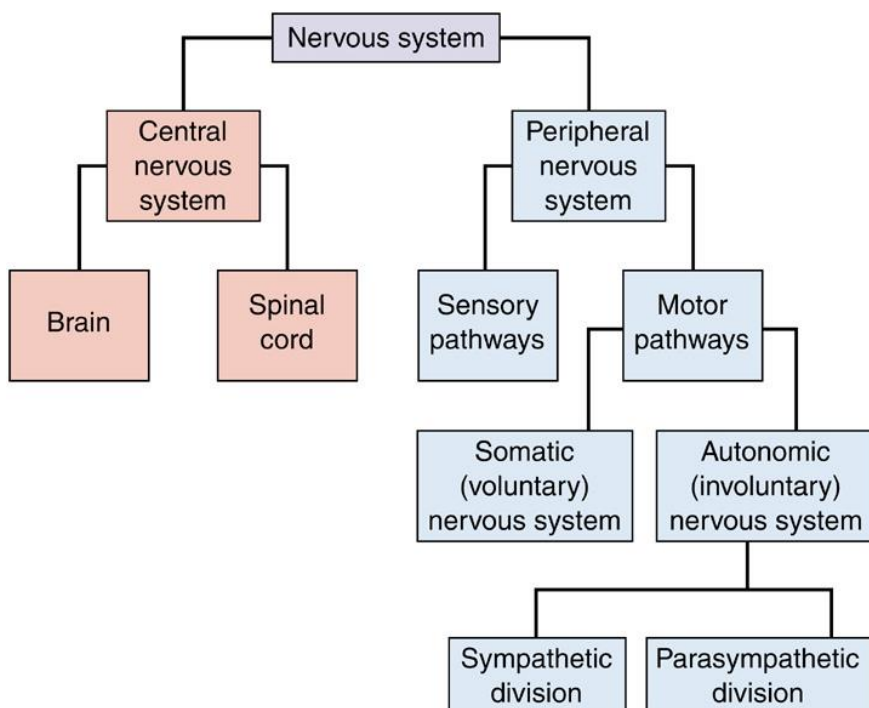


INTRODUCTION TO AUTONOMIC PHARMACOLOGY

Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the ANS are called autonomic drugs.

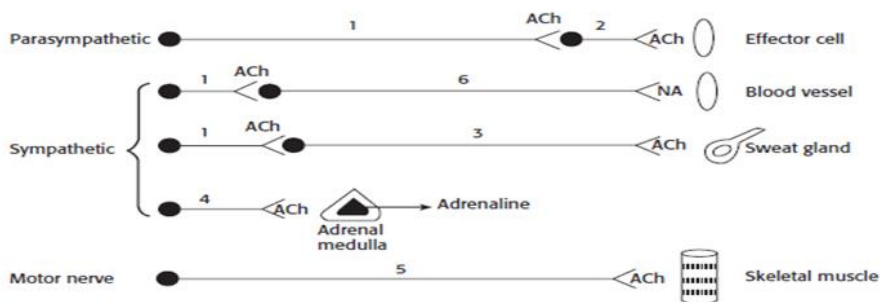
Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in the mechanism of action:

