The Autonomic Nervous System from a Pharmacological Perspective

Nervous system (NS) can be defined as the system of cells, tissues, and organs that regulates the body's responses to internal and external stimuli. The nervous system consists from different parts, which are demonstrated in figure 1.

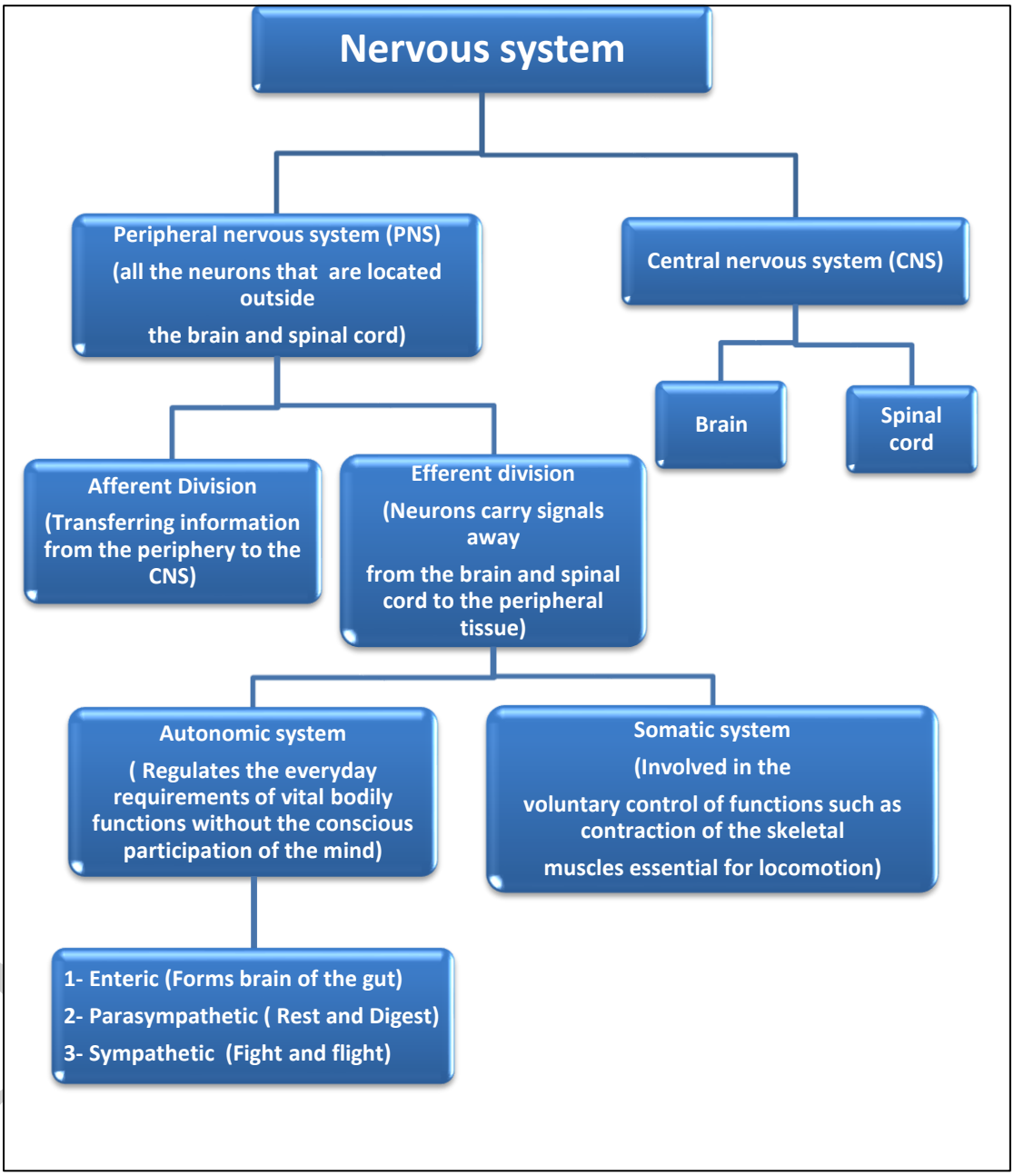


Figure 1: Organisation of the nervous system.

