Cholinomimetic Agents – ANS Pharmacology

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Cholinomimetics are an important class of drugs affecting the autonomic nervous system. They act on receptors that are activated by acetylcholine. They are broadly classified into direct-acting and indirect-acting drugs. In this article, we will study the mechanism of action and pharmacological actions, specific characteristics and clinical uses of individual cholinomimetic drugs.

Definition and Classification of Cholinomimetic Agents

Cholinomimetic drugs are a group of drugs whose actions mimic those of **acetylcholine**.

Cholinomimetic drugs are classified into **directly acting** (those activating acetylcholine receptors by binding to them directly) and **indirectly acting** (those inhibiting hydrolysis of endogeneous acetylcholine and thus increasing its availability to the receptors) drugs.

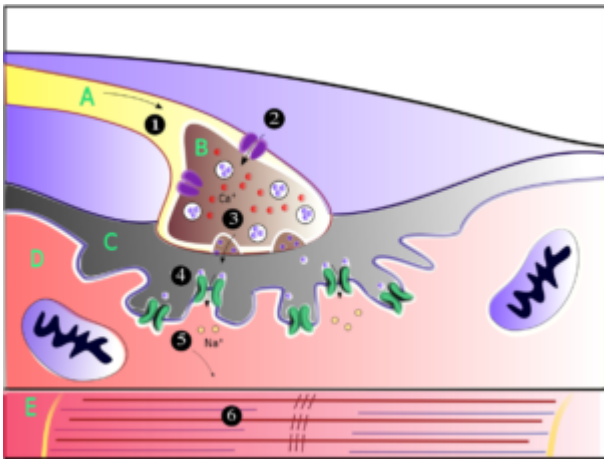

Image: "**Muscles will contract or relax when they receive signals from the nervous system. The neuromuscular junction is the site of the signal exchange. The steps of this process in vertebrates occur as follows:** (1) The action potential reaches the axon terminal. (2) Voltage-dependent calcium gates open, allowing calcium to enter the axon terminal. (3) Neurotransmitter vesicles fuse with the presynaptic membrane and acetylcholine (ACh) is released into the synaptic cleft via exocytosis. (4) ACh binds to postsynaptic receptors on the sarcolemma. (5) This binding causes ion channels to open and allows sodium ions to flow across the membrane into the muscle cell. (6) The flow of sodium ions across the membrane into the muscle cell generates an action potential which travels to the myofibril and results in muscle contraction. Labels: A: Motor Neuron Axon B: Axon Terminal C. Synaptic Cleft D. Muscle Cell E. Part of a Myofibril" by Elliejellybelly13 – Own work. License: CC BY-SA 4.0

Actions of indirectly acting cholinomimetics may be reversible (e.g., ambenonium, physostigmine, neostigmine, pyridostigmine, rivastigmine, donepezil, edrophonium, galantamine) or irreversible (e.g., echothiophate).

Indirectly acting cholinomimetics can also be classified into **short-acting** (e.g., edrophonium), **intermediate-to-long acting** (carbamates), and **very long-acting** (organophosphates).

Directly acting drugs can be further classified into **muscarinic and nicotinic drugs** depending on the type of acetylcholine receptors they act on. They can also be classified into **cholinergic esters** (e.g., acetylcholine, methacholine, carbachol, bethanechol) and **naturally occurring alkaloids** (e.g., muscarine, nicotine, pilocarpine, lobeline).

Cholinergic Receptors (Cholineceptors)

There are two families of cholinergic receptors: **muscarinic receptors and nicotinic receptors**.

