Acetylcholine

- Acetylcholine (ACh), the naturally occurring neurotransmitter for these receptors, has virtually no systemic therapeutic applications because its actions are diffuse, and its hydrolysis, catalyzed by both acetylcholinesterase (AChE) and plasma butyrylcholinesterase, is rapid.
- Muscarinic agonists mimic the effects of ACh at these sites. These agonists typically are longer-acting congeners of ACh or natural alkaloids that display little selectivity for the various subtypes of muscarinic receptors.
- Several of these agents stimulate nicotinic as well as muscarinic receptors.
Mode of Action of Cholinomimetic Drugs

- Direct-acting cholinomimetic agents bind to and activate muscarinic or nicotinic receptors.
- Indirect-acting agents produce their primary effects by inhibiting acetylcholinesterase, which hydrolyzes acetylcholine to choline and acetic acid. By inhibiting acetylcholinesterase, the indirect-acting drugs increase the endogenous acetylcholine concentration in synaptic clefts and neuroeffector junctions.
- The excess acetylcholine, in turn, stimulates cholinceptors to evoke increased responses. These drugs act primarily where acetylcholine is physiologically released and are thus amplifiers of endogenous acetylcholine.
Basic Pharmacology of the Direct-Acting Cholinoceptor Stimulants

- Four important choline esters are shown in the left. Their permanently charged quaternary ammonium group renders them relatively insoluble in lipids.
- Many naturally occurring and synthetic cholinomimetic drugs that are not choline esters have been identified.
- The muscarinic receptor is strongly stereoselective: (S)-bethanechol is almost 1000 times more potent than (R)-bethanechol.

Cholinomimetic Drugs That Are Not Choline Esters

- Choline
- Muscarine
- Pilocarpine
- Nicotine
- Lobeline
- Choline
Absorption, Distribution, And Metabolism (Choline Esters)

• Choline esters are poorly absorbed and poorly distributed into the central nervous system because they are hydrophilic. Although all are hydrolyzed in the gastrointestinal tract (and less active by the oral route), they differ markedly in their susceptibility to hydrolysis by cholinesterase.

• Acetylcholine is very rapidly hydrolyzed; large amounts must be infused intravenously to achieve concentrations sufficient to produce detectable effects. A large intravenous bolus injection has a brief effect, typically 5–20 seconds, whereas intramuscular and subcutaneous injections produce only local effects.

Table 7–2. Properties of Choline Esters.

<table>
<thead>
<tr>
<th>Choline Ester</th>
<th>Susceptibility to Cholinesterase</th>
<th>Muscarinic Action</th>
<th>Nicotinic Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine chloride</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Methacholine chloride</td>
<td>+++</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Carbachol chloride</td>
<td>Negligible</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Bethanechol chloride</td>
<td>Negligible</td>
<td>++</td>
<td>None</td>
</tr>
</tbody>
</table>
Absorption, Distribution, And Metabolism (Tertiary Natural Cholinomimetic Alkaloids)

- The tertiary natural cholinomimetic alkaloids (pilocarpine, nicotine, lobeline) are well absorbed from most sites.
- Nicotine, a liquid, is sufficiently lipid-soluble to be absorbed across the skin.
- Muscarine, a quaternary amine, is less completely absorbed from the gastrointestinal tract than the tertiary amines but is nevertheless toxic when ingested, eg, in certain mushrooms, and even enters the brain.
- Lobeline is a plant derivative similar to nicotine.
- These amines are excreted chiefly by the kidneys. Acidification of the urine accelerates clearance of the tertiary amines.

Effects of Cholinomimetics (1/3)

- **Cardiovascular System:** The primary cardiovascular effects of muscarinic agonists are reduction in peripheral vascular resistance and decrease in heart rate.
- **Respiratory System:** Muscarinic stimulants contract the smooth muscle of the bronchial tree. In addition, the glands of the tracheobronchial mucosa are stimulated to secrete.
- **Miscellaneous Secretory Glands:** Muscarinic agonists stimulate secretion by thermoregulatory sweat, lacrimal, and nasopharyngeal glands.
Effects of Cholinomimetics (2/3)

- **Gastrointestinal Tract:** Administration of muscarinic agonists, like parasympathetic nervous system stimulation, increases the secretory and motor activity of the gut. The salivary and gastric glands are strongly stimulated; the pancreas and small intestinal glands less so. Peristaltic activity is increased throughout the gut, and most sphincters are relaxed.

- **Genitourinary Tract:** Muscarinic agonists stimulate the detrusor muscle and relax the trigone and sphincter muscles of the bladder, thus promoting voiding.

Effects of Cholinomimetics (3/3)

- **Central Nervous System:** The central nervous system contains both muscarinic and nicotinic receptors, the brain being relatively richer in muscarinic sites and the spinal cord containing a preponderance of nicotinic sites.