The Autonomic Nervous system (ANS) is an important part of the nervous system that can exert its influence by the rapid transmission of electrical impulses over nerve fibres

that terminate at effector cells, which specifically respond to the release of neuromediator substances. 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 as demonstrated in figure 2.

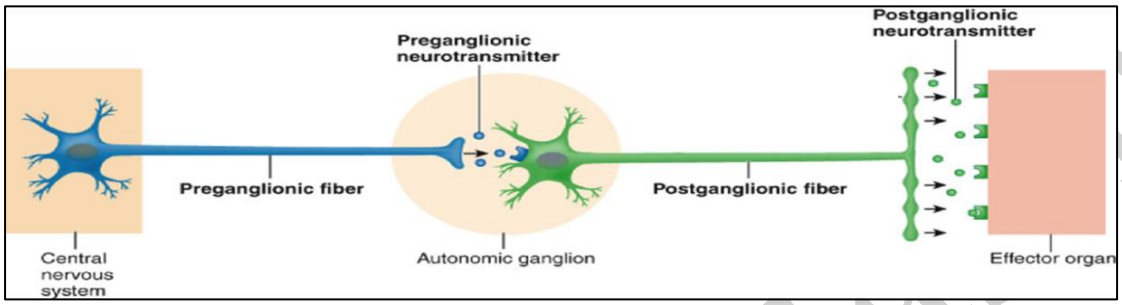


Figure 2: Efferent neurons of the autonomic nervous system.

It is noteworthy to mention that the primary action of some drugs can modulate the action of the ANS, by mimicking or altering the functions of the ANS. These drugs are known as the autonomic drugs, which act either by stimulating portions of the ANS or by blocking the action of the autonomic nerves.

The function of the ANS can be explained by exploring the function of each part as the following:

A) Functions of the sympathetic nervous system

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

a- Increase heart rate and blood pressure.

b- Increase blood flow to skeletal muscles and heart while diverting flow from the skin and internal organs.

c- Increase the secretion of epinephrine and norepinephrine.

Moreover, sympathetic stimulation results in dilation of the pupils and the bronchioles. It also affects GI motility and the function of the bladder and sexual organs.

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, hypoglycaemia, cold, and exercise.

B) **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 fibres 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 summarised 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.

C) **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.

D) **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.

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 centres in the CNS, such as the hypothalamus and spinal cord. These centres 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*.

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 centres 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 recognising 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 fibres 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 3). In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibres 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 fibres, such as those involved in sweating, are cholinergic.

