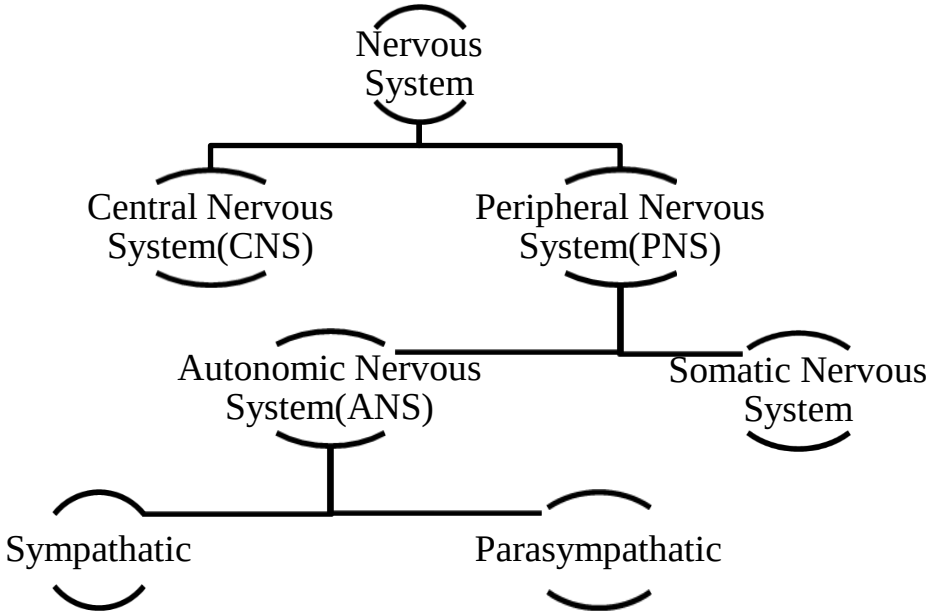
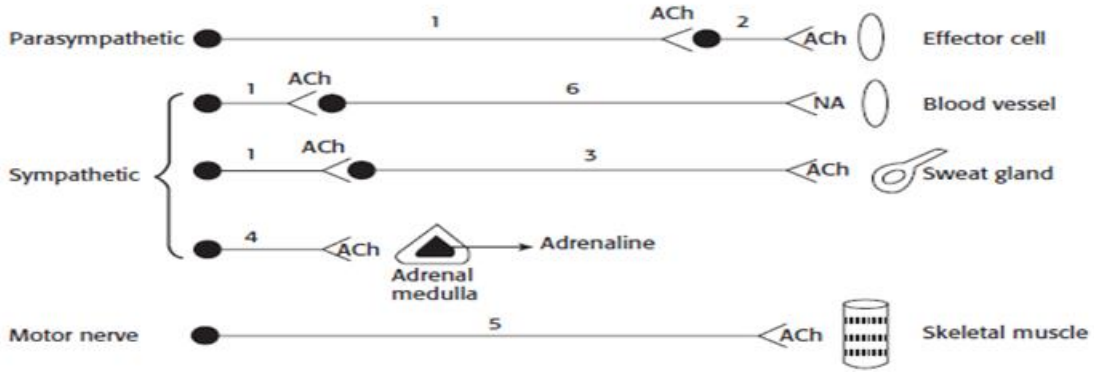
INTRODUCTION TO AUTONOMIC PHARMACOLOGY



Cholinergic Transmission

Acetylcholine (ACh) is the main neurotransmitter in the cholinergic system. The neurons that synthesize, store and release ACh are called cholinergic neurons.

Sites of acetylcholine (ACh) in the PNS: 1, preganglionic fibers of both sympathetic and parasympathetic system; 2, postganglionic fibers of parasympathetic system; 3, sympathetic postganglionic fibers supplying the sweat glands; 4, nerve fibers supplying the adrenal medulla; 5, motor nerve.



