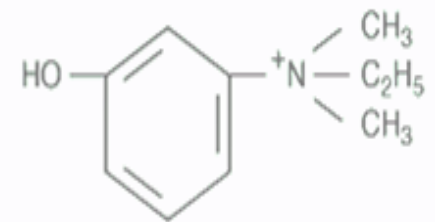
an ester composed of carbamic acid ([1]) and a phenol bearing a quaternary ammonium group ([2]).



### Physostigmine

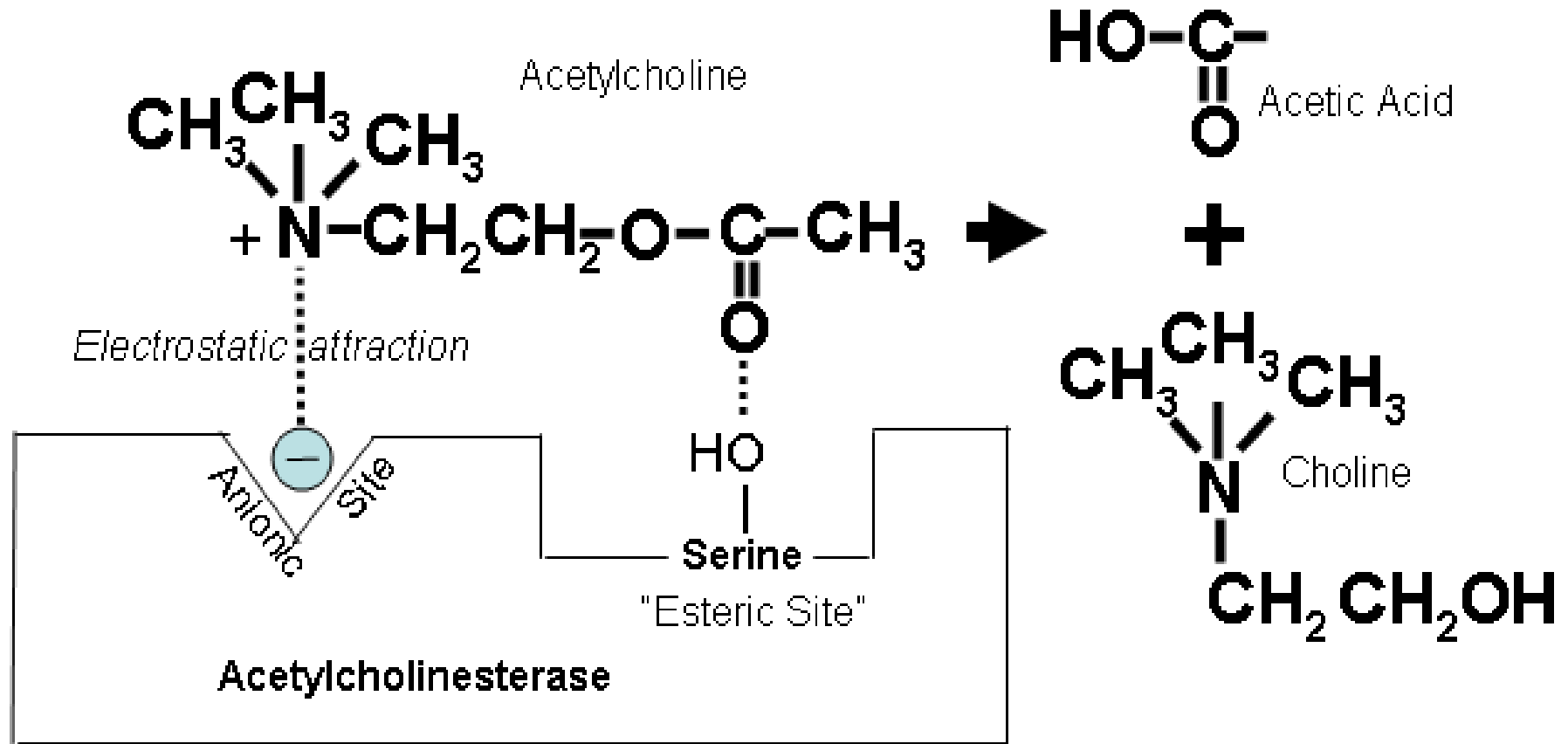
A naturally occurring carbamate, is a tertiary amine.

