Cholinergic Receptors
Agonists and Antagonists

Objectives: At the end of the next four hours the student should:

1. be able to identify the drugs in use today which activate (agonists) or block (antagonists) cholinergic receptors (both nicotinic and muscarinic) by their trade or generic names and if given a structural formula be able to recall the appropriate drug action (i.e. inhibitor, agonist or antagonist) and the neurotransmitter or enzyme system(s) involved.

2. understand the structural and stereochemical basis for the difference in agonist activity between [S]-acetyl-β-methylcholine and [S]-acetyl-α-methylcholine when compared to [1S 2R 4S]-cis-l-muscarine.

3. be able to determine the specificity (M1 or mixed M1 + M2) of hypothetical or new anticholinergic agents by simple structure activity considerations.

4. know the structural aspects of antimuscarinic agents and be able to rank the potency of a simple series of quaternary ammonium ethyl esters of acetic acid.

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I. Muscarinic Receptors

Muscarinic acetylcholine receptors belong to the superfamily of G-protein coupled receptors. Each receptor contains a single subunit with seven transmembrane spanning helices. The following figure shows the hydropathy profile for a typical M2-muscarinic receptor:

Muscarinic receptors are negatively coupled to the production of c-AMP and produce increased turnover of phosphatidyl inositol.

II. Muscarinic Agonists

Acetylcholine is the naturally occurring muscarinic agonist that is released at the end organ to produce a variety of cholinergic actions. In the heart, acetylcholine produces decrease in heart rate, in the intestines, acetylcholine produces contraction of smooth muscle and increase motility of the gut. These actions are typical of the parasympathetic system.

Synthetic parasympathomimetic agents can mimic the actions of acetylcholine and typically have specific action at muscarinic sites as opposed to nicotinic sites. The structures of acetylcholine, muscarine, nicotine, carbamylcholine, and pilocarpine are shown below.

It has been shown that acetic acid esters of quaternary ammonium alcohols of greater length than choline have decreased activity. This led to Ing’s rule of five. There should be no more than five atoms between the nitrogen and the terminal hydrogen for maximal activity.
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Description</th>
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</thead>
</table>
| ![Acetylcholine](image) | Acetylcholine  
Endogenous agonist of nicotinic and muscarinic receptors. Actions in the brain, and periphery, depends on the site at which it is released. |
| ![2S 3R 5S-cis-l-Muscarine](image) | [2S 3R 5S]-cis-l-Muscarine  
Alkaloid from *Amanita muscaria* a mushroom. Classically used to define the properties of muscarinic receptors. |
| ![Nicotine](image) | Nicotine  
Alkaloid from tobacco. Used to define the properties of nicotinic receptors. |
| ![Acetyl-α-methylcholine](image) | Acetyl-α-methylcholine  
Adopts an extended conformation and has greater nicotinic than muscarinic activity. |
| ![Acetyl-β-methylcholine](image) | Acetyl-β-methylcholine (Methacholine®)  
Adopts a gauche conformation and mimics the structure of muscarine. Has greater muscarinic than nicotinic activity. |
| ![Carbamylcholine](image) | Carbamylcholine (Carbachol®)  
Is a choline ester of carbamic acid. Hydrolyses more slowly than acetylcholine and has a longer duration of action. |
| ![Pilocarpine](image) | Pilocarpine  
Alkaloid from *Pilocarpus jaborandi*. Mimics the action of muscarine. Produces sweating, salivation, pupillary constriction, and spasm of accommodation. Use to treat glaucoma. |
III. Nicotinic Receptors

Nicotinic acetylcholine receptors are found in the ganglia and in skeletal muscle. The action of acetylcholine is to create an excitatory postsynaptic potential (EPSP) by opening the nicotinic receptor channel to the flux of Na\(^+\) ions from the outside to the inside of a nerve cell. The flow of Na\(^+\) ions down a concentration gradient causes depolarization of skeletal muscle and post-ganglionic neurons and gives rise to an action potential that propagates an excitatory signal.