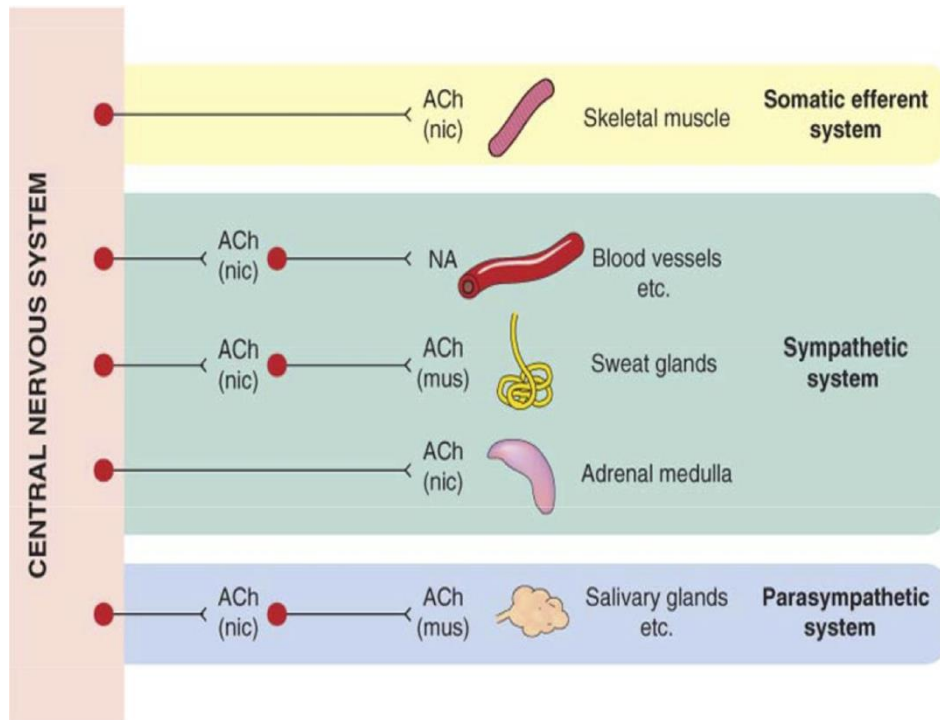
1. The **cholinergic drugs**: act on receptors activated by **acetylcholine** (ACh).
2. The **adrenergic drugs**: act on receptors stimulated by **norepinephrine** or **epinephrine**.

Cholinergic and adrenergic drugs act by either stimulating or blocking receptors of the ANS.

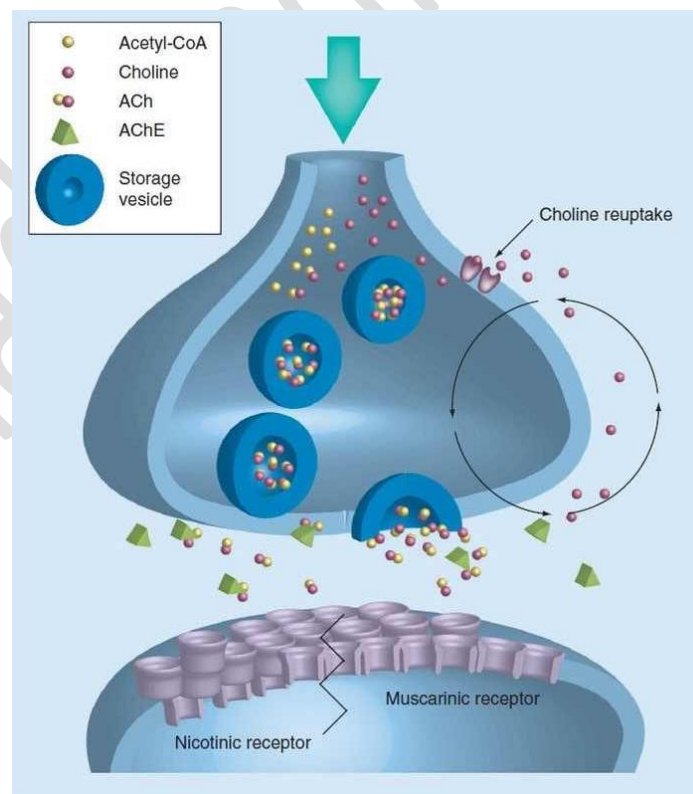
Sites of acetylcholine (ACh) in the PNS:

- 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.