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



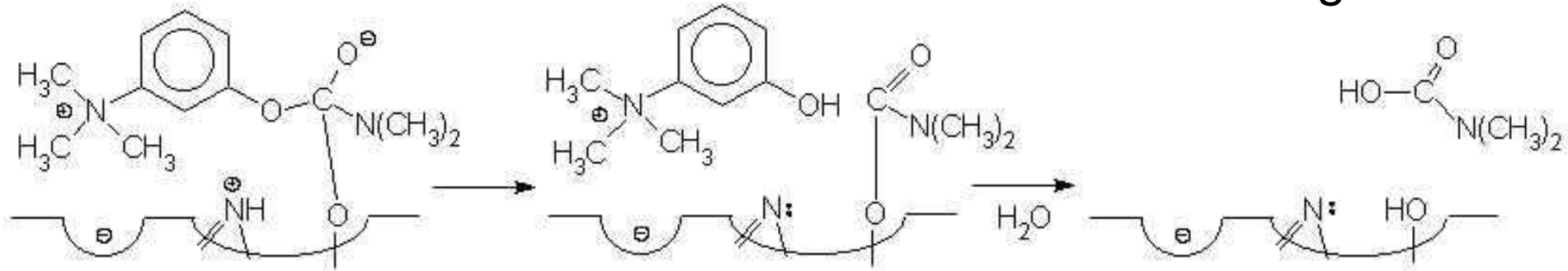
Edrophonium

# Metabolism of Acetylcholine



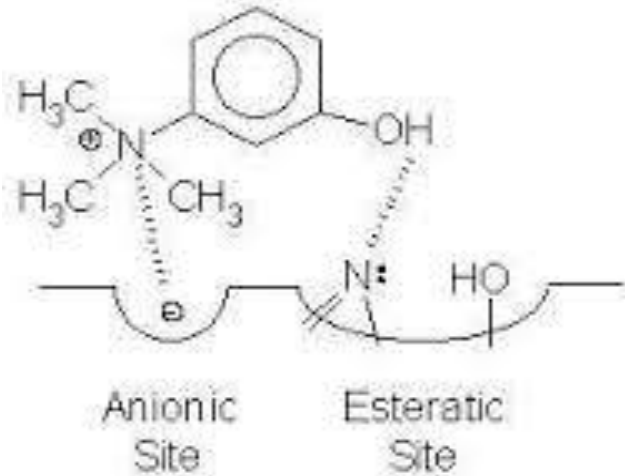
The positively charged nitrogen in the acetylcholine molecule is attracted to the ionic site on acetylcholinesterase, and hydrolysis is catalyzed at the esteric site to form choline and acetic acid.

# 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

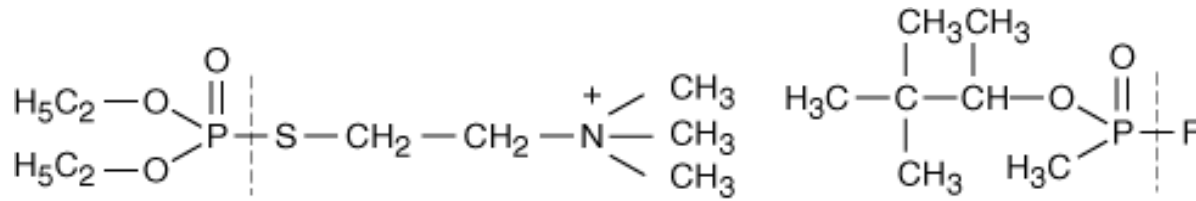
Stabilized by an ionic bond at the anionic site and through weak hydrogen bonding at the esteratic site.



# Irreversible cholinesterase inhibitors. organophosphate

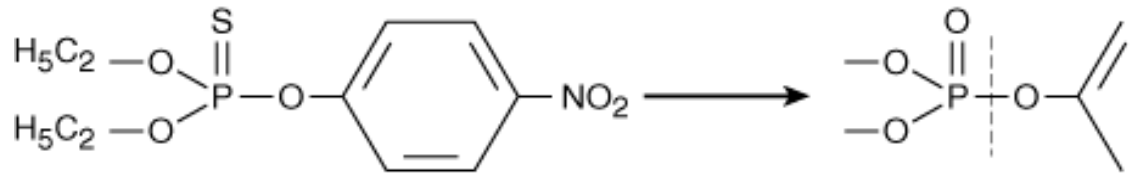
Structures of some organophosphate cholinesterase inhibitors.

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.



