Autonomic Nervous System

The nervous system is divided into two anatomical divisions:

- the central nervous system (CNS), which is composed of the brain and spinal cord,
- the peripheral nervous system, which includes neurons located outside the brain and spinal cord—that is, any nerves that enter or leave the CNS (figure 1)

The autonomic nervous system (ANS) is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions such as cardiac output, blood flow to various organs, and digestion, which are necessary for life.

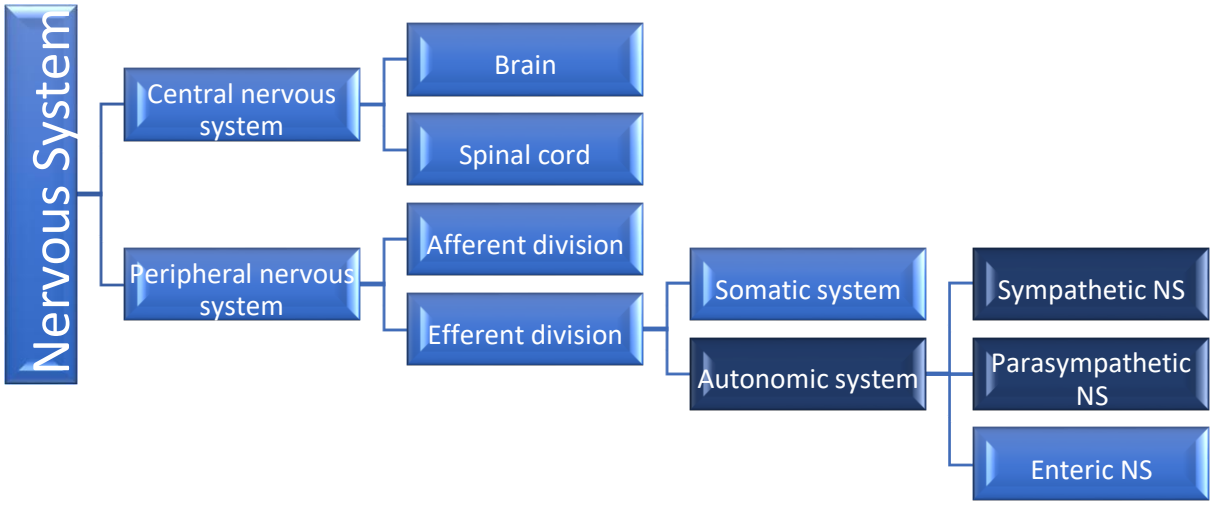


Figure 1: autonomic nervous system part of nervous system

- The ANS carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons: the preganglionic neurons and the postganglionic neurons.
- In this pre and post ganglionic complex the ganglia function is embodied in acting as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron (figure 2).
- In the sympathetic system, the preganglionic fibers are short and postganglionic fibers are long.
- On the other hand, the parasympathetic preganglionic fibers are long and postganglionic fibers are short.

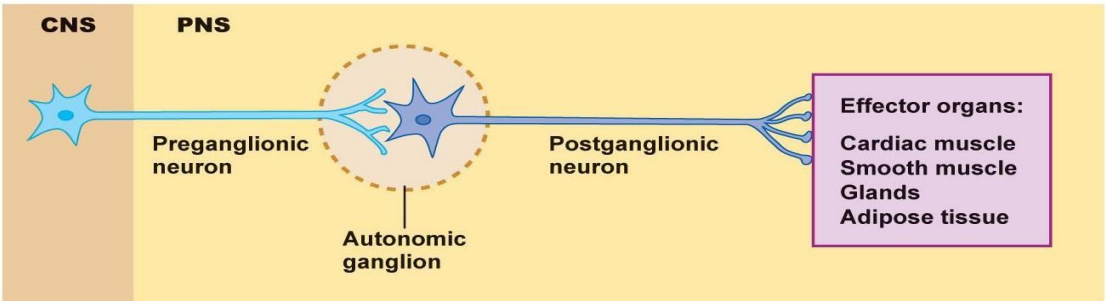


Figure 2: preganglionic and post ganglionic neurons

The function of the ANS can be explained by exploring the function of each part as the following (Figure 3):

