Pharmacology 659

Cholinesterase Inhibitors and Muscarinic Blocking Drugs

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Cholinesterases and Anticholinesterases
Definition of Acetylcholinesterase  
(true, specific “e” type)

- Hydrolyzes acetylcholine more rapidly than any other choline ester. Also hydrolyzes methacholine, but not benzoylcholine.

- Is inhibited by very low concentrations of certain bisquaternary ammonium bases.

- Is located within neurons and at both pre- and postsynaptic sites (two slightly different enzymes)

- Pharmacological effects of cholinesterase inhibitors are due almost solely to inhibition of this enzyme.
Definition of Butyrocholinesterase (pseudo, false, plasma)

- Hydrolyzes butyrocholine more rapidly than any other choline ester. Also hydrolyzes acetylcholine and benzoylcholine, but not methacholine.

- Is more sensitive to inhibition by organophosphorus agents than is acetylcholinesterase.

- Is located in plasma, liver, glial cells, and a variety of organs.

- Selective inhibition of this enzyme at most sites has no pharmacological consequences.
Diagram of acetylcholinesterase

Esteratic site

Anionic site

Choline

Acetate
Classes of Cholinesterase Inhibitors
Reversible, Quaternary Compounds

These drugs act at an anionic site, are readily reversible and of short duration. Prototype: edrophonium
Reversible, Quaternary Compounds

These drugs form a carbamyl ester linage and are hydrolyzed by acetylcholinesterase.

Prototypes: physostigmine (eserine, comes from the Calabar bean) and neostigmine.
The Calabar Bean
Neostigmine

AChE

Trp
Glu
Ser

AChE

Trp
Glu
Ser

AChE

Trp
Glu
Ser
Organophosphorus Inhibitors

These drugs phosphorylate cholinesterases to form an extremely stable linkage.

Prototypes: diisopropylfluorophosphate (DFP); insecticides (Malathion, Parathion), and chemical warfare agents (nerve gases like Tabun, Soman, and Sarin).
Diisopropylfluorophosphate (DFP)

Phosphorylated enzyme

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These drugs have significant effects upon the cardiovascular, gastrointestinal, genitourinary, and central nervous systems. They also affect the eye, secretory glands, and the neuromuscular junction.

In essence their actions are the same as that of acetylcholine since they act by allowing acetylcholine to accumulate at all cholinergic synapses.
Therapeutic Uses of Cholinesterase Inhibitors

- Glaucoma
- Atony of the bladder and bowel
- Myasthenia gravis
- Poisoning with anticholinergic drugs
- Alzheimer’s Disease
Treatment of Poisoning with Cholinesterase Inhibitors

• Muscarinic antagonists, such as atropine, are best used to treat intoxication with these drugs.

• Cholinesterase “reactivators”, such as pralidoxime and obidoxine, were introduced to treat poisoning with organophosphorus cholinesterase inhibitors. Such drugs have proven to be of very limited usefulness.
Muscarinic Receptor Blocking Agents
Muscarinic Receptor Blocking Agents

Naturally Occurring

Atropine
Scopolamine
Belladonna atropa
Muscarinic Receptor Blocking Agents

CNS Actions

Small doses of atropine cause mild vagal stimulation. Rate and depth of breathing is increased.

Toxic doses cause restlessness, irritation, disorientation, hallucinations, or delirium.
Higher doses cause depression, circulatory collapse and respiratory failure, and death after a period of paralysis and coma.

Scopolamine causes CNS depression with drowsiness, amnesia, fatigue and dreamless sleep, decreased REM, and euphoria.
Muscarinic Receptor Blocking Agents

GI Actions

Decreased motility

Decreased salivary and gastric secretions

Eye

Mydriasis (dilation of the pupil)

Paralysis of accommodation
Muscarinic Receptor Blocking Agents

Cardiovascular Actions

1. Small doses initially slow heart rate
2. Large doses cause tachycardia
3. Little effect on blood pressure
4. Toxic doses cause vasodilation (atropine flush)
Muscarinic Receptor Blocking Agents

Respiratory Actions
Bronchodilation
Decreased secretions
Sweat Glands
Decreased sweating
Warm, dry skin
Atropine Poisoning

- Tachycardia
- Dry mouth
- Dilated pupils
- Warm, dry, red skin
- Restlessness
- Hallucinations
- Delirium
- Coma
- Death
"red as a beet, dry as a bone, blind as a bat, mad as a hatter, and hot as a hare."

Remember common signs and symptoms of atropine or scopolamine poisoning with the mnemonic.
Quaternary Ammonium Antimuscarinic Drugs

Homatropine, less antimuscarinic and more ganglionic blocking activity than atropine

Methantheline, more ganglionic activity and more GI activity than atropine.

Propantheline, 2-5 times more potent than methanthelene

Ipratropium, less CNS activity than atropine.
Tertiary-Amine Antimuscarinic Drugs

Cyclopentolate, tropicamidine

Short acting drugs used in ophthalmology.

Trihexyphenidyl, benztropine

Readily penetrate the CNS and are used to treat Parkinson’s Disease.
Therapeutic Uses of Antimuscarinic Drugs

- Motion sickness
- Cycloplegia and mydriasis
- Nerve gas and mushroom poisoning
- Adjunct to anesthesia
- Parkinson’s Disease
- Bronchodilation in asthma
- Peptic ulcer disease