Case 1: Anticholinesterase

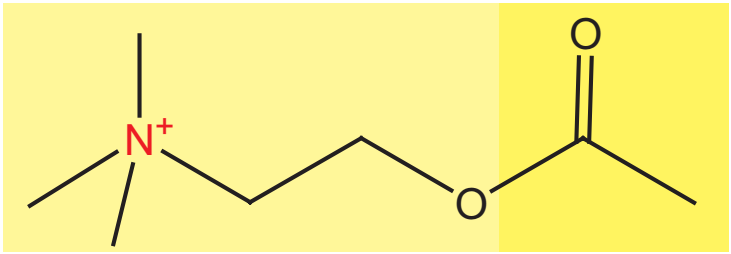
February 3, 2005

1. Cholinergic Pharmacology
2. Anticholinesterase inhibitors
3. Therapeutic use
4. Managing toxicity

Case: Organophosphate Poisoning

A 55 yr old crop duster calls because he has lost control over his chronic twitch, and he is now beginning to have problems with blurry vision and control of his bowels and bladder. He wants to go back to the airfield to finish his crop dusting, but his supervisor makes him call you first.

Acetylcholine



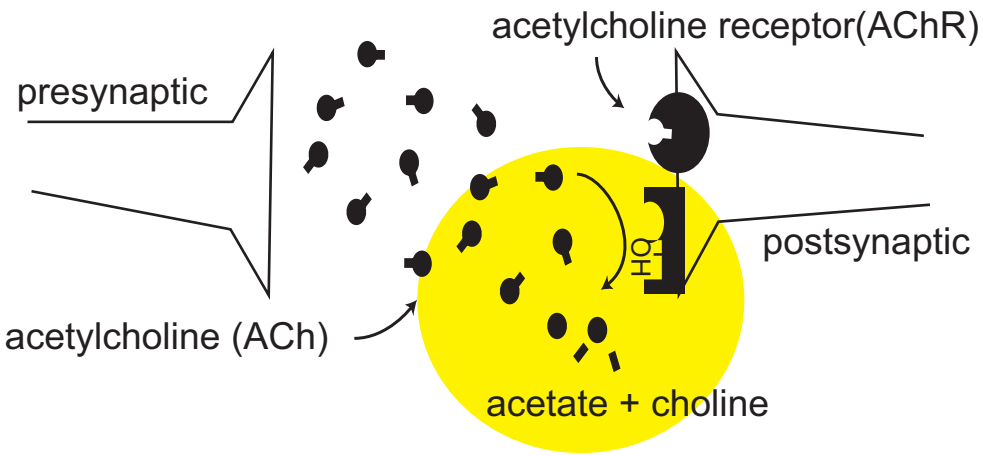
Synthesized from acetyl-CoA and choline by choline acetyltransferase (ChAT)

Poor absorption and low lipophilicity due to charge on quaternary ammonium

Multiple systemic effects, esp autonomic pathways and at the neuromuscular junction (NMJ)

Receptor class	***Locations***
Muscarinic M_1	Post-synaptic ANS ganglia, CNS
Muscarinic M_2	Heart, smooth muscle
Muscarinic M_3	Vessels (smooth muscle), exocrine glands
Muscarinic M_4	CNS
Muscarinic M_5	CNS
Nicotinic N_M	NMJ
Nicotinic N_N	Pre-synaptic ANS ganglia, adrenal medulla, CNS

Acetylcholinesterase (AChE)



Clears Ach from site of action (also degraded by plasma butyrylcholinesterase)