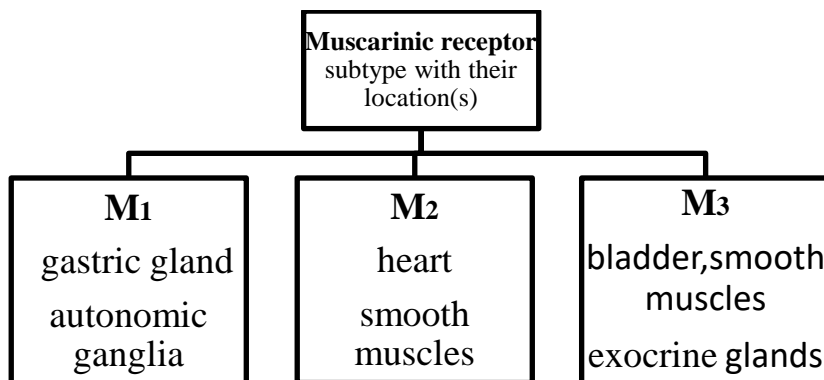




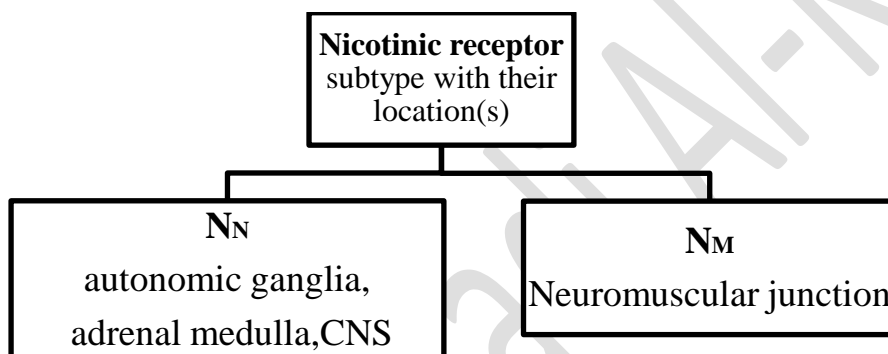
Acetylcholine is synthesized in cholinergic neurons. Acetylcholine is stored in nerve terminals and released by nerve depolarization. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap. Released acetylcholine binds to postsynaptic muscarinic and/or nicotinic receptors. 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: M1–M5. All muscarinic receptors are G-protein-coupled receptors and regulate the production of intracellular second messengers.



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



Receptor Type(s)	Functional Response
M1 and M3	Promotes glandular secretion and smooth muscle contraction
M2	Depressant effect on heart
NN	Depolarization
NM	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).

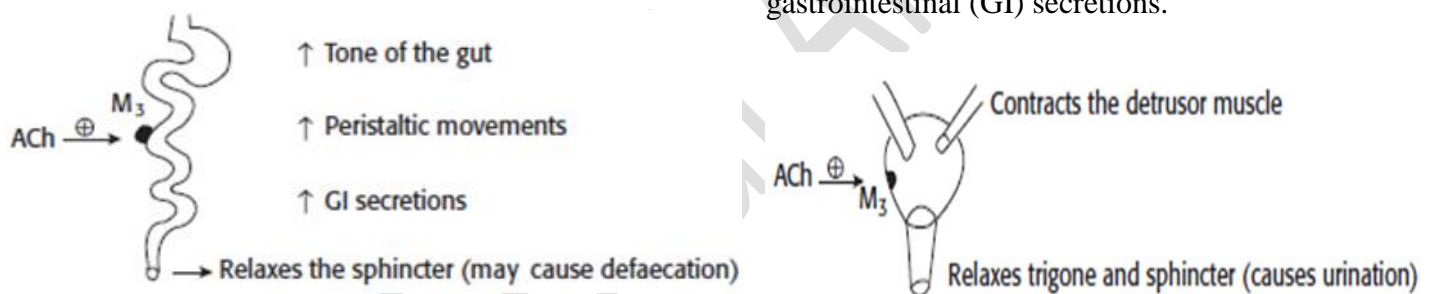
Acetylcholine: it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include the following:

1. Decrease in heart rate and cardiac output: due to stimulation of M2 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.



SIDE EFFECTS OF CHOLINERGIC DRUGS

- Diarrhoea
- Urination
- Miosis, muscle weakness
- Bronchorrhea
- Bradycardia
- Emesis
- Lacrimation
- Salivation, sweating



Bethanechol:

- It has selective **muscarinic** actions on gastrointestinal tract (GIT) and urinary bladder. It is preferred in postoperative urinary retention and paralytic ileus. 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:

- 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).

Methacholine:

- 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.
- 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.