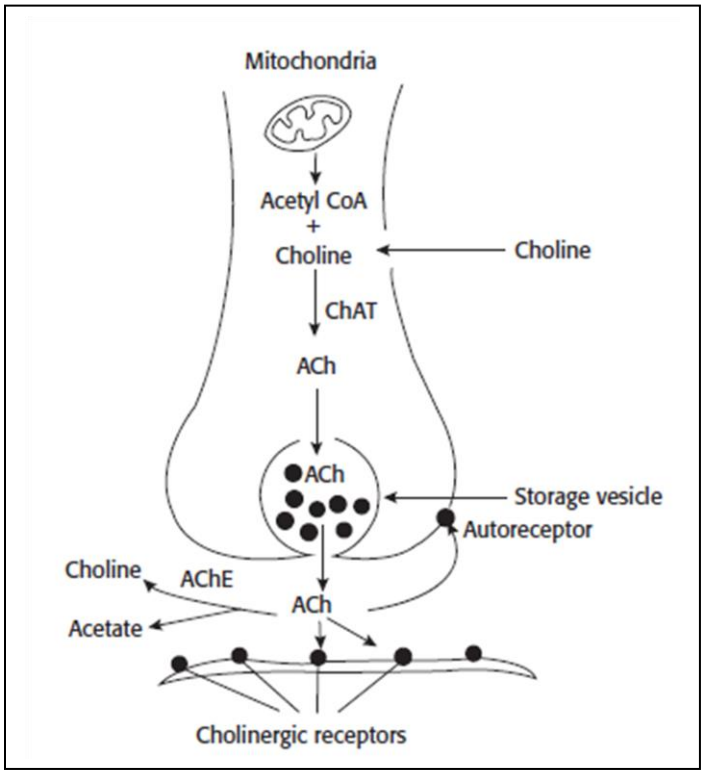
Synthesis of Acetylcholine: Choline enters the cytoplasm of the cholinergic neuron by carrier-mediated transport, where it reacts with acetyl-CoA with the help of choline acetyltransferase (ChAT) to form ACh.

Storage of acetylcholine in vesicles: The ACh is then stored in presynaptic vesicles.

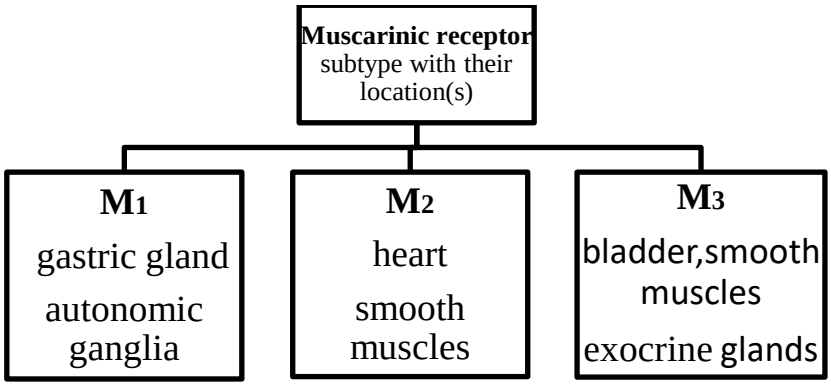
Release of acetylcholine: When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.

Action of acetylcholine: The released ACh interacts with cholinergic receptors on effector cell and activates them.

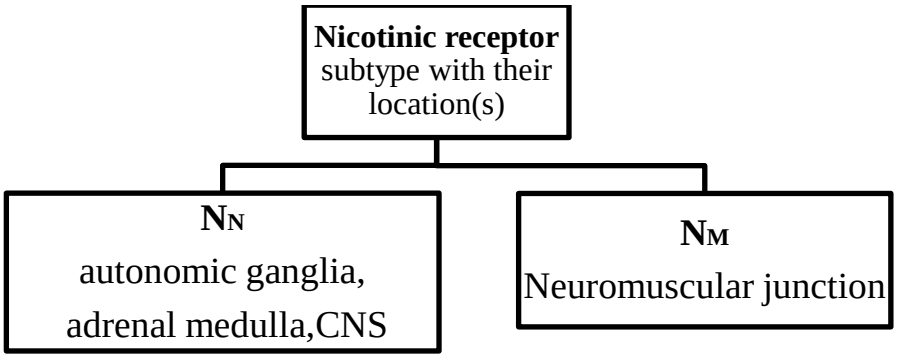
Fate of acetylcholine: In the synaptic cleft, the ACh is rapidly hydrolysed by acetylcholinesterase (AChE) enzyme.



Cholinergic Receptors (Cholinoceptors): They are divided into two types—muscarinic and nicotinic. Muscarinic receptors are further divided into five different subtypes: M_1–M_5. All muscarinic receptors are G-protein-coupled receptors and regulate the production of intracellular second messengers.