Bound on post-synaptic membrane

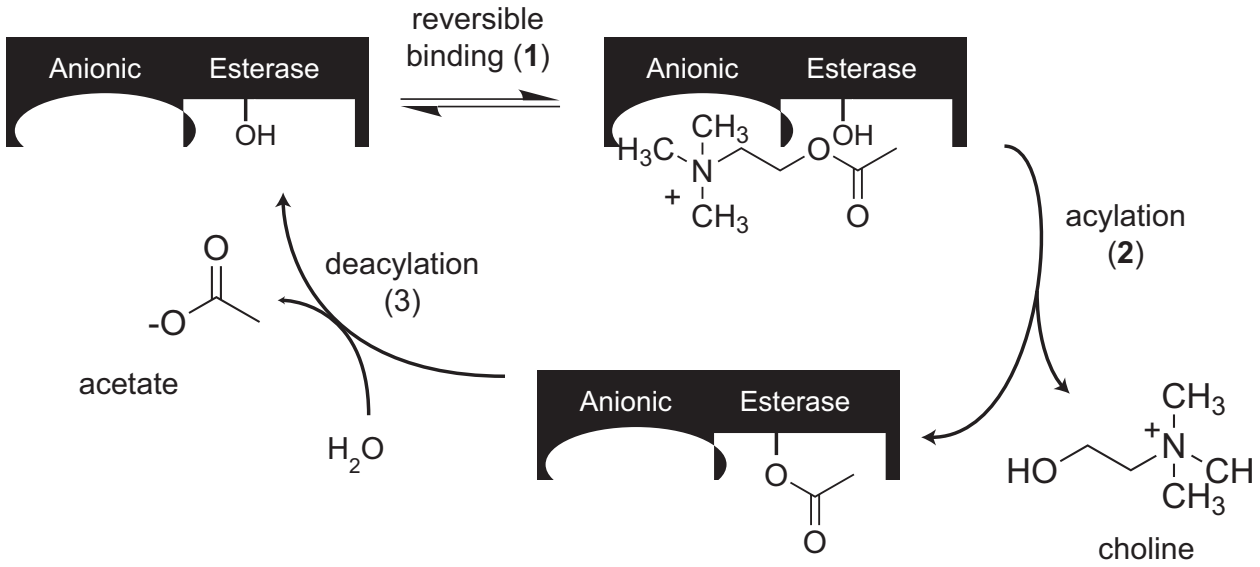
Rate = 400,000 per min

Inhibition of AchE results in build up of Ach at muscarinic and nicotinic synapses!

Step 1: Binding

Step 2: Formation of covalent intermediate and release choline

Step 3: Hydrolysis of acyl-enzyme intermediate



Direct-acting agonists

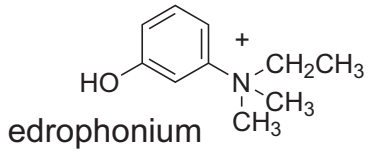
Mimics acetylcholine by binding Ach receptor and activating downstream signaling

Examples: methacholine, carbachol, bethanechol, pilocarpine

Indirect agonists

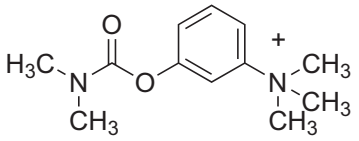
Inhibits AchE from breaking down acetylcholine at synapse

Quaternary alcohols
- competes w/ ACh for binding to AChE (step 1)
Examples: edrophonium



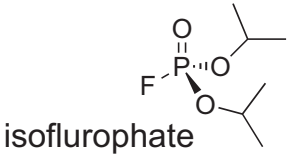
edrophonium

Carbamate esters
- formation of carbamylated enzyme intermediate (step 2)
Examples: neostigmine, pryidostigmine