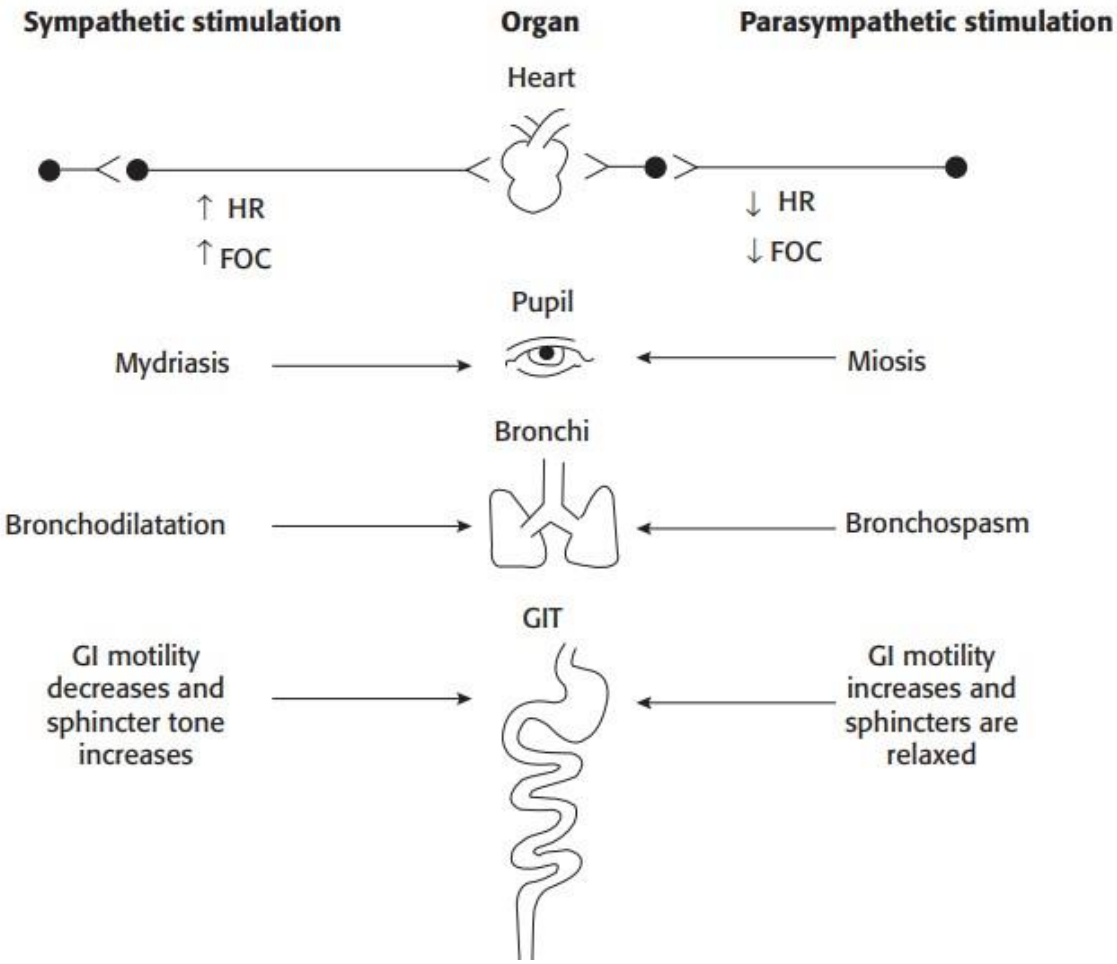


Figure 3: difference between parasympathetic and sympathetic division

Functions of the sympathetic nervous system

1- Effects of stimulation of the sympathetic division: The effect of sympathetic output is to:

1. Increasing heart rate and contractility, and thus, increasing blood pressure.
2. Constriction of the blood vessels of skin, mucous membranes, and splanchnic area, and dilation of skeletal muscles vessels.
3. Dilation of the pupils (mydriasis).
4. Bronchodilation.

5. Inhibit salivation.
6. Decrease GI motility.
7. Stimulation of ejaculation.
8. Inhibit bladder contraction.
9. Stimulate glucose production and release.

2- Fight-and-flight response: The changes experienced by the body during emergencies are referred to as the "fight and flight" response. These reactions are triggered both by direct sympathetic activation of the effector organs and by stimulation of the adrenal medulla to release epinephrine and lesser amounts of norepinephrine. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors. The sympathetic nervous system tends to function **as a unit and often discharges as a complete system**, for example, during severe exercise or in reactions to fear.

Accordingly, the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise.

Functions of the parasympathetic nervous system

The parasympathetic division is involved with maintaining homeostasis within the body. It is required for life, since it maintains essential bodily functions, such as digestion and elimination of wastes. The parasympathetic division usually acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in **"rest-and-digest"** situations. Unlike the sympathetic system, the parasympathetic system **never discharges as a complete system**. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation. Instead, parasympathetic fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.

So, the effect of parasympathetic output can be summarized in:

1- Pupil contraction (miosis).
2- Bronchoconstriction.
3- Stimulation of erection.
4- Stimulation tears and saliva secretion.
5- Decreasing heart rate and contractility.
6- Increasing the muscle motility and tone of the gastrointestinal system.

Functions of the enteric nervous system (ENS)

The enteric nervous system is a collection of neurons in the **gastrointestinal tract** that constitutes the "brain of the gut" and can function independently of the central nervous system. This system controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract.

