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)

<table>
<thead>
<tr>
<th><strong>Receptor class</strong></th>
<th><strong>Locations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscarinic $M_1$</td>
<td>Post-synaptic ANS ganglia, CNS</td>
</tr>
<tr>
<td>Muscarinic $M_2$</td>
<td>Heart, smooth muscle</td>
</tr>
<tr>
<td>Muscarinic $M_3$</td>
<td>Vessels (smooth muscle), exocrine glands</td>
</tr>
<tr>
<td>Muscarinic $M_4$</td>
<td>CNS</td>
</tr>
<tr>
<td>Muscarinic $M_5$</td>
<td>CNS</td>
</tr>
<tr>
<td>Nicotinic $N_M$</td>
<td>NMJ</td>
</tr>
<tr>
<td>Nicotinic $N_N$</td>
<td>Pre-synaptic ANS ganglia, adrenal medulla, CNS</td>
</tr>
</tbody>
</table>
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

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

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

*Quaternary alcohols*

1. Reversible binding
2. Acylation
3. Deacylation

**Organophosphates**

**Carbamate esters**

- half-life >100 hrs!
- half-life 1-6 hrs
Inhibition by organophosphate: "Aging"

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

untreatable
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

<table>
<thead>
<tr>
<th>Muscarinic</th>
<th>Nicotinic</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciliary spasm, Miosis</td>
<td>Weakness</td>
<td>Confusion</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>Fasciculation</td>
<td>Anxiety, Agitation</td>
</tr>
<tr>
<td>Bronchosecretion</td>
<td>Twitching</td>
<td>Restlessness, Tremor</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Flaccid Paralysis (resp.)</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Salivation, Lacrimation</td>
<td></td>
<td>Convulsions</td>
</tr>
<tr>
<td>Bradycardia, Hypotension</td>
<td></td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Incontinence, Diarrhea</td>
<td>Severe Cases: also include</td>
<td>CV collapse</td>
</tr>
<tr>
<td>GI spasms (cramping)</td>
<td>conduction block,</td>
<td>Coma</td>
</tr>
<tr>
<td>Emesis, Nausea</td>
<td>pulmonary edema</td>
<td></td>
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**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 (O₂, 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

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