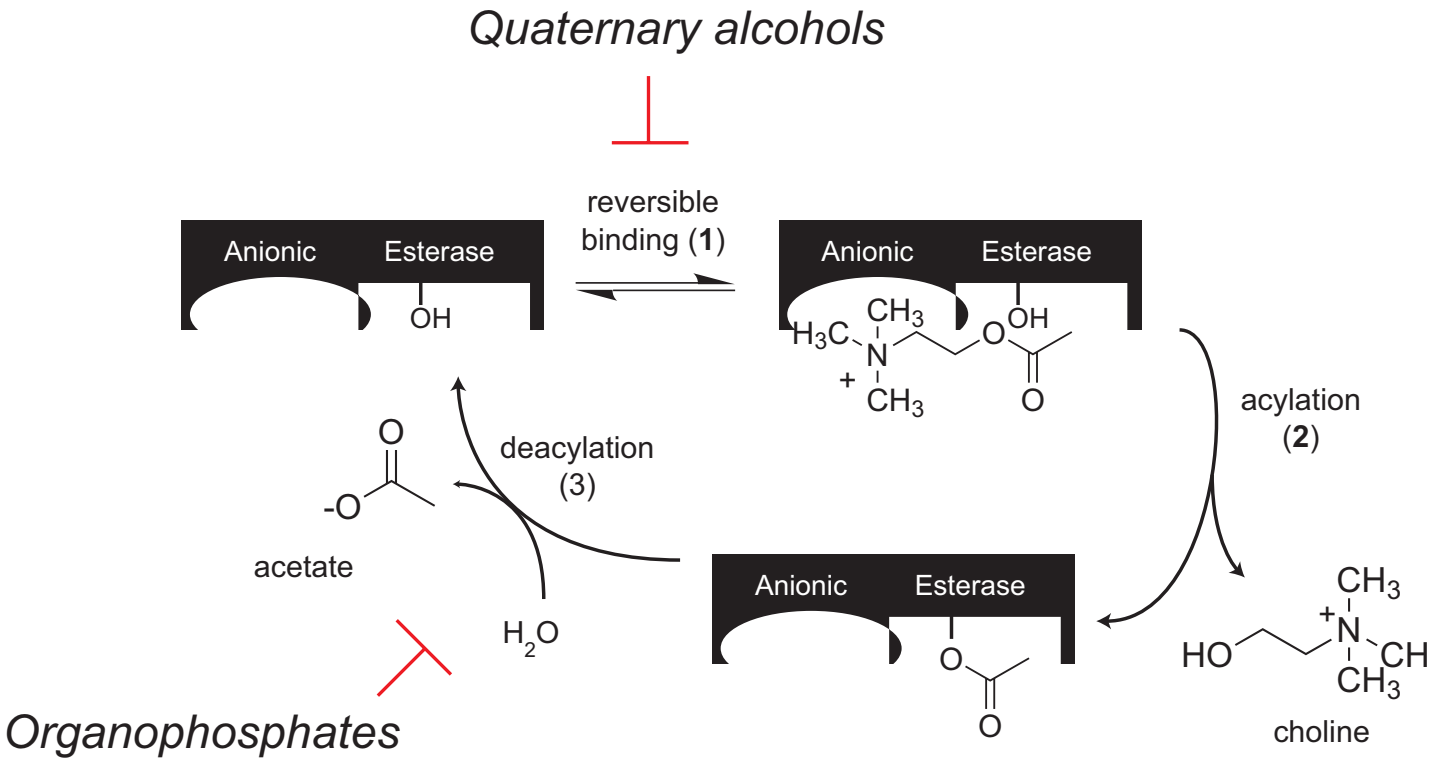
neostigmine

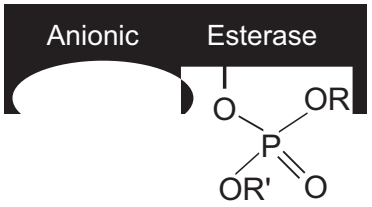
Organophosphates
- formation of phosphorylated enzyme intermediate (step 2)
Examples: parathion, malathion are insecticides
soman, sarin are nerve agents