Functions of the somatic nervous system

- The somatic system is the part of the peripheral nervous system that is responsible for carrying **motor** and **sensory** information both **to** and **from** the central nervous system ***without the mediation of ganglia*.**
- This system is made up of nerves that connect to the skin, sensory organs, and all skeletal muscles.
- The system is responsible for nearly all voluntary muscle movements as well as for processing sensory information that arrives via external stimuli including hearing, touch, and sight.

Figure 4 shows the main differences between autonomic and somatic nervous system.

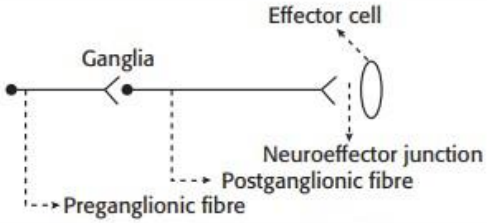
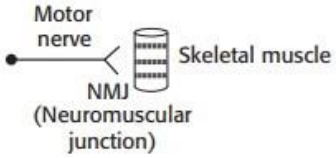
Autonomic Nervous System	Somatic Nervous System
Auto: self; *nomos*: governing; this system is involuntary and maintains homeostasis	Somatic nervous system is under voluntary control
Each autonomic fibre is made up of two neurons arranged in series	Each somatic fibre is made up of single motor neuron, which connects CNS to skeletal muscle
	
It innervates the heart, smooth muscles and exocrine glands	It innervates skeletal muscle
It controls visceral functions such as circulation, digestion, excretion, etc.	It controls skeletal muscle tone

Figure 4: main differences between autonomic and somatic nervous system

The ANS requires sensory input from peripheral structures to provide information on the current state of the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus and spinal cord. These centers respond to the stimuli by sending out efferent reflex impulses via the ANS. **This process of initiating an afferent impulse that travel to the CNS and replying by efferent impulse to get a response is called *reflex arc*** (figure 5).

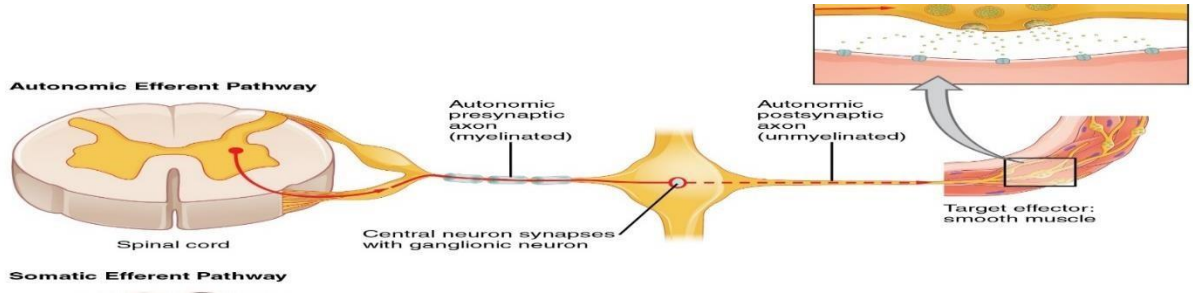


Figure 5: Somatic and autonomic reflex arc

Usually, most of the afferent impulses are involuntary translated into reflex responses. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the

heart, vena cava, aortic arch, and carotid sinuses) to send fewer impulses to cardiovascular centers in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and tachycardia.
According to the above explanation, the reflex arcs of the ANS comprise a sensory (or afferent) arm and a motor (or efferent or effector) arm.

Neurotransmitters

- Neurotransmission in the ANS is an example of the more general process of chemical signalling between cells using neurotransmitters.
- Neurotransmitters are specific chemical signals that are released from nerve terminals to establish the communication between nerve cells, and between nerve cells and effector organs.
- In spite of recognizing more than 50 signals molecules (neurotransmitters) in the nervous system, just **norepinephrine** (and the closely related **epinephrine**), **acetylcholine**, **dopamine**, **serotonin**, **histamine**, **glutamate**, and **γ-aminobutyric acid** are the most commonly involved neurotransmitters in the actions of therapeutically useful drugs.
- Each type of neurotransmitters can bind with a specific receptor in order to give the biological desirable response.
- The primary chemical signals in the ANS are the **acetylcholine** and **norepinephrine** as they are involved in conducting wide variety functions in the CNS.
- The autonomic nerve fibers can be classified to **cholinergic** and **adrenergic** neurons based on the type of the released neurotransmitters whether they are acetylcholine or epinephrine and norepinephrine.
- Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs also involve the release of acetylcholine (figure 6).
- In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and voluntary muscles) is also cholinergic.
- In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs except few sympathetic fibers, such as those involved in sweating, are cholinergic.