Muscarinic receptors are G protein-coupled receptors divided into five subclasses: M1 to M5, out of which **M1, M2 and M3** are clinically important receptors. All subtypes of muscarinic receptors are found in neurons. **In addition to neurons, M1 receptors are present on gastric parietal cells, M2 receptors are present on cardiac cells and smooth muscle, and M3 receptors are present on the bladder, exocrine glands, and smooth muscle.**

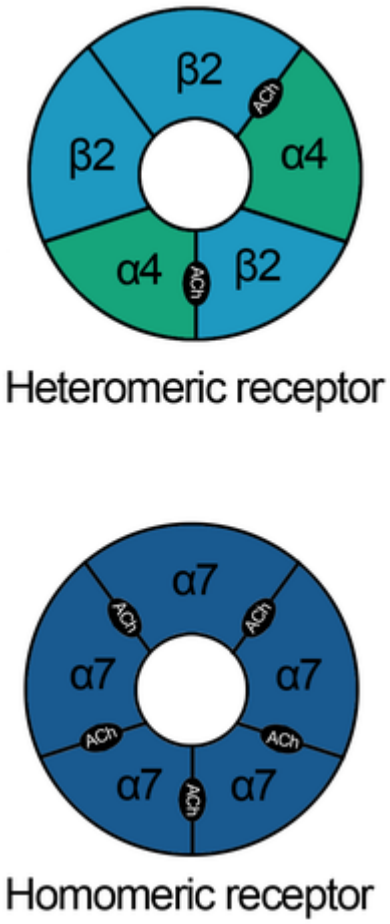

Image: "Two nicotinic acetylcholine receptors" by Hopur52009 – Own work. License: CC BY-SA 3.0

M1, M3, and M5 receptors act by Gq protein-mediated activation of phospholipase C, while M2 and M4 receptors act by Gi protein-mediated inhibition of adenylyl cyclase. M2 receptors also act by increasing K^+.

A nicotinic receptor is a **ligand-gated ion channel** composed of five subunits. The binding of two acetylcholine molecules causes conformational change, thus allowing entry of Na^+ ions across the ion channel and leading to depolarization.

At low concentrations, nicotine stimulates the nicotinic receptors, while the same are blocked at high concentrations of nicotine.

There are two types of nicotinic receptors: **NN receptors** are located in the central nervous system, adrenal medulla, and autonomic ganglia, while **NM receptors** are located at skeletal muscle neuromuscular junctions.

The central nervous system contains both muscarinic and nicotinic receptors, with the predominance of muscarinic receptors in the brain and of nicotinic receptors in the spinal cord.

Overview

Muscarinic Cholinergic	Nicotinic Cholinergic

Choline Esters • Acetylcholine • Methacholine • Carbachol and bethanechol Alkaloids • Pilocarpine	Choline Esters • Acetylcholine • Methacholine • Carbachol

Direct-Acting Cholinomimetics

Choline esters are hydrophobic, rapidly hydrolyzed in the gastrointestinal tract, poorly absorbed and poorly distributed in the central nervous system.

Acetylcholine is very rapidly hydrolyzed by cholinesterase, while methacholine is more resistant to hydrolysis; carbachol and bethanechol are the most resistant to hydrolysis.

Acetylcholine and carbachol act on both muscarinic and nicotinic receptors, while methacholine and bethanechol act selectively on muscarinic receptors.

Natural alkaloids are rapidly absorbed from the site of absorption and are excreted by the kidneys. Their clearance is enhanced by the acidification effect of the urine.

Actions Mediated by Muscarinic Receptors

- **Contraction of the sphincter muscle of the iris** (M3 receptors) causing miosis, and contraction of the ciliary muscle (M3 receptors) causing accommodation of the eyes.
- **Negative chronotropic effect** (reduction in heart rate) by action on a sinuatrial node (M2 receptors) in the heart.
- **Negative inotropic effect** (reduction in force of contraction) by action on smooth muscles in the atria and ventricles (atria > ventricles). Also, a decrease in the refractory period in the atria.
- **Negative dromotropic effect** (reduction in conduction velocity) by action on the atrioventricular node (M2 receptors) in the heart, thus increasing the refractory period.
- **Increased potassium current** in the cells of the sinoatrial and atrioventricular nodes, in Purkinje cells and in the atrial and ventricular cells; **decreased inward calcium current** in the heart cells and decreased hyperpolarization-activated current, underlying diastolic depolarization, contribute to reduced heart rate caused by stimulation of M2.
- Cholinomimetic drugs can also cause **tachycardia,** resulting from reflex sympathetic activation caused by hypotension.
- **Vasodilation** by the release of endothelium-derived relaxing factor (EDRF) from endothelial cells (M3 receptors).
- **Contraction of bronchial smooth muscles** (M3 receptors) and **stimulation of secretions from glands of tracheobronchial mucosa** (M3 receptors) in the respiratory tract.
- **Increased peristalsis and relaxation of sphincters in the gastrointestinal tract** (M3 receptors).
- **Stimulation of secretions from the glands of the gastrointestinal tract** (M1 receptors).
- **Stimulation of secretions from the thermoregulatory, sweat, salivary and lacrimal glands** (M3 receptors).
- **Facilitation of voiding** by detrusor muscle contraction and relaxation of trigone and sphincter muscles of the urinary bladder.