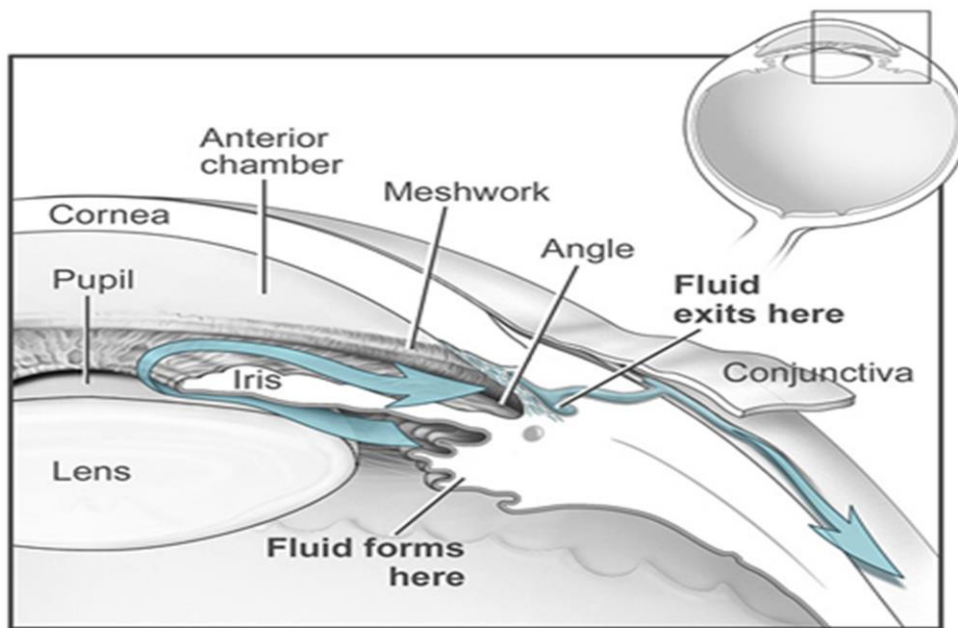
Nicotine: is obtained from tobacco leaves. It has initial stimulating and later a prolonged blocking effect on the autonomic ganglia.* Nicotine is of no value in clinical practice except in the form of transdermal patch and chewing gum for the treatment of tobacco addiction.

INTRAOCULAR PRESSURE(IOP): is the fluid pressure inside the eye. IOP is determined by the **production** and **drainage** of aqueous humor. Aqueous humor is secreted by the ciliary processes and flows from the posterior chamber, through the pupil, and into the anterior chamber and leaves the eye primarily by the trabecular meshwork and canal of Schlemm, thence to an episcleral venous plexus and into the systemic circulation. This conventional pathway accounts for 80%–95% of aqueous humor outflow and is the main target for cholinergic drugs used in glaucoma therapy. Another outflow pathway is the uveoscleral route (i.e., fluid flows through the ciliary muscles and into the suprachoroidal space), which is the target of selective prostanoids.

Normal eye pressure is usually considered to be between 10-20 mm Hg. Elevated eye pressure can cause glaucoma and nerve damage.

Current medical therapy of open-angle glaucoma (which is the most common type) is aimed at:

- decreasing aqueous humor production or
- increasing aqueous outflow.



Ciliary Body:

The ciliary body serves two very specialized roles:

- Production and secretion of aqueous humor by the epithelial bilayer.
- Accommodation by the ciliary muscle: contraction of the ciliary muscles results in thickening of the lens which focuses on close objects (it changes the shape of the lens not the size of the pupil).

Contraction of the longitudinal fibers, which insert into the trabecular meshwork in the anterior chamber of the eye, cause an increase in the meshwork pore size which will increase aqueous humor flow into the Schlemm canal.

Pilocarpine:

- The alkaloid pilocarpine produces muscarinic and nicotinic effects by directly interacting with the receptors.
- It has predominant muscarinic actions especially on secretory activity.
- It is used primarily in ophthalmology. Pilocarpine produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation.
- Pilocarpine is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity.
- Pilocarpine is used to treat glaucoma and is the drug of choice for emergency lowering of IOP of both open-angle and angle-closure glaucoma. Pilocarpine is extremely effective in opening the trabecular meshwork around the Schlemm canal, causing an immediate drop in intraocular pressure because of the increased drainage of aqueous humor.
- The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine.
- The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and *cevimeline*, a cholinergic drug that also has the drawback of being nonspecific.
- Adverse effects are salivation, sweating, bradycardia, diarrhoea, bronchospasm; pulmonary oedema can occur following systemic therapy.