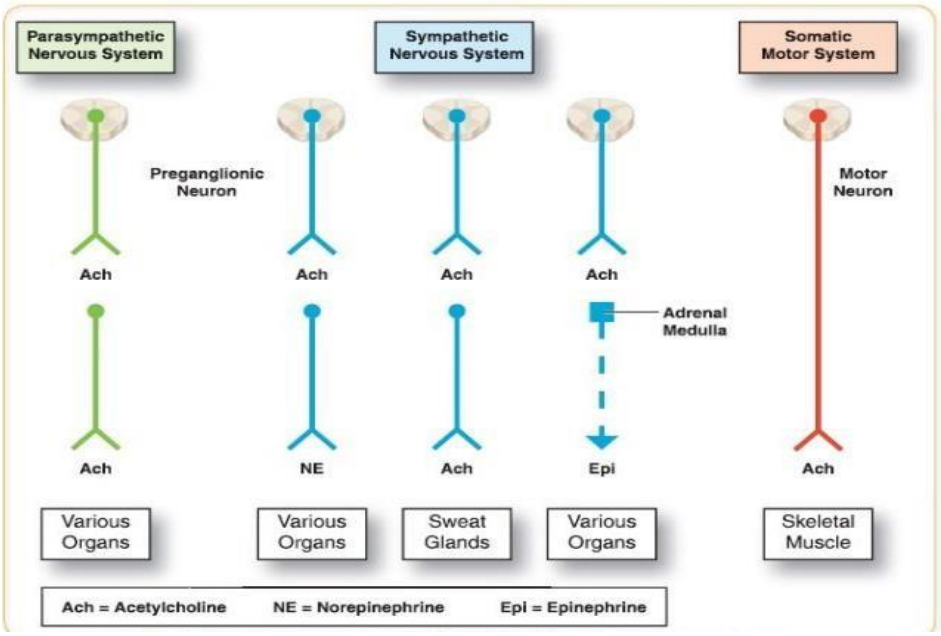


Figure 6: Neurotransmitters

Cholinergic Agonists

- ✓ The cholinergic drugs act on receptors that are activated by acetylcholine (ACh).
- ✓ These receptors include **nicotinic** and **muscarinic** receptors and can be mainly recognized in **sympathetic** and **parasympathetic** nervous system and **somatic** nervous system as well (Figure 7).
- ✓ The two classes of receptor for Ach are defined on the basis of their preferential activation by the alkaloids *nicotine* and *muscarine.*

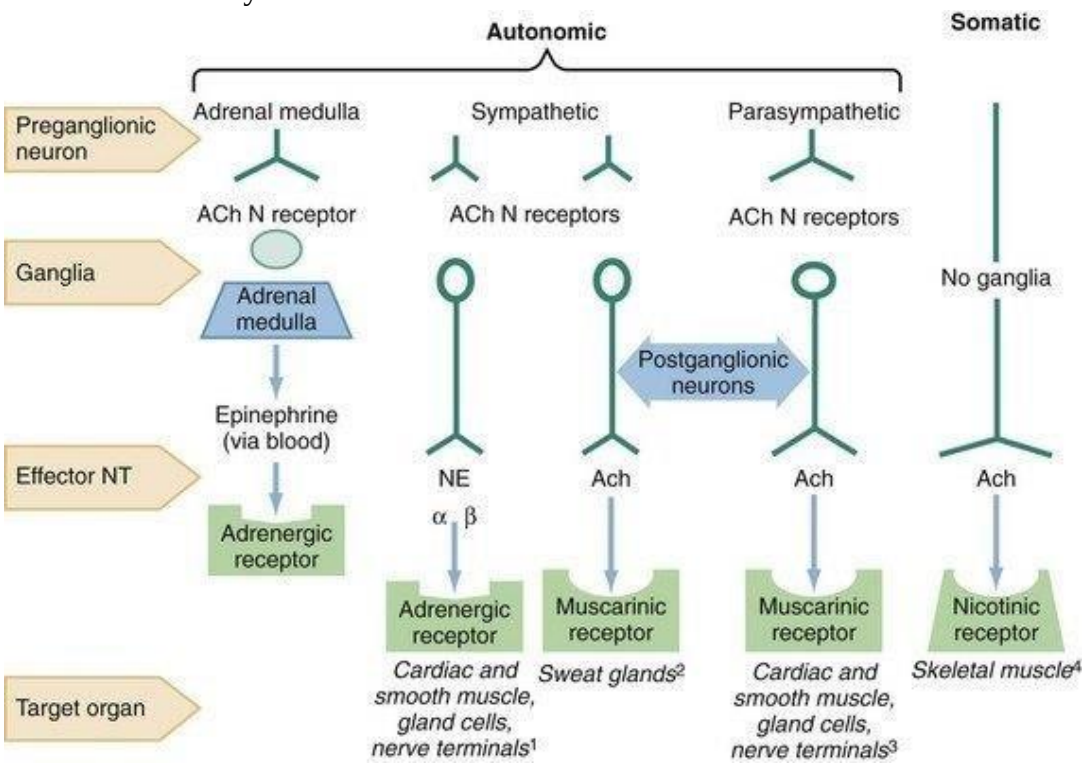


Figure 7: Ach receptors muscarinic and nicotinic receptors, the nicotinic receptors located on autonomic ganglia (Nn subtype) and on neuromuscular junction on somatic nervous system (Nm subtype)

Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps:

1) synthesis,
2) storage,
3) release,
4) binding of ACh to a receptor,
5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and
6) recycling of choline and acetate (figure 8)

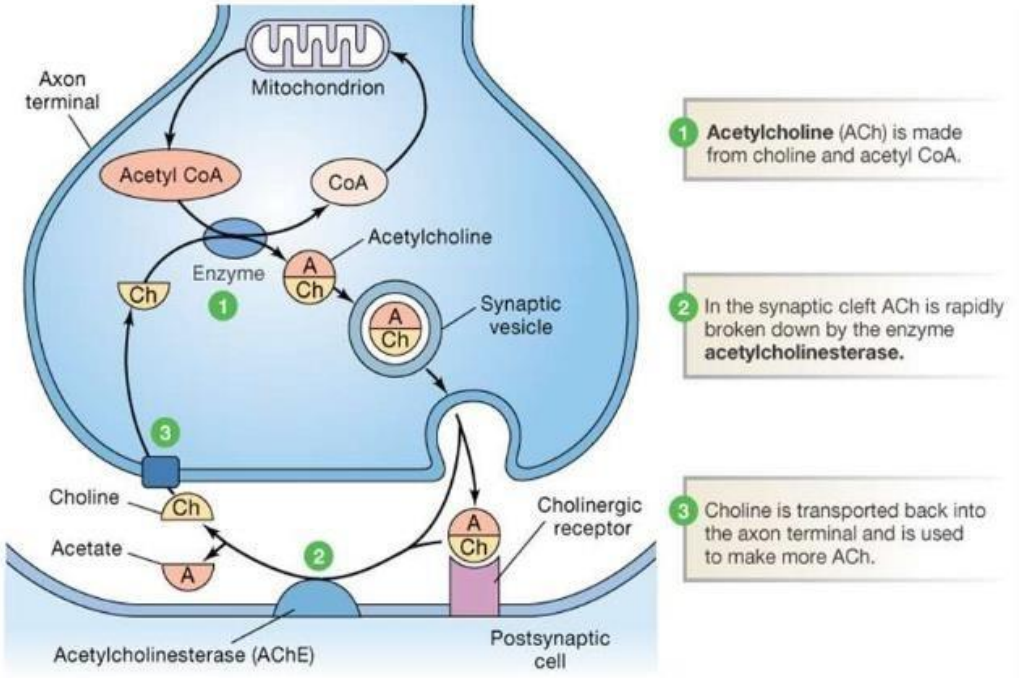


Figure 8: Ach synthesis

1. Synthesis of acetylcholine: Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.

2. Storage of acetylcholine in vesicles: ACh is packaged and stored into presynaptic vesicles.

3. Release of acetylcholine: When an action potential propagated 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 their contents into the synaptic space.

4. Binding to the receptor: ACh released from the synaptic vesicles diffuses across the synaptic space and binds its receptors. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic. Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells.

5. Degradation of acetylcholine: The signal at the post- junctional effector site is rapidly terminated, because AChE (acetylcholine esterase) cleaves ACh to choline and acetate in the synaptic cleft.

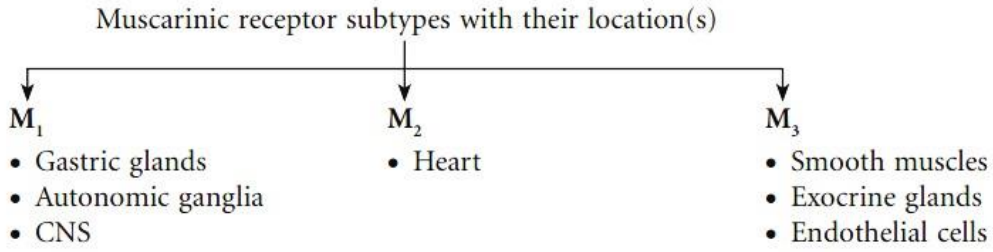
6. Recycling of choline: Choline may be recaptured by a sodium-coupled uptake system that transports the molecule back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Cholinoceptors can be classified into two types: muscarinic and nicotinic receptors. They are different mainly in their affinities for agents that mimic the action of ACh (cholinomimetic agents).