Nicotinic receptors are comprised of five subunits that form a ligand-gated ion channel. Each subunit has four hydrophobic transmembrane spanning helical segments of protein.

**Acetylcholine Neuronal Nicotinic Human receptor (Na\(^+\))**
II. **Ganglionic Blocking Agents**

Ganglionic blockers simultaneously block sympathetic and parasympathetic ganglia. Side effects include: orthostatic (postural) hypotension, dilated pupils, blurred vision, decreased libido, impotence (inhibition of erection and ejaculation), anorexia, nausea, vomiting, constipation, and urinary retention.

**Nicotine**

(S)-3-(1-methyl-2-pyrrolidinyl)pyridine

Depolarizing ganglionic blocker

**Hexamethonium (Bistrium Bromide)**

RN 60-26-4.
Hexamethylenebis(trimethylammonium).
Introduced in the 1950’s, was the beginning of antihypertensive drug therapy. No longer approved in the US.

**Mecamylamine (Inversine)** RN 826-39-1.
N,2,3,3-tetramethyl-2-norbornanamine HCl.
Mecamylamine hydrochloride is a secondary amine nondepolarizing ganglionic blocking agent.
Because of adverse effects, mecamylamine is reserved for hypertension refractory to all other hypotensive drugs.
Should be limited to that dosage which causes slight faintness or dizziness in the standing position.

**Trimethaphan camsylate (Arfonad)**

RN 68-91-7.
Decahydro-2-oxo-1,3-bis(phenylmethyl)thieno(1’;2’,1;2)thieno(3,4)imidazol-5-iium, salt with (+)-7,7-dimethyl-2-oxobicyclo(2.2.1)heptane-1-methanesulfonic acid (camsylate)
Very short duration (minutes).
Injection at a rate adjusted to maintain blood pressure at a desired level during surgery.
Results of Ganglionic Blockers on Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Predominate System</th>
<th>Results of Ganglionic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>Parasympathetic</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Heart</td>
<td>Sympathetic</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Arterioles</td>
<td>Sympathetic</td>
<td>Dilation</td>
</tr>
<tr>
<td>Veins</td>
<td>Sympathetic</td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>Parasympathetic</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Iris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>Parasympathetic</td>
<td>Cycloplegia</td>
</tr>
<tr>
<td>GI Tract</td>
<td>Parasympathetic</td>
<td>Relaxation (constipation)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Parasympathetic</td>
<td>Urinary Retention</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Parasympathetic</td>
<td>Dry Mouth</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Sympathetic</td>
<td>Anhidrosis</td>
</tr>
</tbody>
</table>

Cervical Sympathetic Ganglion

Neurotransmission in the autonomic sympathetic ganglion has been found to be more complex than previously thought. Release of acetylcholine at sympathetic ganglia results in a triphasic response of membrane potential. Stimulation of sympathetic ganglia results in a fast (1 ms) initial excitatory postsynaptic potential (EPSP) followed by an inhibitory postsynaptic potential (IPSP) (35 ms), and then finally a slow (~300 ms) EPSP. These three currents are the result of the action of Ach at three sites. First, Ach action on the N2 neuronal nictinic receptor results in the fast EPSP. Second, Ach action on the muscarinic M1 receptors of the small-intensity fluorescent (SIF) cells results in the release of dopamine on the cell body of the postsynaptic neuron (D1 receptors) causing an increase in cAMP and the moderately fast IPSP. Finally, Ach action directly on muscarinic M1 receptors on the cell body of the postsynaptic neuron results in a very slow EPSP mediated by cGMP.