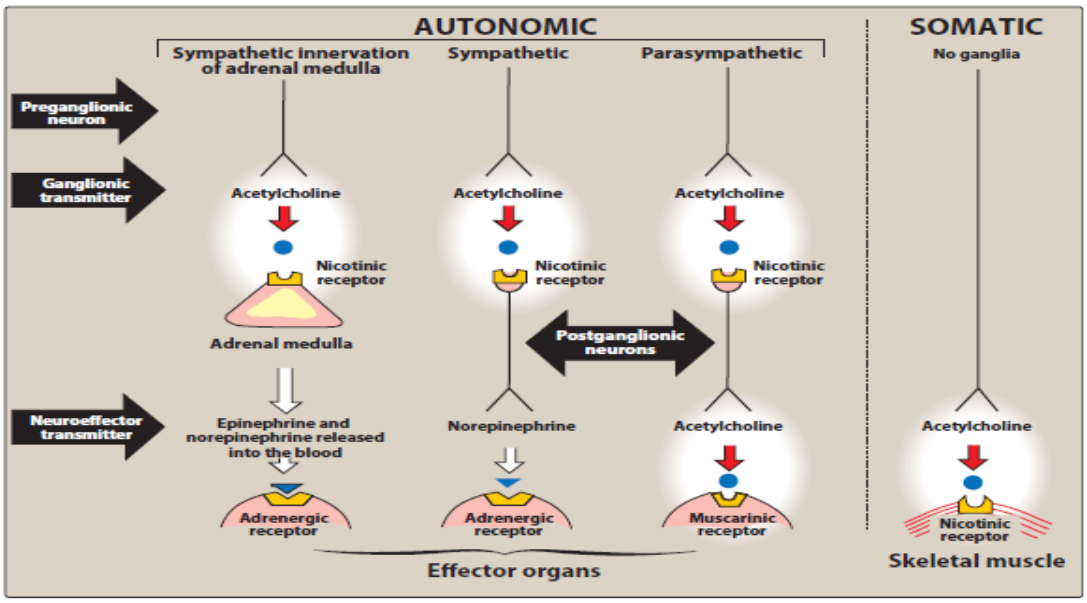


Figure 3: Summary of the neurotransmitters released, types of receptors, and types of neurons within the autonomic and somatic nervous systems.

Cholinergic agonist

The cholinergic drugs act on receptors that are activated by acetylcholine (ACh). These receptors include nicotinic and muscarinic receptors and can be mainly recognised in sympathetic and parasympathetic nervous system and somatic nervous system as well.

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 4).