1- Muscarinic receptors: It is one of the G protein–coupled receptors that have high affinity to bind with muscarine (an alkaloid that is present in certain poisonous mushrooms) and ACh but low affinity to bind with nicotine. Five sub-classes are recognized for this receptor family; however, only M1, M2, and M3 receptors have been functionally characterized.

a- Locations of muscarinic receptors:

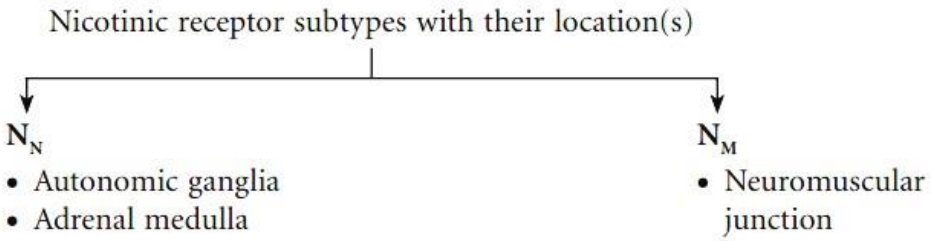


b- Muscarinic agonists: *Pilocarpine* is an example of a nonselective muscarinic agonist used in clinical practice to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. M1 receptor agonists are being investigated for the treatment of Alzheimer's disease.

2- Nicotinic receptors

These receptors, in addition to binding ACh, also recognise nicotine but show only a weak affinity for muscarine. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. The nicotinic receptor functions as a ligand-gated ion channel.

Location: Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.



Those at the NMJ are sometimes designated N_M, and the others, N_N. The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, ganglionic receptors are selectively blocked by *mecamylamine*, whereas NMJ receptors are specifically blocked by *atracurium.*

Below is a table summarizing the function of each cholinergic receptor

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

DIRECT-ACTING CHOLINERGIC AGONISTS

Definition: Materials that mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic).

Types:

1) Endogenous choline esters, which include ACh and synthetic esters of choline, such as *carbachol* and *bethanechol*.

2) Naturally occurring alkaloids, such as *nicotine* and *pilocarpine*. The main advantage of this group of drugs that have a longer duration of action than ACh.

The more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. As a group, the direct acting agonists demonstrate little specificity in their actions, which limits their clinical usefulness.

Acetylcholine

Acetylcholine is a quaternary ammonium compound; hence it cannot penetrate membranes. In spite of considering the ACh as a neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its pluralism of actions 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:** The actions of ACh on the heart imitate the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (negative chronotropy) and stroke volume as a result of a reduction in the rate of firing at the sino-atrial (SA) node.

2- **Decrease in blood pressure:** As a result of ACh injection, vasodilation and lowering of blood pressure can be observed. This is due to an indirect mechanism of action because the ACh activates M3 receptors that found on endothelial cells lining the smooth muscles of blood vessels. This leads to produce a nitric oxide that act as a vasodilator from arginine. In the absence of administered cholinergic agents, the vascular cholinergic receptors have no known function, because ACh is never released into the blood in significant quantities. *Atropine* blocks these muscarinic receptors and prevents ACh from producing vasodilation.

3- **Other actions**

ACh administration can stimulate:

a- Salivary secretion stimulates intestinal secretions and motility.

b- Bronchiolar secretions.

c- Urination.

Moreover, ACh causes miosis (marked constriction of the pupil). Accordingly, ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

Therapeutic uses of direct-acting cholinergic agonists:

- ✓ bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.
- ✓ Carbachol eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.
- ✓ Pilocarpine is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure in glaucoma. It is also beneficial in promoting salivation in patients with xerostomia (dry mouth) resulting from irradiation therapy of the head and neck cancer or due to Sjogren's syndrome (an autoimmune disease in which the moisture-producing glands of the body are affected causing mainly symptoms of dry eyes and dry mouth).

Adverse effects of Ach and other cholinergic agonists: causes the effects of generalized cholinergic stimulation.

- Bronchospasm and increase secretions.
- GI: nausea, vomiting, and diarrhea.
- Miosis.
- Urinary urgency.

- Sweating (diaphoresis) and salivation.
- *Pilocarpine* can enter the brain (because it's a tertiary amine (unionized)) and cause CNS disturbances. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects.

To counteract the poisoning effect of the pilocarpine and Bethanechol, Parenteral *atropine*, at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of *the cholinergic material*.

INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTERASE AGENTS (REVERSIBLE))

ACh is usually deactivated by the AChE (Acetylcholine esterase), which is an enzyme that specifically cleaves ACh to acetate and choline. It can be found at both pre- and post synaptically in the nerve terminal where it is membrane bound.
Accordingly, inhibition of AchE can indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space. This process can be carried out by using the anticholinesterase agents or cholinesterase inhibitors. These drugs can provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain.