- M3 receptors are important for **cognition**, while M1 receptors may play a role in **appetite**.

Actions Mediated by Nicotinic Receptors

- **Regulation of the release of neurotransmitters in the central nervous system** by presynaptic nicotinic receptors.
- **Initial activation** followed by desensitization with chronic nicotine exposure leading to increased alertness and addiction potential.
- **Tremors, vomiting, respiratory stimulation, and convulsions** at high concentrations of nicotine.
- **Stimulation of autonomic ganglia** leading to **hypertension** **and tachycardia** (sympathetic stimulation) as well as **nausea, vomiting, diarrhea, and urination** (parasympathetic stimulation).
- At skeletal muscle neuromuscular junctions, contraction followed by depolarization blockade leading to **flaccid paralysis**.

Acetylcholine

Both muscarinic and nicotinic actions. During **ophthalmic surgery**, 1% solution is instilled into the anterior chamber of the eye to produce **miosis**.

Bethanechol

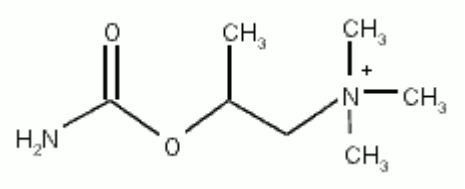

Image: “Chemical structure of Bethanechol” by MattKingston at English Wikipedia – Transferred from en.wikipedia to Commons. License: Public Domain

- Selective muscarinic actions; main actions are on the smooth muscles of the urinary bladder and gastrointestinal tract.
- Used in treatment of **postpartum or postoperative urinary retention and neurogenic atonic bladder**.
- Used in treatment of **neurogenic ileus** and **congenital megacolon**.

Carbachol

- Both muscarinic and nicotinic actions with main focus on the cardiovascular and gastrointestinal tract.
- Rarely used systemically because of non-selectivity and long duration of action.
- Used locally in the eyes to produce **miosis** and to **reduce intraocular pressure in glaucoma**.

Methacholine

Muscarinic actions more than nicotinic actions. Used in challenge test for diagnosis of **bronchial hyperreactivity**.

Pilocarpine

Image: “Mydriasis ” by Bin im Garten – Own work (own picture).
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- An alkaloid with mainly muscarinic actions
- Used topically in the eyes to produce **miosis** and to **reverse atropine-induced mydriasis**.
- Used to reduce the intraocular pressure in **acute angle-closure glaucoma** in an emergency; acts within a few minutes by opening the trabecular meshwork around Schlemm canal.
- Not frequently used in open

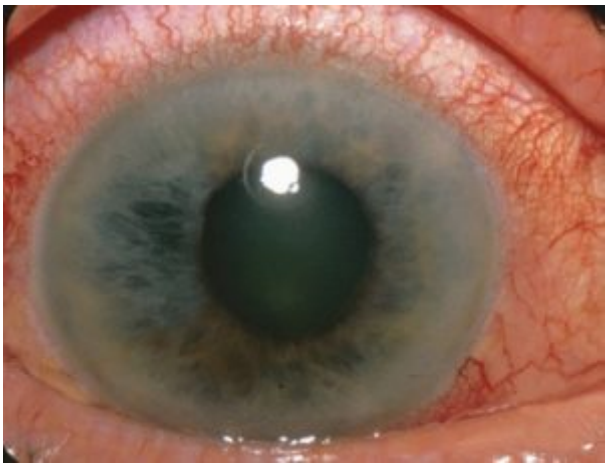

Image: “Acute angle-closure glaucoma” by Jonathan Trobe, M.D. – The Eyes Have It. License: CC BY 3.0

