Autonomic Pharmacology: Cholinergic agonists

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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.

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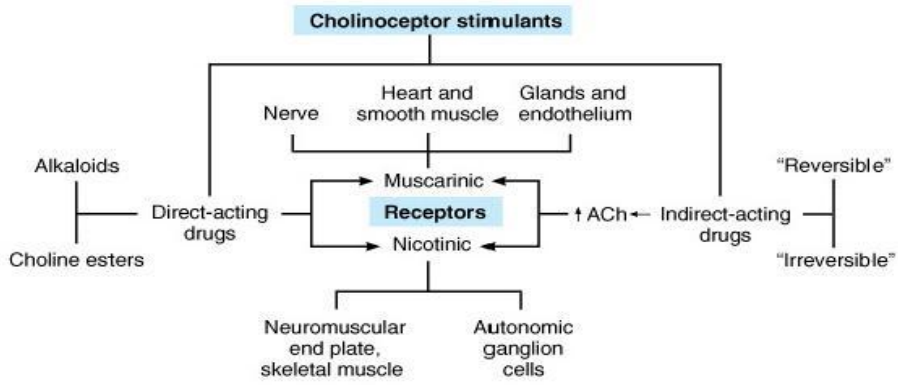

Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition: http://www.accessmedicine.com

The major groups of cholinoceptor-activating drugs, receptors, and target tissues.

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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 cholinoceptors to evoke increased responses. These drugs act primarily where acetylcholine is physiologically released and are thus *amplifiers* of endogenous acetylcholine.

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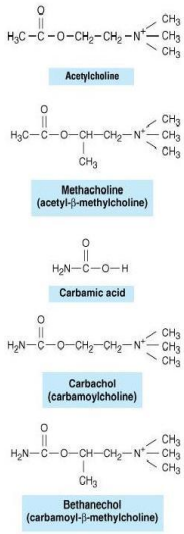
Basic Pharmacology of the Direct-Acting Cholinoceptor Stimulants



- 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.

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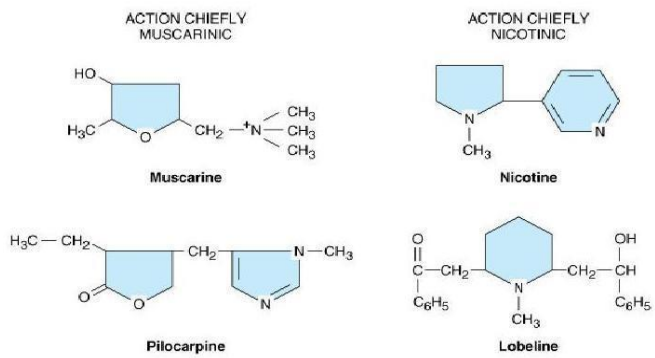
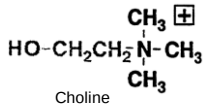
Cholinomimetic Drugs That Are Not Choline Esters





Choline

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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.

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Table 7–2. Properties of Choline Esters.

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Methacholine chloride	+	++++	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible	++	None

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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.

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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.

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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.

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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.

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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.

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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).

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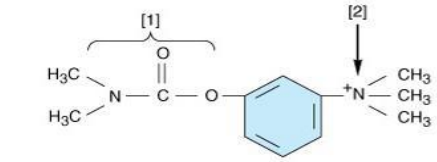
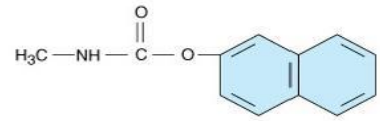
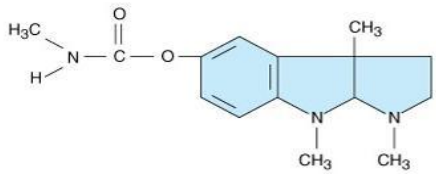


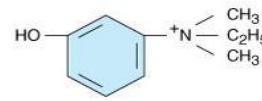
Neostigmine



Carbaryl



Physostigmine



Edrophonium

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- 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.

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Mode of action

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

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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).

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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 cholinoceptors directly.

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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).

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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.

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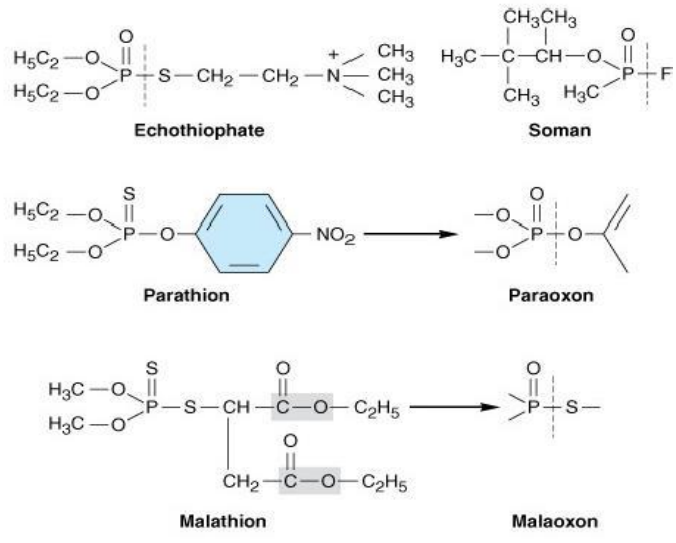

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Organophosphates (continued)

- 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.