Nicotinic receptors are divided into two subtypes—N_N and N_M. Activation of these receptors directly opens the ion channels and causes depolarization of the membrane**.**



Receptor Type(s)	**Functional Response**
M_1 and M_3	Promotes glandular secretion and smooth muscle contraction
M_2	Depressant effect on heart
N_N	Depolarization
N_M	Skeletal muscle contraction

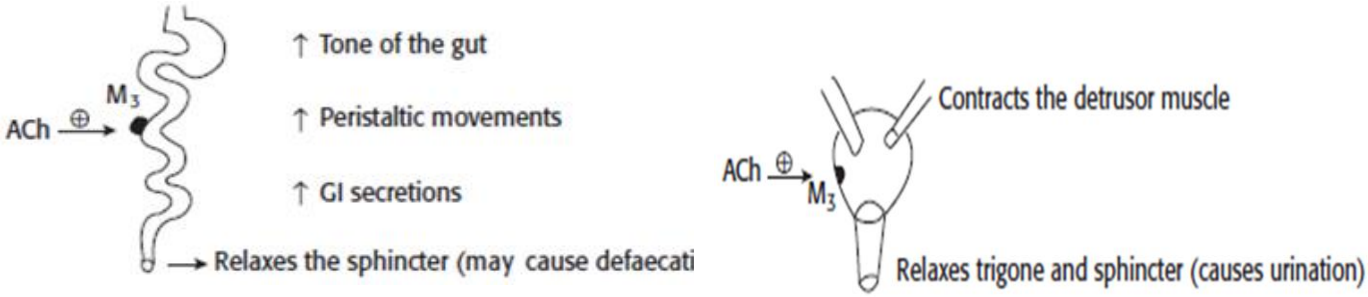
CHOLINERGIC AGENTS (CHOLINOMIMETICS, PARASYMPATHOMIMETICS)

Direct-Acting Cholinergic Agonists: Cholinergic agonists mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic).

Acetylcholine: it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include the following:

1. Decrease in heart rate and cardiac output: due to stimulation of M_2 receptors.
2. Decrease in blood pressure: due to activation of M3 receptors found on the vascular endothelial cells which release nitric oxide leading to vasodilatation and a fall in blood pressure.
3. Other actions:

- In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion, increases gastric acid secretion, and stimulates intestinal secretions and motility.
- It also enhances bronchiolar secretions and causes bronchoconstriction therefore, cholinergic drugs are contraindicated in asthmatics.
- In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing urination.
- In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.
- Exocrine glands: All parasympathomimetic agents stimulate salivary secretion. They also increase lacrimal, sweat, bronchial, gastric and other gastrointestinal (GI) secretions.



Bethanechol:

- It has no nicotinic actions.
- It has selective **muscarinic** actions on gastrointestinal tract (GIT) and urinary bladder. It is preferred in postoperative urinary retention and paralytic ileus.
- In urinary retention, it causes voiding of urine by contracting the detrusor muscle and relaxing the trigone sphincter.
- In paralytic ileus, it stimulates peristaltic movement and increases the tone by interacting with M3 receptors of the gut.
- Bethanechol may also be used to treat neurogenic atony as well as megacolon.
- Its muscarinic side effects (sweating, salivation, flushing, decreased blood pressure with reflex tachycardia, nausea, abdominal pain, diarrhea, and bronchospasm) are completely antagonized by atropine.

Carbachol:

- Carbachol has both **muscarinic** and **nicotinic** actions.
- Carbachol has profound effects on both the CVS and GI systems because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems.
- It can cause release of epinephrine from the adrenal medulla by its nicotinic action.
- Locally instilled into the eye, it mimics the effects of ACh, causing miosis.
- Because of its high potency, receptor nonselectivity, and relatively long duration of action, carbachol is rarely used.
- Intraocular use provides miosis for eye surgery and lowers intraocular pressure in the treatment of glaucoma. With ophthalmologic use, few adverse effects occur due to lack of systemic penetration (quaternary amine).

Methacoline:

- Methacholine differs from ACh chiefly in its greater duration and selectivity of action. Its action is more prolonged because its resistance to hydrolysis by cholinesterases.
- Its muscarinic selectivity is predominant in the CVS. It has only minor nicotinic actions.
- It is used in the diagnosis of asthma due to its bronchoconstricting properties.

Muscarine: an alkaloid in certain poisonous mushrooms. It has no therapeutic application.

Nicotine: is obtained from tobacco leaves. It has initial stimulating and later a prolonged blocking effect on the autonomic ganglia.* Nicotine is of no value in clinical practice except in the form of transdermal patch and chewing gum for the treatment of tobacco addiction.