Therapeutic uses of acetylcholinesterase inhibitors (reversible)

Edrophonium, pyridostigmine, and ambenonium: They are used in the diagnosis and management of myasthenia gravis, which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs. This causes their degradation, making fewer receptors available for interaction with the neurotransmitter.

Physostigmine

- It increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ.
- used to treat glaucoma, but *pilocarpine* is more effective.
- as an antidote for drugs with anticholinergic actions.

Neostigmine

- used to stimulate the bladder and GI tract.
- as an antidote for *tubocurarine* and other competitive neuromuscularblocking agents.
- also used to treat myasthenia gravis.

Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of

cognitive function. *Tacrine* was the first to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of *donepezil*, *rivastigmine*, and *galantamine* to delay the progression of Alzheimer disease, none can stop its progression.

Adverse effects of acetylcholinesterase inhibitors (reversible):

- Adverse effects include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.
- Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, results in paralysis of skeletal muscle.
- *Physostigmine* can enter and stimulate the cholinergic sites in the CNS. The effects on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur.

INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTRASE AGENTS (IRREVERSIBLE))

A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as *parathion* and *malathion*, are used as insecticides.

Table: Summary of echothiophate actions, therapeutic uses and its adverse effect.

Anticholinesterase agent (Irreversible)	**Actions**	**Therapeutic uses**	**Adverse effect**
Echothiophate	*Covalently binds to the AChE.	*A topical solution of the drug is for the treatment of open-angle glaucoma.	*Represented by the generalised cholinergic stimulation. *Paralysis of motor function (causing breathing difficulties). *Convulsions.

Cholinergic Antagonists

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

There are three types of cholinergic antagonist drugs, which are:

1- Anti-muscarinic agents (anticholinergic drugs) block muscarinic receptors, causing inhibition of muscarinic functions. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, anti-muscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs).

2- Ganglionic blockers (specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia)

3- The neuromuscular-blocking agents (mostly nicotinic antagonists), which block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle

1- Atropine (anti-muscarinic agents): It is an alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents ACh from binding to those sites. Atropine acts both centrally and peripherally. Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days. Neuro-effector organs have varying sensitivity to atropine.

Effects:

- CNS: confusion, delirium.
- Decrease GI motility and acid secretions without interfering with hydrochloric secretion.
- **Increase heart rate at high doses, i.e. higher than (0.5 mg). At low doses slight decrease in heart rate:** At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of the M1 receptors on the inhibitory pre-junctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of atropine cause a progressive increase in heart rate by blocking the M2 receptors on the sino-atrial node
- Decrease body secretions like saliva (xerostomia), bronchial secretions, and sweat (elevate body temperature).
- Mydriasis (cycloplegic to permits the measurement of refractive errors without interference by the accommodative capacity of the eye).

Therapeutic uses:

- As mydriatic and cycloplegic: Atropine is used topically for producing mydriasis and cycloplegia. The action of atropine lasts 7–10 days.
- As pre-anesthetic medication: Atropine is used prior to the administration of general anesthetics: To prevent vagal bradycardia during anesthesia. To prevent laryngospasm

by decreasing respiratory secretions. Anti-secretory agent to block the secretions in the upper and lower respiratory tracts before surgery.

- Anticholinergics are useful as antispasmodics in dysmenorrhoea, intestinal and renal colic.
- Poisoning:

  a. In organophosphorous poisoning, atropine is the life-saving drug.

  b. In some types of mushroom poisoning, atropine is the drug of choice.

  c. Atropine is used in curare poisoning with neostigmine to counteract the muscarinic effects of neostigmine.