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

	Uses	Approximate Duration of Action
Alcohols		
Edrophonium	Myasthenia gravis, ileus, arrhythmias	5–15 minutes
Carbamates and related agents		
Neostigmine	Myasthenia gravis, ileus	0.5–2 hours
Pyridostigmine	Myasthenia gravis	3–6 hours
Physostigmine	Glaucoma	0.5–2 hours
Ambenonium	Myasthenia gravis	4–8 hours
Demecarium	Glaucoma	4–6 hours
Organophosphates		
Echothiophate	Glaucoma	100 hours

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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

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Adverse Reactions of Parasympathomimetics

- Salivation, sweating
- Nausea, vomiting
- Bradycardia
- Hypotension
- Bronchospasm
- Blurred vision

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Contraindications of Parasympathomimetics

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

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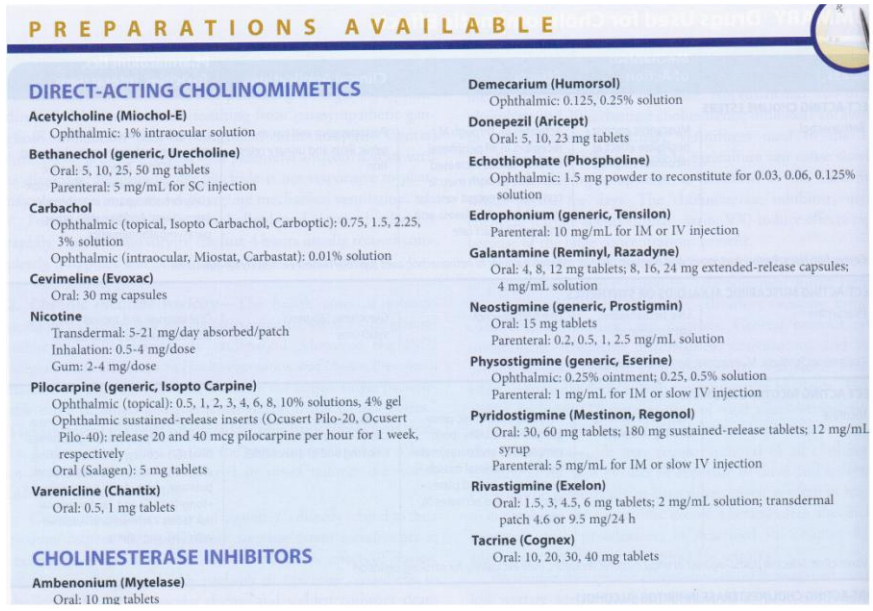

PREPARATIONS AVAILABLE

DIRECT-ACTING CHOLINOMIMETICS

Acetylcholine (Miochol-E)
Ophthalmic: 1% intraocular solution

Bethanechol (generic, Urecholine)
Oral: 5, 10, 25, 50 mg tablets
Parenteral: 5 mg/mL for SC injection

Carbachol
Ophthalmic (topical, Isopto Carbachol, Carboptic): 0.75, 1.5, 2.25, 3% solution
Ophthalmic (intraocular, Miostat, Carbastat): 0.01% solution

Cevimeline (Evoxac)
Oral: 30 mg capsules

Nicotine
Transdermal: 5-21 mg/day absorbed/patch
Inhalation: 0.5-4 mg/dose
Gum: 2-4 mg/dose

Pilocarpine (generic, Isopto Carpine)
Ophthalmic (topical): 0.5, 1, 2, 3, 4, 6, 8, 10% solutions, 4% gel
Ophthalmic sustained-release inserts (Ocusert Pilo-20, Ocusert Pilo-40): release 20 and 40 mcg pilocarpine per hour for 1 week, respectively
Oral (Salagen): 5 mg tablets

Varenicline (Chantix)
Oral: 0.5, 1 mg tablets

CHOLINESTERASE INHIBITORS

Ambenonium (Mytelase)
Oral: 10 mg tablets

Demecarium (Humorsol)
Ophthalmic: 0.125, 0.25% solution

Donepezil (Aricept)
Oral: 5, 10, 23 mg tablets

Echothiophate (Phospholine)
Ophthalmic: 1.5 mg powder to reconstitute for 0.03, 0.06, 0.125% solution

Edrophonium (generic, Tensilon)
Parenteral: 10 mg/mL for IM or IV injection

Galantamine (Reminyl, Razadyne)
Oral: 4, 8, 12 mg tablets; 8, 16, 24 mg extended-release capsules; 4 mg/mL solution

Neostigmine (generic, Prostigmin)
Oral: 15 mg tablets
Parenteral: 0.2, 0.5, 1, 2.5 mg/mL solution

Physostigmine (generic, Eserine)
Ophthalmic: 0.25% ointment; 0.25, 0.5% solution
Parenteral: 1 mg/mL for IM or slow IV injection

Pyridostigmine (Mestinon, Regonol)
Oral: 30, 60 mg tablets; 180 mg sustained-release tablets; 12 mg/mL syrup
Parenteral: 5 mg/mL for IM or slow IV injection

Rivastigmine (Exelon)
Oral: 1.5, 3, 4.5, 6 mg tablets; 2 mg/mL solution; transdermal patch 4.6 or 9.5 mg/24 h

Tacrine (Cognex)
Oral: 10, 20, 30, 40 mg tablets

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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 parasymphathomimetics.

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Thank you...

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