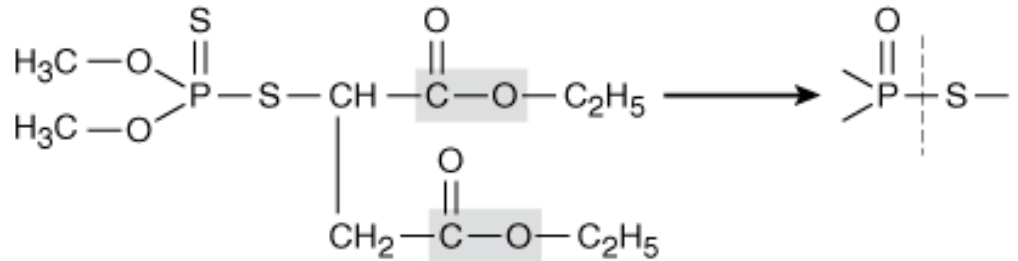
**Echothiophate**

**Soman**



**Parathion**

**Paraoxon**



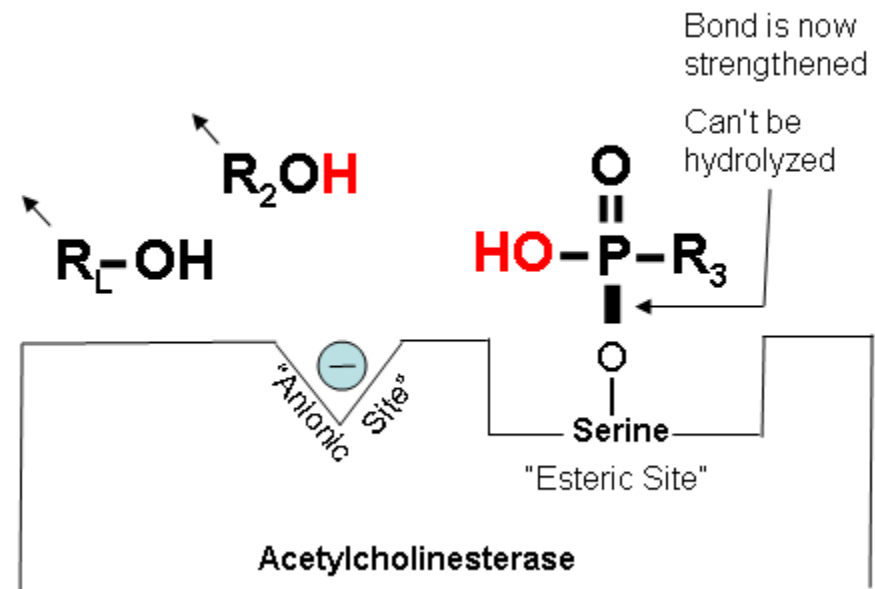
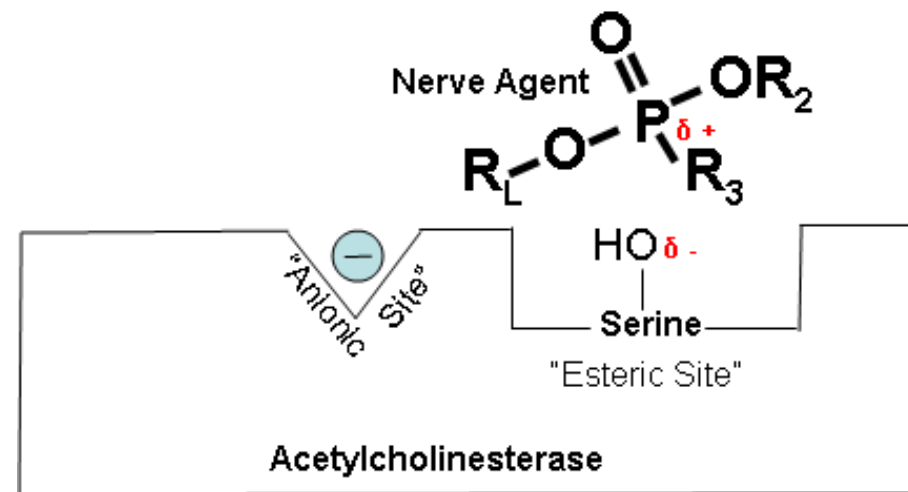
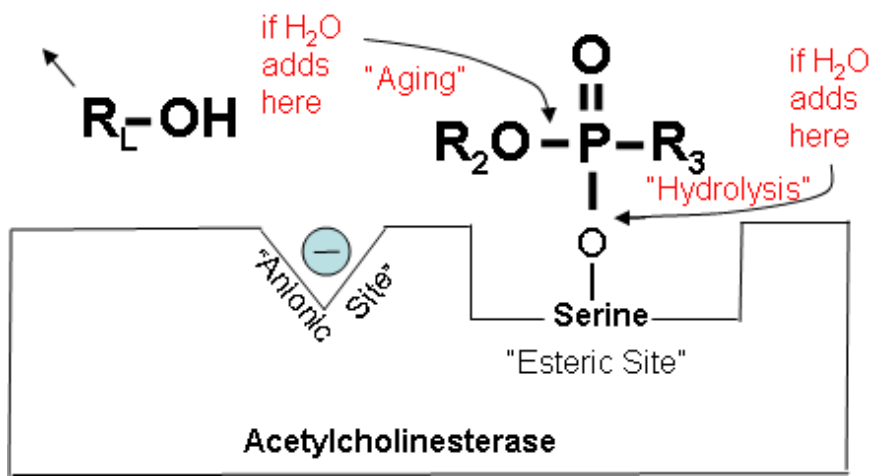
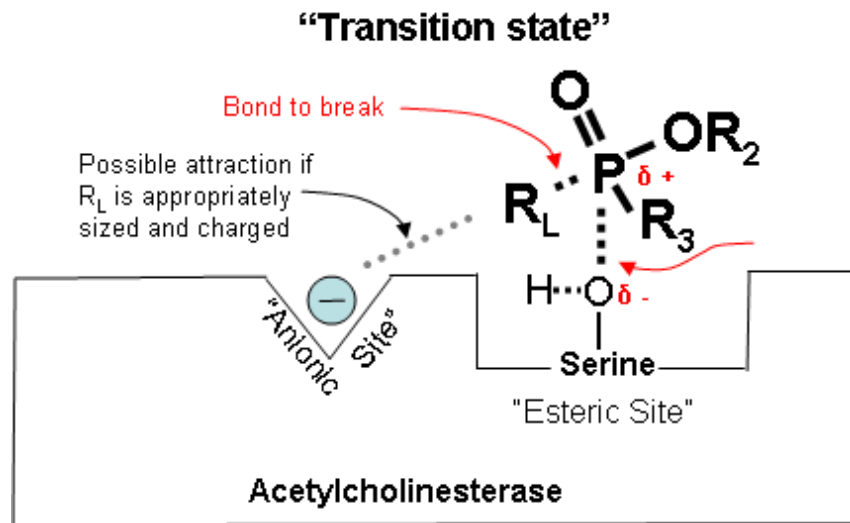
**Malathion**