- **Peripheral Nervous System:** Autonomic ganglia are important sites of nicotinic synaptic action.
Basic Pharmacology of the Indirect-Acting Cholinomimetics

- The actions of acetylcholine released from autonomic and somatic motor nerves are terminated by enzymatic hydrolysis of the molecule.
- The indirect-acting cholinomimetics have their primary effect at the active site of this enzyme, although some also have direct actions at nicotinic receptors. The chief differences between members of the group are chemical and pharmacokinetic—their pharmacodynamic properties are almost identical.

Structure of the Indirect-Acting Cholinomimetics

- There are three chemical groups of cholinesterase inhibitors:
  - (1) simple alcohols bearing a quaternary ammonium group, eg, edrophonium;
  - (2) carbamic acid esters of alcohols bearing quaternary or tertiary ammonium groups (carbamates, eg, neostigmine);
  - (3) organic derivatives of phosphoric acid (organophosphates, eg, echothiophate).
• Edrophonium, neostigmine, and pyridostigmine are synthetic quaternary ammonium agents used in medicine.
• Physostigmine (eserine) is a naturally occurring tertiary amine of greater lipid solubility that is also used in therapeutics.
• Carbaryl (carbaril) is typical of a large group of carbamate insecticides designed for very high lipid solubility, so that absorption into the insect and distribution to its central nervous system are very rapid.
**Mode of action**

- All of the cholinesterase inhibitors increase the concentration of endogenous acetylcholine at cholinceptors by inhibiting acetylcholinesterase.
- However, the molecular details of their interaction with the enzyme vary according to the three chemical subgroups mentioned before.

**Edrophonium**

- The first group, of which edrophonium is the major example, consists of quaternary alcohols. These agents reversibly 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 correspondingly short-lived (on the order of 2–10 minutes). 

Neostigmine and Physostigmine

- The second group consists of carbamate esters, eg, neostigmine and physostigmine. These agents undergo a two-step hydrolysis sequence analogous to that of acetylcholine.
- However, the covalent bond of the carbamoylated enzyme is considerably more resistant to the second (hydration) process, and this step is correspondingly prolonged (on the order of 30 minutes to 6 hours).
- Neostigmine also activates neuromuscular nicotinic cholinoreceptors directly.

Organophosphates

- The third group consists of the organophosphates. These agents also 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).
Organophosphates: aging

- After the initial binding-hydrolysis step, the phosphorylated enzyme complex may undergo a process called **aging**.
- This process apparently involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor and further strengthens the phosphorus-enzyme bond. The rate of aging varies with the particular organophosphate compound.
- If given before aging has occurred, strong nucleophiles like pralidoxime are able to break the phosphorus-enzyme bond and can be used as "cholinesterase regenerator" drugs for organophosphate insecticide poisoning.
Organophosphates (continued)

• A few of the estimated 50,000 organophosphates were shown before this slide.
• Many of the organophosphates (echothiophate is an exception) are highly lipid-soluble liquids.
• Echothiophate, a thiocholine derivative, is of clinical value because it retains the very long duration of action of other organophosphates but is more stable in aqueous solution.
• Soman is an extremely potent "nerve gas".
• Parathion and malathion are thiophosphate prodrugs that are inactive as such; they are converted to the phosphate derivatives in animals and plants and are used as insecticides.

Table 7–4. Therapeutic Uses and Durations of Action of Cholinesterase Inhibitors.

<table>
<thead>
<tr>
<th>Uses</th>
<th>Approximate Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohols</strong></td>
<td></td>
</tr>
<tr>
<td>Edrophonium</td>
<td>Myasthenia gravis, ileus, arrhythmias</td>
</tr>
<tr>
<td><strong>Carbamates and related agents</strong></td>
<td></td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Myasthenia gravis, ileus</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Ambenonium</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Demecarium</td>
<td>Glaucoma</td>
</tr>
<tr>
<td><strong>Organophosphates</strong></td>
<td></td>
</tr>
<tr>
<td>Echothiophate</td>
<td>Glaucoma</td>
</tr>
</tbody>
</table>
Indications of Parasympathomimetics

- Intoxications (atropine, phenothiazine, antihistaminic and tricyclic antidepressant)
- Glaucoma
- Atonic bladder
- Myasthenia gravis
- Neurogenic bladder
- Paralytic ileus
- Reflux esophagitis
- Alzheimer’s disease
- Smoking cessation
- Treatment of dry mouth

Adverse Reactions of Parasympathomimetics

- Salivation, sweating
- Nausea, vomiting
- Bradycardia
- Hypotension
- Bronchospasm
- Blurred vision
Contraindications of Parasympathomimetics

- Asthma
- Pregnancy
- Hyperthyroidism
- Peptic ulcer
- Coronary artery disease, peripheral circulatory disorders
- Mechanical obstruction (gastrointestinal system, urethra)
Study questions

1. Make a table for the indications and duration of actions of direct cholinergic stimulants.
2. Make a table comparing the actions of direct and indirect acting parasympathomimetics.

Thank you...