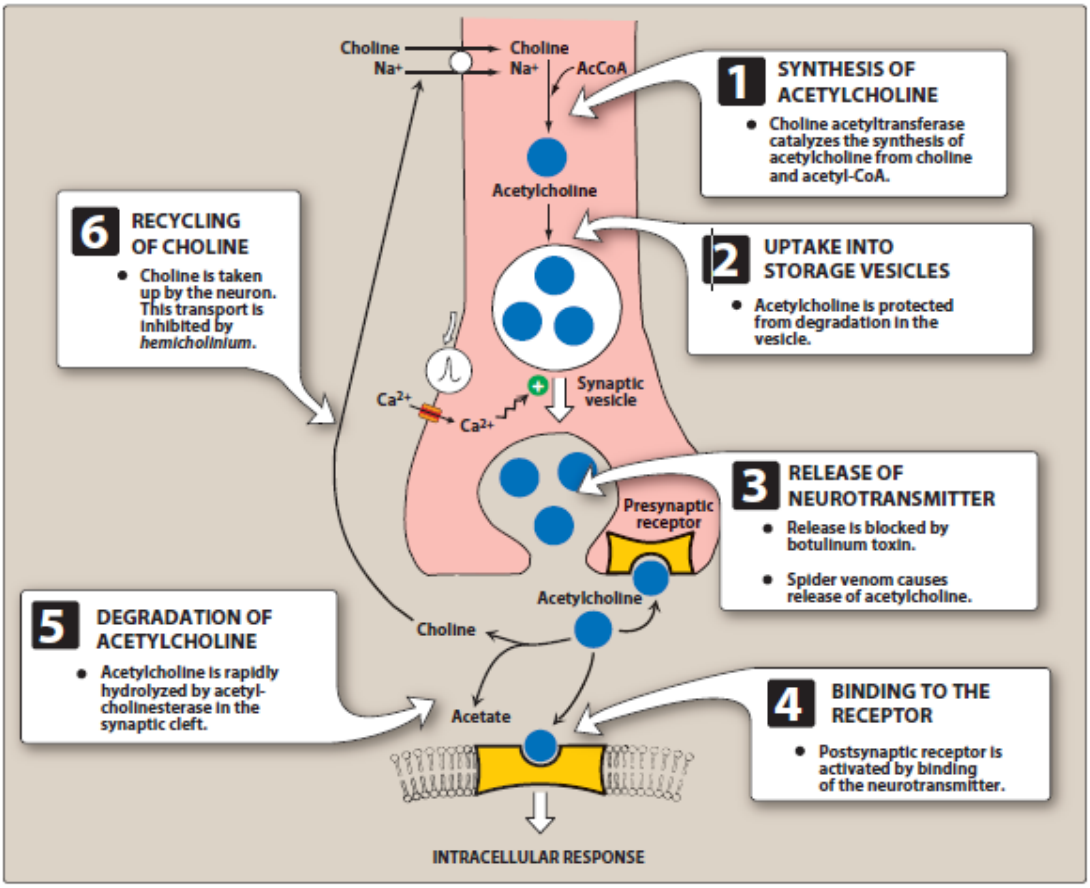


Figure 4: Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

1) **Synthesis of acetylcholine:** Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system. The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyses the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol (figure 4).

2) **Storage of acetylcholine in vesicles:** After synthesis of Ach, it is packaged and stored into presynaptic vesicles to protect it from degradation (figure4).

3) **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 their contents into the synaptic space (figure 4). 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.

4) **Binding to the receptor:** ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, or to presynaptic receptors on the membrane of the neuron that released the

ACh. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic (figure 3). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fibre or activation of specific enzymes in effector cells, as mediated by second messenger molecules.

5) **Degradation of acetylcholine:** The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft (figure 4).

6) **Recycling of choline:** Choline may be recaptured by a sodium coupled, high-affinity 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 recognised for this receptor family; however, only M1, M2, and M3 receptors have been functionally characterised.

   a- Locations of muscarinic receptors: These receptors are found:
   - On ganglia of the peripheral nervous system.
   - On the autonomic effector organs (such as the heart, smooth muscle, brain, and exocrine glands).
   - In addition, M1 receptors are also found on gastric parietal cells, M2 receptors on cardiac cells and smooth muscle, and M3 receptors on the bladder, exocrine glands, and smooth muscle.

   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.*

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. [Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.] However, 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 (figure 5). 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 sinoatrial (SA) node.

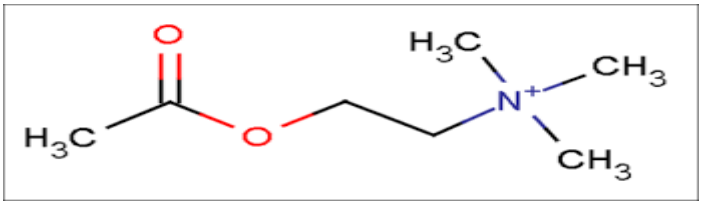


Figure 5: Acetylcholine structure.

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.

The other direct cholinergic drugs are summerised in table 1, which illustrates the actions, therapeutic and adverse effects of them.

Table 1: Summary of actions of some cholinergic agonists. CNS = central nervous system.

A cholinergic agonist drug	Mode of action	Therapeutic uses	Adverse effect
Bethanechol	*Binds preferentially at muscarinic receptors leading to increasing the intestinal motility and urination.	*Mainly used in treatment of urinary retention.	*These include sweating, salivation, flushing, bronchospasm decreased blood pressure, nausea, abdominal pain and diarrhoea.
Carbachol	*Binds to muscarinic and nicotinic receptors. *Has profound effects on both the cardiovascular 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.	*Miosis during ocular surgery. *Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*.	*At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine).
Pilocarpine	*Binds preferentially at muscarinic receptors. *Uncharged, tertiary amine that can penetrate the CNS	Reduces intraocular pressure in open-angle and narrow-angle glaucoma	*Blurred vision night *Blindness and brow ache. *Salivation *Sweating

To counteract the poisoning effect of the pilocarpine an**d 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 uaually 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 postsynaptically 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 (Figure 6). 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.