**Malaoxon**

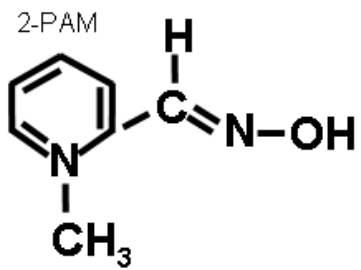
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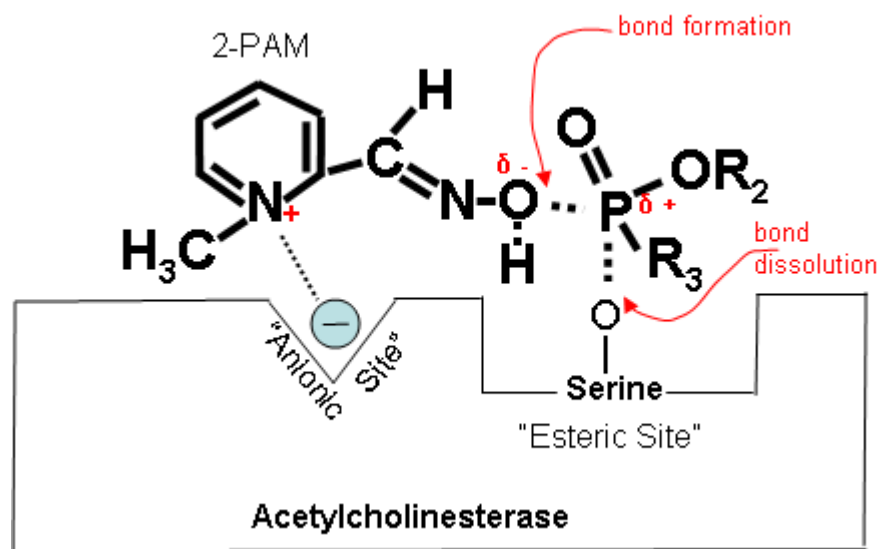
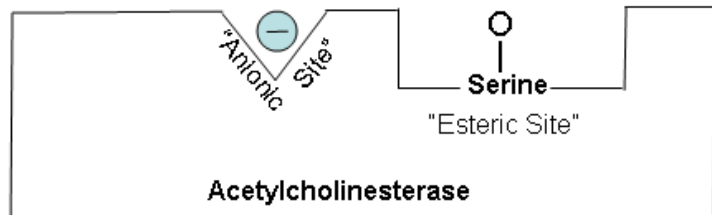
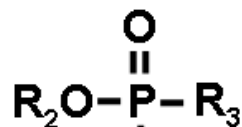
a cholinesterase inhibitor attaches to the serine hydroxyl group on ACh.E. This prevents acetylcholine from interacting with the cholinesterase enzyme and being broken down.