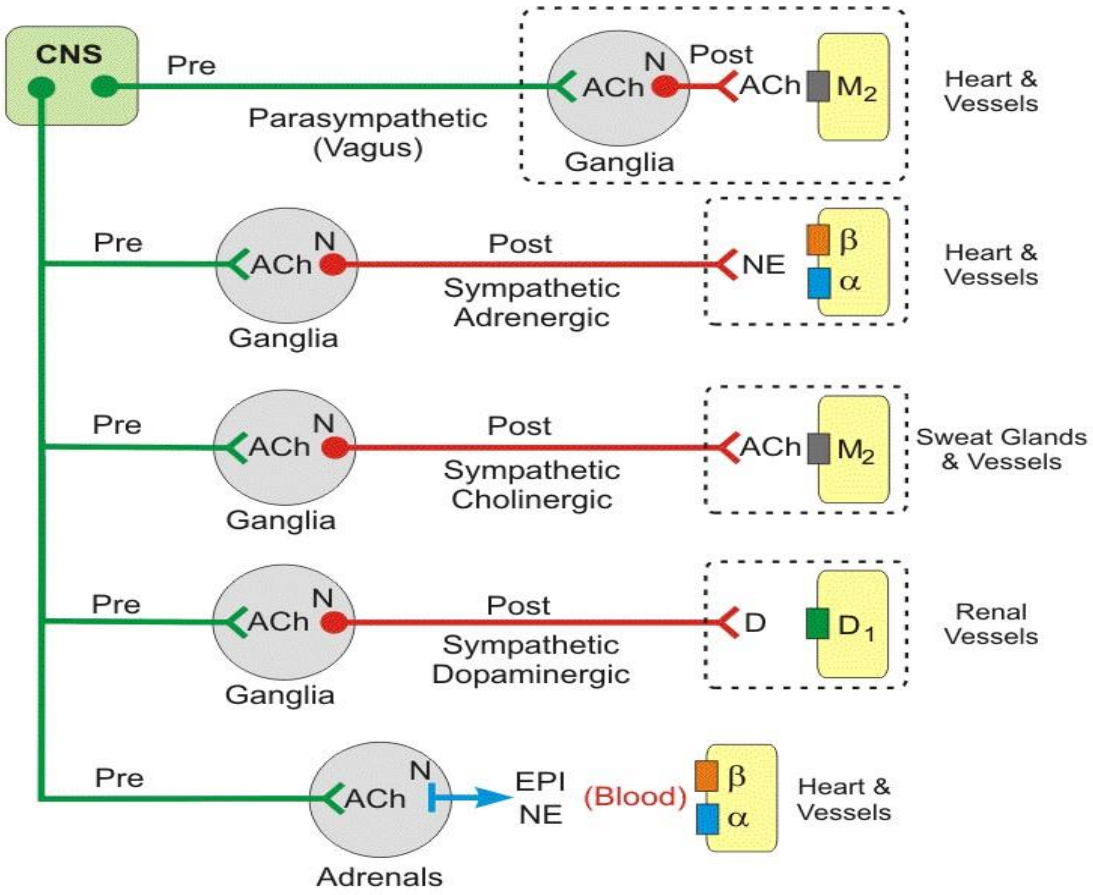
- As vagolytic: Atropine is used to treat sinus bradycardia and partial heart block due to increased vagal activity.

Side effects: Blurred vision, decrease secretions, hyperthermia, constipation, urinary retention, delirium, and hallucinations.

- ✓ ***Scopolamine*** is another antagonist used for motion sickness.
- ✓ ***Ipratropium*** used as inhaler to decrease bronchoconstriction and bronchial secretions in COPD (chronic obstructive pulmonary disease) and asthma.

2- Nicotine (Ganglionic blockers)**:** although nicotine considers as an agonist at nicotinic receptors, but at higher dose it blocks the autonomic ganglia (figure 9). Nicotine produces initial stimulation and varying degrees of subsequent block through a mechanism analogous to that of succinylcholine (see later).

Nicotine is a component of cigarette smoke, is a poison with many undesirable actions. However, it can be used in a controlled way to help in giving up smoking. It is found in more than one pharmaceutical dosage forms like sublingual tablets, lozenges and as chewing gum. Its action can be summarized in these points: Increasing the blood pressure and cardiac rate and at higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.



CNS = central nervous system; Pre = preganglionic; Post = postganglionic; ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine; D = dopamine; M_2 = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor; D_1 = dopaminergic receptor

Figure 9: position of nicotinic receptor in autonomic ganglia

3- **The neuromuscular-blocking agents:** These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle. They possess some chemical similarities to ACh, and they act either as antagonists (non-depolarizing type) or as agonists (depolarizing type) at the receptors on the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery to facilitate tracheal intubation and provide complete muscle relaxation at lower anaesthetic doses, allowing for more rapid recovery from anesthesia and reducing postoperative respiratory depression.

1- **Non- depolarising (competitive) blockers: At low doses:** Non-depolarizing agents competitively block ACh at the nicotinic receptors. That is, they compete with ACh at the receptor without stimulating it. Thus, these drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction. On the other hand, **on high doses**, these drugs can lead to complete blockade and the muscle does not respond to direct electrical stimulation. All neuromuscular-blocking agents are injected intravenously or occasionally intramuscularly since they are not effective orally. In general, these agents are safe with minimal side effects; however, they can rarely cause bronchospasm.

2- **Depolarizing agents:** Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarize the muscle fibers. *Succinylcholine* is the only depolarizing muscle relaxant in use today. *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarize the junction. This leads to a transient twitching of the muscle. Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses leading to flaccid paralysis. Therapeutically, *succinylcholine (which is administered IV)* is useful when rapid endotracheal intubation is required during the induction of anesthesia. The main side effects of this drug are the hyperthermia, apnea and hyperkalemia.