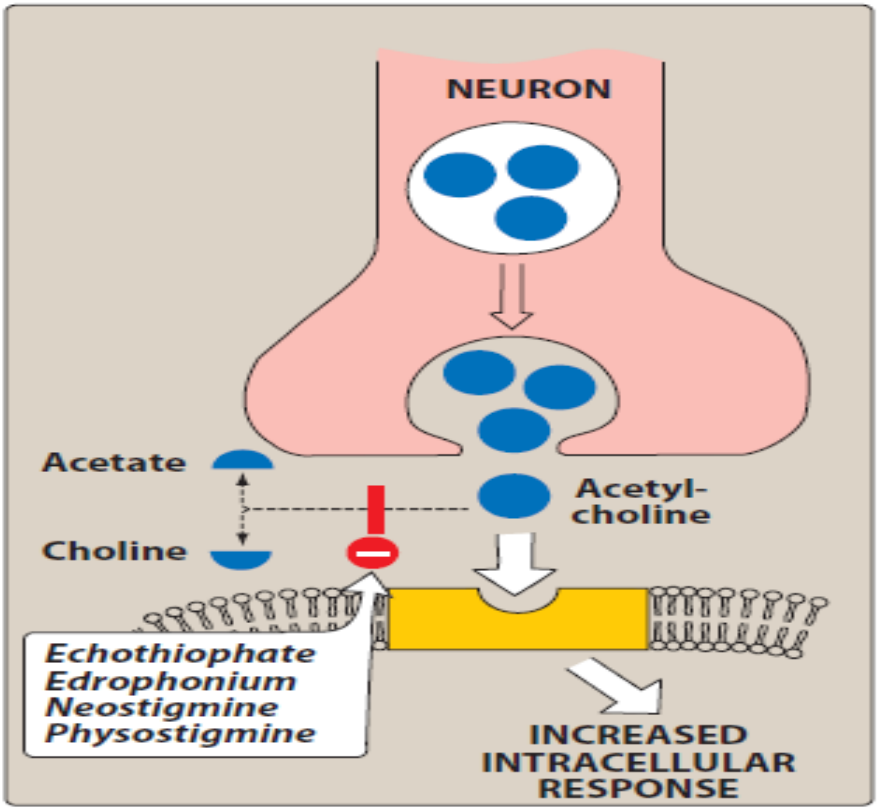


Figure 6: Mechanisms of action of indirect cholinergic agonists.

Anticholinesterase agents' actions, therapeutic uses and adverse effect were summarised in table 2.

Table 2: Summary of actions of some cholinergic agonists. CNS = central nervous system.

Anticholinesterase agents (Reversible)	Actions	Therapeutic uses	Adverse effect
Edrophonium	*Binds reversibly to the active centre of AChE, leading to prevente hydrolysis of ACh for 10-20 mins and then eliminated rapidly by renal system.	*Used for diagnosis of myasthenia gravis. *Used as an antidote for competitive neuromuscular blockers	*Represented by the generalised cholinergic stimulation such as: salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhoea, and bronchospasm.
Physostigmine	*Bind Reversibly to AChE, resulting in potentiating of cholinergic activity throughout the body by stimulating the muscarinic and nicotinic receptors for 30 min -2 hrs.	*Increases intestinal and bladder motility. *Reverses CNS effects of *atropine.*	*Convulsions (at high doses). *Bradycardia and a fall in cardiac output. *Paralysis of skeletal muscle. (All of these side effects are rarely Observed with therapeutic doses)
Neostigmine	*Its effect on skeletal muscle is greater than that of *physostigmine.* *Duration of action is 30 min-2 hrs	*Prevents postoperative abdominal distention and urinary retention *Used in treatment of myasthenia gravis	*Represented by the generalised cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. **Neostigmine* does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as *atropine.*
Pyridostigmine and ambenonium	*Inhibit the cholinesterase action	*For chronic management of myasthenia gravis.	*Similar to those of *neostigmine.*
Tacrine, donepezil, rivastigmine, and galantamine	Inhibit the cholinesterase action	*Used as first-line treatments for Alzheimer's disease	*GI distress

Indirect-acting cholinergic agonists (anticholinesterase 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 3: 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 ophthalmic solution of the drug is available 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- Antimuscarinic agents (anticholinergic drugs) block muscarinic receptors (figure 6), causing inhibition of muscarinic functions. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) as demonstrated in figure 7.