angle glaucoma because of the availability of safer and newer drugs

- Used orally in treatment of **post-irradiation xerostomia** and **Sjogren syndrome**

Cevimeline

- Synthetic alkaloid selectively acting on M3.
- Used in treatment of **post-irradiation xerostomia** and **Sjogren syndrome**.

Nicotine

- Agonist at nicotinic receptors
- Available as oral gum and patch for smoking cessation
- Non-medical uses: for smoking and in insecticides

Varenicline

- Partial agonist at **α4β2 nicotinic receptors**
- Used to reduce craving in nicotine addiction

Indirect-Acting Cholinomimetics (Cholinesterase Inhibitors)

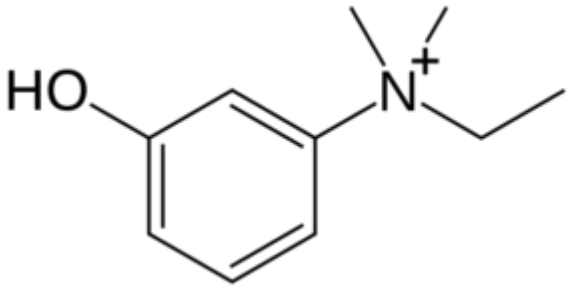

Image: "Skeletal formula of edrophonium." by Fvasconcellos – Own work. License: Public Domain

Indirect-acting cholinomimetics inhibit acetylcholinesterase – an enzyme present in cholinergic synapses that causes hydrolysis of acetylcholine. Chemically, they can be classified into **simple alcohols, bearing a quaternary ammonium group** (e.g., edrophonium), **carbamates** (e.g., neostigmine) and **organophosphates** (e.g., echothiophate).

Carbamates have a quaternary ammonium group and are poorly soluble in lipids, poorly absorbed by the skin and mucosae as well as poorly distributed in the central nervous system; an exception to the group is physostigmine, which is a tertiary carbamate with good absorption from all sites.

Carbamates are metabolized by both **acetylcholinesterase** and **non-specific esterases** in the body.

Organophosphates are lipid-soluble and well absorbed from the skin and mucosae, well distributed in the body and can cause **significant toxicity**; an exception is echothiophate. After binding organophosphates with an active site of cholinesterase, the enzyme-inhibitor complex undergoes a process called aging (strengthening of the phosphorus-enzyme bond), so it is difficult to reverse the toxicity of organophosphates by oximes once aging has occurred (See Overdose and Side Effects of Cholinomimetic Agents – ANS Pharmacology).

Pharmacological actions of indirect-acting cholinomimetics

- Subjective **alerting response** at low doses and **convulsions, coma and respiratory depression** at high doses
- Increased **lacrimation and miosis in the eyes**
- Negative chronotropic, negative dromotropic and negative inotropic effects on the heart; reduced cardiac output
- **Increased blood pressure** due to sympathetic stimulation
- Increased gastrointestinal peristalsis, relaxation of sphincters and increased gastrointestinal secretions
- Contraction of the detrusor and relaxation of the trigone and the urinary bladder sphincter
- At neuromuscular junctions, increased strength of contraction of skeletal muscles at low concentrations; fibrillations and fasciculations at high concentrations
- Some quaternary carbamates (e.g., neostigmine) also have additional **direct nicotinic agonist action**

Edrophonium

- Short-acting cholinesterase inhibitor with rapid absorption and rapid renal elimination; duration of action ~10-20 minutes.
- Used in diagnosis of **myasthenia gravis** (**edrophonium test**): intravenous administration of edrophonium causes a rapid increase in muscle strength in myasthenia gravis patients.
- Can be used to assess **cholinesterase inhibitor therapy** and to **differentiate cholinergic crisis from a myasthenic crisis**.
- Used to **reverse the effects of non-depolarizing neuromuscular blocking agents** after surgery.
- In the past was used in treatment of **supraventricular tachyarrhythmias**.