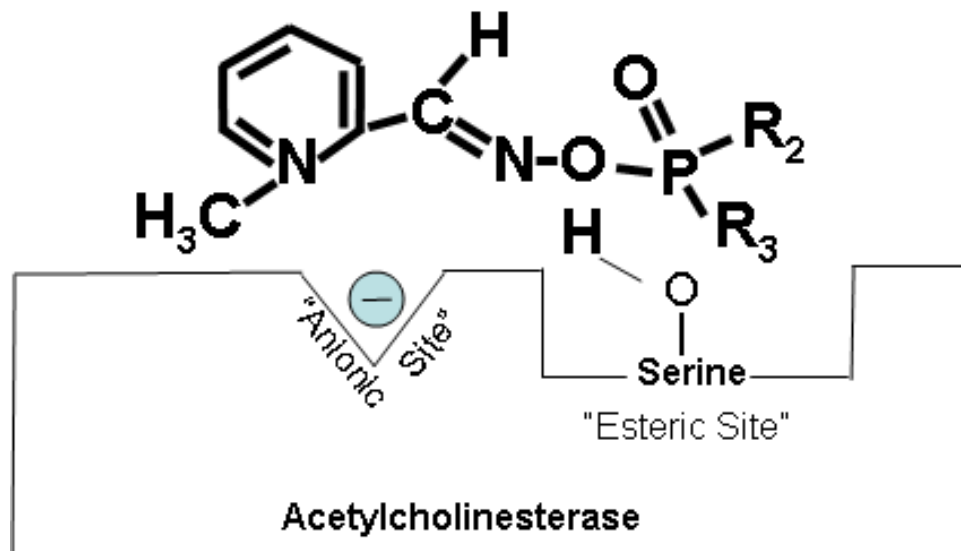
2-PAM



pralidoxime



"Regenerated  
cholinesterase"



- **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 can be 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 (except for echothiophate) 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**
- All the cholinesterase inhibitors **increase** the concentration of endogenous **acetylcholine** at cholinergic receptors.
- **Edrophonium** is a quaternary alcohol, **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, eg, **neostigmine** and **physostigmine**. undergo a two-step hydrolysis sequence analogous to acetylcholine.
- However, the covalent bond of the *carbamoylated* enzyme is considerably 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 **diffuse activation on the electroencephalogram** and a subjective alerting response.
- In **higher concentrations**, they cause generalized **convulsions**, which may be followed by coma and respiratory arrest.

- **Eye, Respiratory Tract, Gastrointestinal Tract, 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 attributable 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 innervation.

The *net* cardiovascular effects of moderate doses of cholinesterase inhibitors consist of modest **bradycardia**, a fall in cardiac output, and an increased vascular resistance (**sympathetic ganglion stimulation**) that result in a rise in blood pressure.