2- Ganglionic blockers (specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia (figure 7))

3- The neuromuscular-blocking agents (mostly nicotinic antagonists), which block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle (figure 7).

An example for each type of cholinergic antagonists will be discussed below.

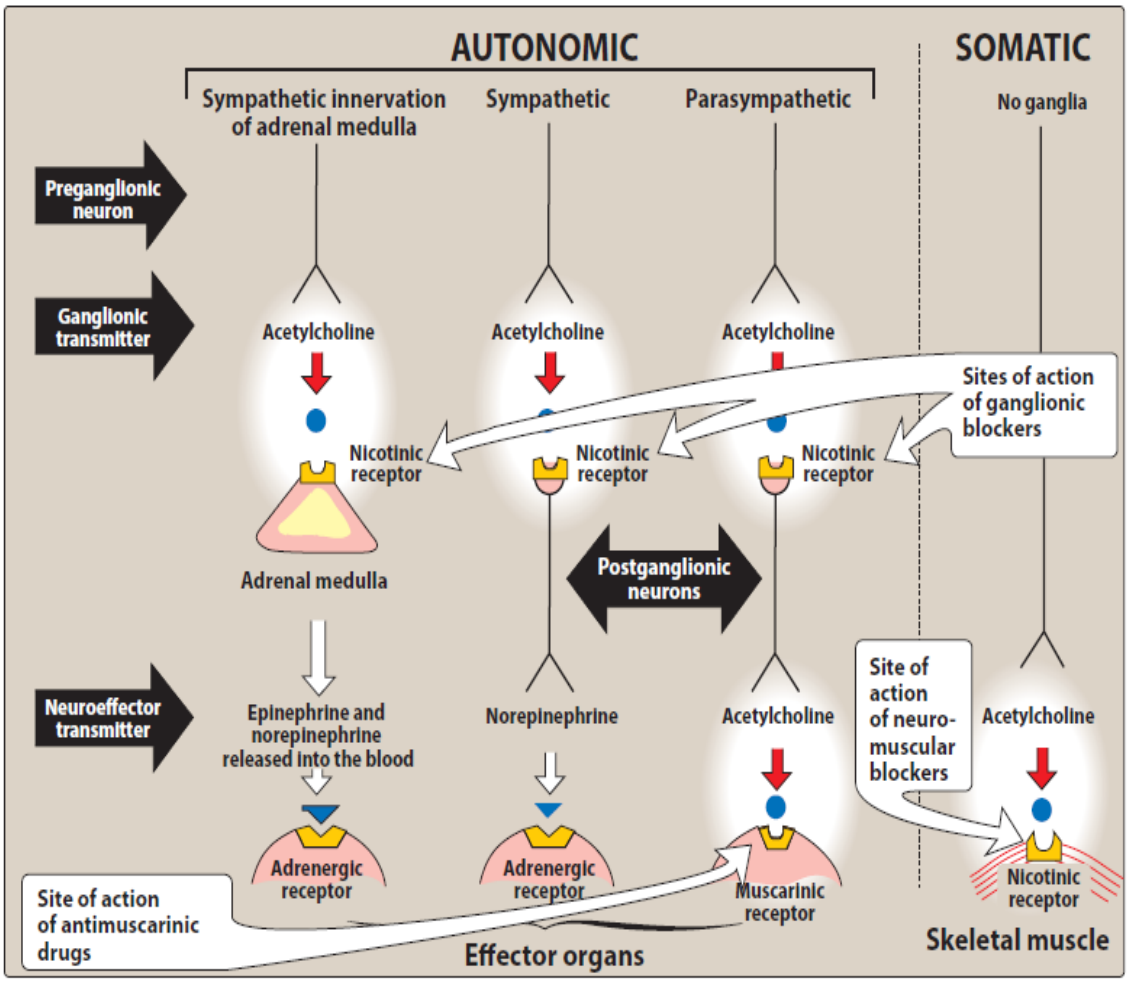
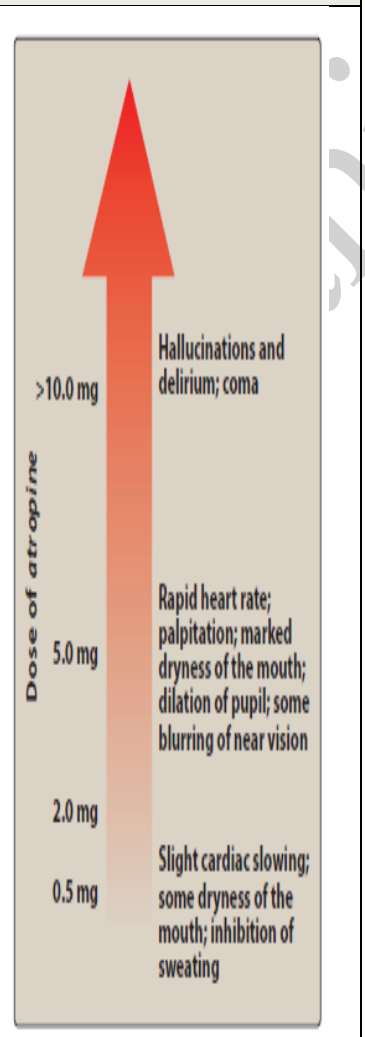