Physostigmine

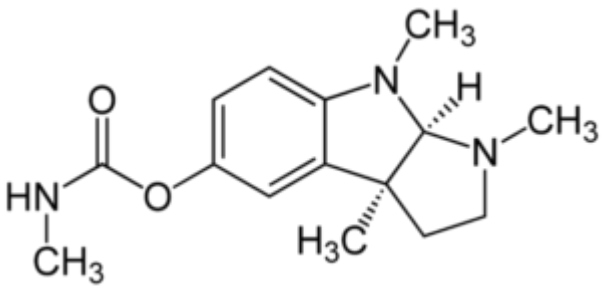

Image: “Physostigmine structural formula” by Jü – Own work.
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- A tertiary amine found naturally in plants that is well absorbed and penetrates the central nervous system.
- Duration of action ~ 30 to 120 minutes
- Used to **increase motility of the intestines and urinary bladder in cases of atony**
- Used in the **management of an overdose of drugs/poisons with**

anticholinergic actions (atropine, tricyclic antidepressants, atropa belladonna, etc.)

Neostigmine

- A synthetic carbamate with quaternary amine that is poorly absorbed from sites and does not enter the central nervous system.
- Duration of action ~ 30 to 120 minutes
- Used to **prevent postoperative abdominal distention and urinary retention** by stimulating gastrointestinal and urinary bladder motility
- Used as an **antidote for competitive neuromuscular blocking agents**
- Used in treatment of **myasthenia gravis**

Pyridostigmine

- Intermediate duration of action (~3 to 6 hours)
- Used in **chronic management of myasthenia gravis**

Ambenonium

- Intermediate duration of action (~4 to 8 hours)
- Used in **chronic management of myasthenia gravis**

Anticholinesterases Used in Alzheimer's Disease

A deficiency of cholinergic neurons in the central nervous system in patients with Alzheimer's disease has been observed. This explains why anticholinesterases play a role in the management of Alzheimer's disease.

Tacrine was the first anticholinesterase to be used in Alzheimer's disease, but it is not used at present due to significant **hepatotoxicity**.

Donepezil, rivastigmine, and galantamine are anticholinesterases used to delay the progression of Alzheimer's disease.

None of them can stop the progression of the disease.

Echothiophate

- Irreversibly inactivates cholinesterase, and the enzyme-inhibitor complex undergoes aging so oximes cannot reverse its effects.
- A long duration of action (~100 hours)
- Topically used in treatment of **open-angle glaucoma**

Insecticides and poisons

- Organophosphates **malathion and parathion** are used as pesticides as they are metabolized to active forms in insects but not in humans.
- Organophosphates **malathion and metrifonate** are used as a scabicide and antihelminthic agent, respectively.
- Organophosphate **sarin** is a nerve gas that can cause **asphyxia and death within minutes and permanent neurological damage**; it was used in a terrorism attack in 1995 in Tokyo.

- **Carbaryl** is a carbamate that is used as an insecticide in agriculture.

Special topic: myasthenia crisis vs. cholinergic crisis

Myasthenic crisis	Cholinergic crisis
• Destruction of the acetylcholine receptors • Increased heart rate, blood pressure • Bowel and bladder incontinence • Absent cough and swallow reflex • Edrophonium gives temporary relief • Acetylcholinesterase inhibitor • Atropine will not help symptoms	• Excess acetylcholine (i.e. Sarin gas) • Decreased blood pressure • Abdominal cramps, N/V, diarrhea • Blurred vision • Pallor • Facial muscle twitching • Edrophonium has no effect (but may precipitate a cholinergic crisis through overdose) • Atropine will improve symptoms

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Notes