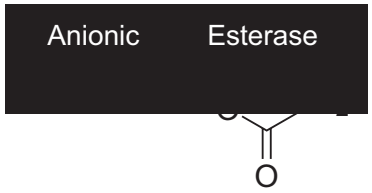
isoflurophate

AchE inhibitors: reversible versus irreversible



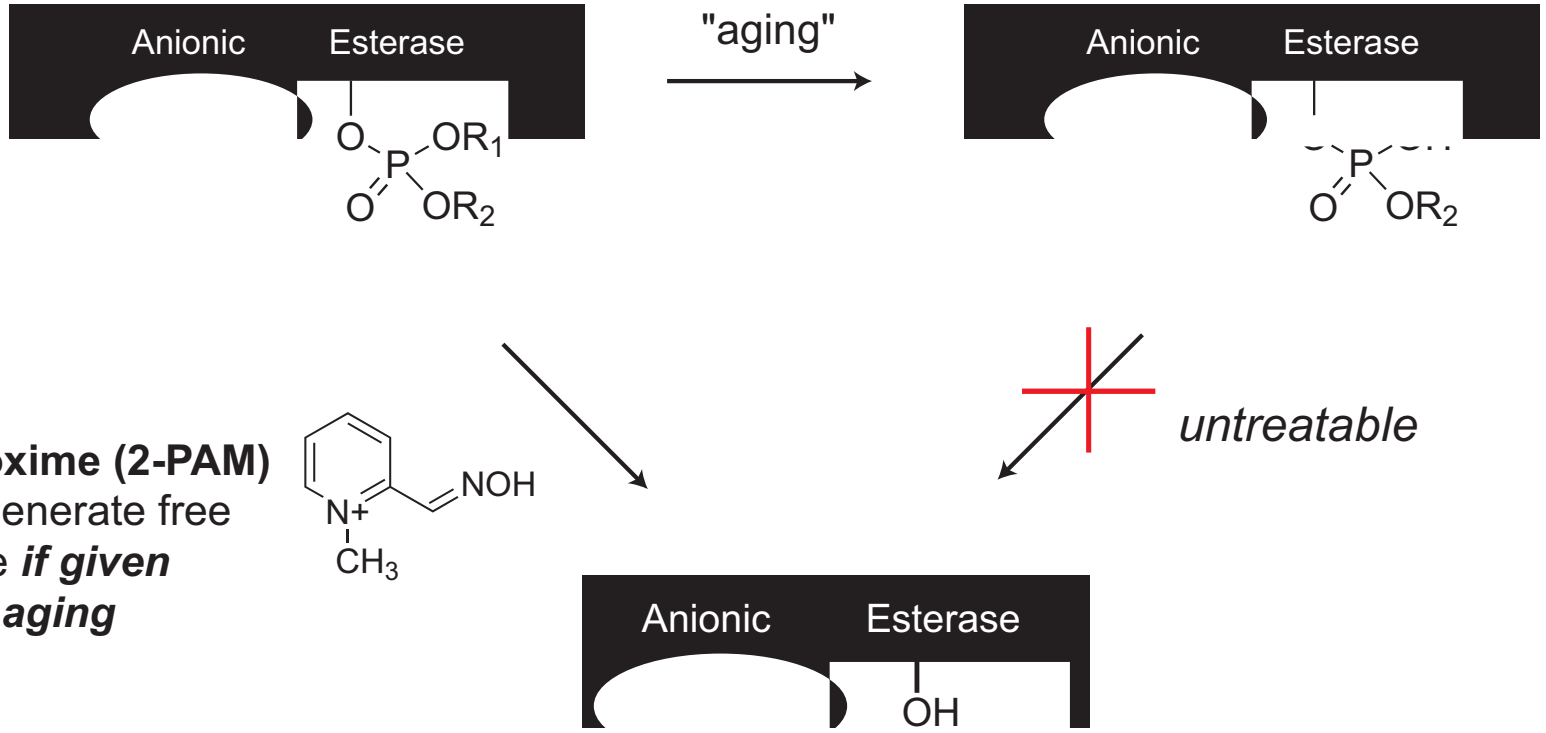


half-life >100 hrs!



half-life 1-6 hrs

Inhibition by organophosphate: "Aging"



Pralidoxime (2-PAM) can regenerate free enzyme ***if given before aging***

Pharmacokinetics of organophosphates

Parathion and malathion are biotransformed in the liver to become active (insects perform this process more efficiently)

Highly lipid soluble, widely distributed and penetrates CNS

When used as insecticides, can be dispersed as aerosols or dusts and absorbed by all possible routes: GI, skin, mucous membranes, lungs

Slow hepatic metabolism; urine excretion of hydrolysis products

Lipid-soluble drug can remain in systems for weeks to months!

Effects of acute O/P overdose

Muscarinic	Nicotinic	CNS
Ciliary spasm, Miosis Bronchoconstriction Bronchosecretion Diaphoresis Salivation, Lacrimation Bradycardia, Hypotension Incontinence, Diarrhea GI spasms (cramping) Emesis, Nausea	Weakness Fasciculation Twitching Flaccid Paralysis (resp.) Severe Cases: also include conduction block, pulmonary edema	Confusion Anxiety, Agitation Restlessness, Tremor Ataxia Convulsions Respiratory depression CV collapse Coma

DUMBBELLS: Diarrhea (Diaphoresis), Urination, Miosis, Bronchospasm (secretion) Bradycardia, Excite skeletal muscle and CNS (Emesis), Lacrimation, Lethargy, Salivate

Mode of death: respiratory failure via flaccid muscular paralysis exacerbated by bronchosecretion and bronchoconstriction

Chronic Exposure to Low Doses:
blurred vision, incontinence, twitching***
neuropathy associated with axonal demyelination

Treatment

Lethal Dose

Remove contaminated clothing; remove from exposure site

Wash skin with soap, bleach (alkaline hydrolysis)

Respiratory support (O_2, ventilatory assistance, treat Sz)

Atropine – anti-muscarinic agent

- reverses dangerous parasympathetic effects (respiratory)
- 0.5-2 mg IV q15min until respiratory secretions dry (days!)

Pralidoxime (2-PAM) - specific for organophosphate poisoning

Therapeutic use of AchE inhibitors

Photos removed for copyright reasons.

Myasthenia gravis (edrophonium, pyridostigmine, neostigmine)

Alzheimer's Disease (tacrine and donepezil)

Reversal of neuromuscular blockers (neostigmine, physostigmine)

Glaucoma (physostigmine, echothiophate)

Summary of Key Points

Reversible versus irreversible inhibition of AchE causes build up of Ach at synapse

Toxicity associated with AchE inhibitors (patient case!) include global nicotinic, muscarinic, & CNS effects (*DUMBBELLS*)

Treatment for Exposure to Irreversible Inhibitors
Atropine – counteract ACh agonism
2-Pralidoxime – prevent aging