Figure 7: Sites of actions of cholinergic antagonists.

1- **Atropine (**antimuscarinic 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. Neuroeffector organs have varying sensitivity to atropine.
Atropine actions therapeutic uses and side effects were summarised in table 4.

Table 4: Summary of pharmaceutical properties of atropine.

pharmaceutical properties of atropine		
Actions	**Therapeutic uses**	**Adverse effect (Dose dependent)**
Eye: Mydriasis	**Ophthalmic:** Topical atropine exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye.	
GI tract: gastric motility is reduced without affecting the hydrochloric acid secretion.	**Antispasmodic**	
Cardiovascular: Dose dependent i.e. at low dose (0.5 mg), atropine causes slight decrease in heartrate while at higher doses can cause progressive increase in heart rate.	**Cardiovascular:** The drug is used to treat bradycardia of varying etiologies.	
Secretions: Atropine may cause dryness of the mouth (xerostomia) and inhibit the secretion from sweat gland can cause elevated body temperature, which can be dangerous in children and the elderly.	**Antisecretory agent:** Atropine is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.	
	Antidote for cholinergic agonists.	

Another cholinergic antagonist is the *Scopolamine, which* has greater action on the CNS and a longer duration of action as compared to *atropine*. Mainly used for preventing of motion sickness and postoperative nausea and vomiting.

2- **Nicotine (**Ganglionic blockers)**:** 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 summarised 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.

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 (nondepolarising type) or as agonists (depolarising 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- **Nondepolarising (competitive) blockers: At low doses:** Nondepolarising agents competitively block ACh at the nicotinic receptors. That is, they compete with ACh at the receptor without stimulating it. Thus, these drugs prevent depolarisation 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- **Depolarising agents:** Depolarising blocking agents work by depolarising the plasma membrane of the muscle fibre, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarise the muscle fibres. *Succinylcholine* is the only depolarising muscle relaxant in use today. *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarise the junction. This leads to a transient twitching of the muscle. Continued binding of the depolarising 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 anaesthesia. The main side effects of this drug are the hyperthermia, apnea and hyperkalaemia.