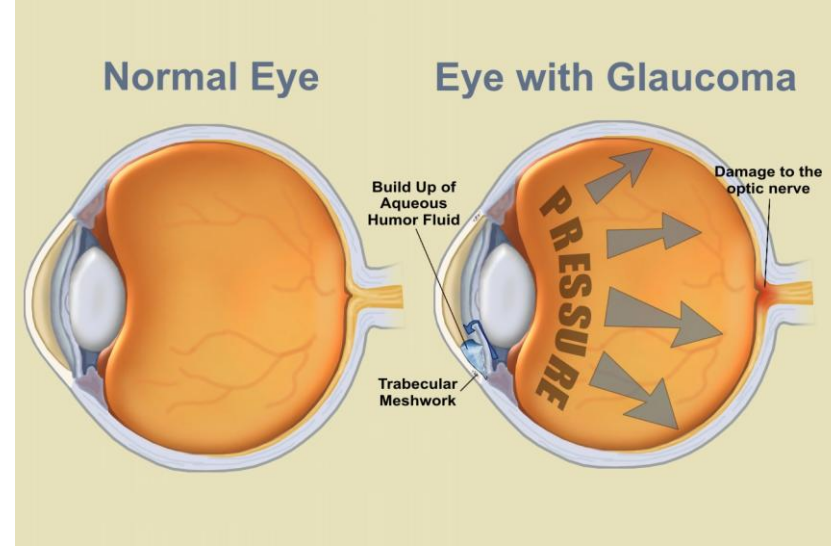
- **Neuromuscular Junction**
- Low concentrations **prolong and intensify the actions of physiologically released acetylcholine**. This increases the strength of contraction, especially in muscles weakened by **curare-like neuromuscular blocking agents or by myasthenia gravis**.
- At higher concentrations, the accumulation of acetylcholine may result in 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 and that may be followed by a phase of **nondepolarizing blockade** as seen with succinylcholine.
- Some quaternary carbamate cholinesterase inhibitors, eg, **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

- In the past, **glaucoma** was treated with pilocarpine, methacholine, carbachol) or ChEIs (physostigmine, demecarium, echothiophate, isofluorophate).
- These drugs have been largely replaced by **topical - $\beta$ -blockers** and **prostaglandin** derivatives.
- **Acute angle-closure glaucoma** is a medical emergency that usually requires **surgery** for permanent correction.
- Initial therapy consists of a combination of a direct muscarinic agonist and a cholinesterase inhibitor (eg, pilocarpine plus physostigmine)





- **GI and Urinary Tracts**
- **Postoperative ileus** (atony or paralysis of the stomach or bowel following surgical manipulation) and **congenital megacolon**.
- **Urinary retention** postoperatively or postpartum or may be secondary to spinal cord injury or disease (neurogenic bladder).
- **Bethanechol** and **Neostigmine** are the most widely used for these applications.
- In all of these situations, it must be certain that there is no mechanical obstruction to outflow before using the cholinomimetic.
- **Pilocarpine** has long been used to increase salivary secretion.

- **Cevimeline**

A derivative of acetylcholine, is a new direct-acting muscarinic agonist used for the treatment of dry mouth associated with Sjögren's syndrome (shoh-grinz, a systemic autoimmune disease in which immune cells attack and destroy the exocrine glands<sup>2</sup> that produce tears and saliva. ) and that caused by radiation damage of the salivary glands.

- **Neuromuscular Junction**
- **Myasthenia gravis** is an autoimmune disease affecting skeletal muscle neuromuscular junctions. **Antibodies** are detected in 85% of myasthenic patients.
- 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..

Ptosis (drooping of the eyelid)



- The disease resembles the neuromuscular paralysis produced by  $\alpha$ -tubocurarine.
- Patients with myasthenia are very sensitive to the action of neuromuscular blockers and other drugs that interfere with neuromuscular transmission, eg, 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 (steroids, cyclosporine, and azathioprine).
- In some patients, the **thymus** gland is removed.

- **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 about 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**).

- Long-term therapy is usually accomplished with **pyridostigmine**; **neostigmine** or **ambenonium** are alternatives.
- 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, it is usually desirable to **reverse this pharmacologic paralysis promptly**. This can be easily accomplished with cholinesterase inhibitors; **neostigmine** and **edrophonium** are the drugs of choice.

- **Central Nervous System**
- **Tacrine** is a drug with anticholinesterase has been 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 acetylcholinesterase inhibitors used in treatment of cognitive dysfunction in **Alzheimer's** patients.
- It is 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. Ingestion of these mushrooms causes typical signs of muscarinic excess within 15–30 minutes.
- Treatment is with **atropine**, 1–2 mg parenterally. (*Amanita muscaria*, the first source of muscarine, contains very low concentrations of the alkaloid.)





- **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 usually treated with parenteral anticonvulsants such as **diazepam**. Neuromuscular blockade is not responsive to pharmacologic treatment and may require 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**. It also has **antagonist properties** that persist because of its long half-life; this 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** use in agriculture and in the home.
- **pesticides** can cause slowly or rapidly developing symptoms which persist for days.
- chemical warfare agents (**soman, sarin, VX**) induce effects rapidly because of the large concentrations present.
- **Miosis, 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 signs of muscarinic excess.

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

- **Preventive therapy for cholinesterase inhibitors**
- Used as chemical warfare agents has been developed to protect soldiers and civilians. 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**; its origin is not known but it appears to be related to cholinesterase inhibition.