Note: the fast initial EPSP is blocked by the traditional ganglionic blockers and is considered to be the primary pathway for ganglionic transmission.
III. Muscarinic Blocking Agents

A wide variety of compounds act as muscarinic blockers (also known as anticholinergics, parasympatholytics, or cholinolytics). These include Solanaceous alkaloids, aminoalcohol esters, aminoalcohol ethers, aminoamides, and many other tertiary and quaternary amines which have anticholinergic side effects. These agents are used to relax smooth muscle. Specifically they have **mydriatic** (pupillary dilation, and paralysis of accommodation) effects, **antispasmodic** (gastrointestinal and genitourinary) effects, and **antisecretory** (salivation, perspiration, and gastric acid) effects. Common side effects include: dryness of the mouth, mydriasis, and urinary retention.

![Chemical structure of Atropine](image1)

Atropine (Atropisol is the sulfate) is the tropine ester of racemic (dl) tropic acid. Isolated from deadly nightshade Atropa belladonna in 1832. Hyoscamine is the levorotatory (-)[S] isomer. Used topically in the eye to induce mydriasis. In small doses preoperatively to "dry up secretions". Also used as an antidote to nerve gas poisoning to block the effects of excessive Ach action.

![Chemical structure of Scopolamine](image2)

Scopolamine Hyoscine 6,7-b-epoxy-tropine ester of tropic acid. Tends to produce more CNS depression than atropine even though both atropine and scopolamine have similar ability to enter the CNS. Active ingredient in Transderm-Scop to prevent nausea. Used to decrease rigidity in Parkinson’s disease and as a preoperative medication.
Minimal Structure Activity requirements for synthetic antimuscarinic:

\[
\begin{align*}
R_1 & \quad \text{R} \quad R_2 = \text{cyclic structure} \\
R_3 & \quad \text{H, OH, CH}_2\text{OH, CH}_3 \\
X & \quad \text{H-bonding group} \\
Y & \quad \text{Tertiary amino or quaternary ammonium}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Ach pA$_2$</th>
<th>Rel. Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Stimulates</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>4.0-4.3</td>
<td>1-2%</td>
</tr>
<tr>
<td>C</td>
<td>Phenyl</td>
<td>H</td>
<td>H</td>
<td>5.0-5.3</td>
<td>10-20%</td>
</tr>
<tr>
<td>D</td>
<td>Phenyl</td>
<td>H</td>
<td>OH</td>
<td>5.3-5.7</td>
<td>20-50%</td>
</tr>
<tr>
<td>E</td>
<td>Phenyl</td>
<td>Phenyl</td>
<td>H</td>
<td>6.0</td>
<td>100%</td>
</tr>
<tr>
<td>F</td>
<td>Phenyl</td>
<td>Phenyl</td>
<td>OH</td>
<td>7.6</td>
<td>4000%</td>
</tr>
<tr>
<td>G</td>
<td>Phenyl</td>
<td>Phenyl</td>
<td>Phenyl</td>
<td>5.0</td>
<td>10%</td>
</tr>
</tbody>
</table>

Optimal Structure for anti-muscarinic activity
Subtype selective anti-muscarinic agents:

At present the existence of M1 and M2 muscarinic subtypes are recognized. In addition, up to six subtypes have been proposed. The muscarinic receptor is one member of the G-protein coupled receptors which have seven transmembrane spanning regions in one subunit. M1 receptor specific drugs have a stronger effect to inhibit the secretions of exocrine glands. M1 receptors in the brain are responsible for arousal, attention, memory, and learning. M2 receptor specific drugs have their primary action on the smooth muscle of the heart.

Pirenzepine

5,11-Dihydro-11-[4-methyl-1-piperazinyl]acetate]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one.

M1 specific antagonist

Used as an anti-ulcerative by specifically blocking gastric acid secretion. The lack of side effects can be attributed in part to the polar nature of the molecule and inability to enter the CNS.

McN-A-343

M1 agonist.

Primarily useful for research.

AF-DX 116

M2 antagonist.

Is currently in phase II clinical trials for treatment of AV-block or sinus bradycardia.