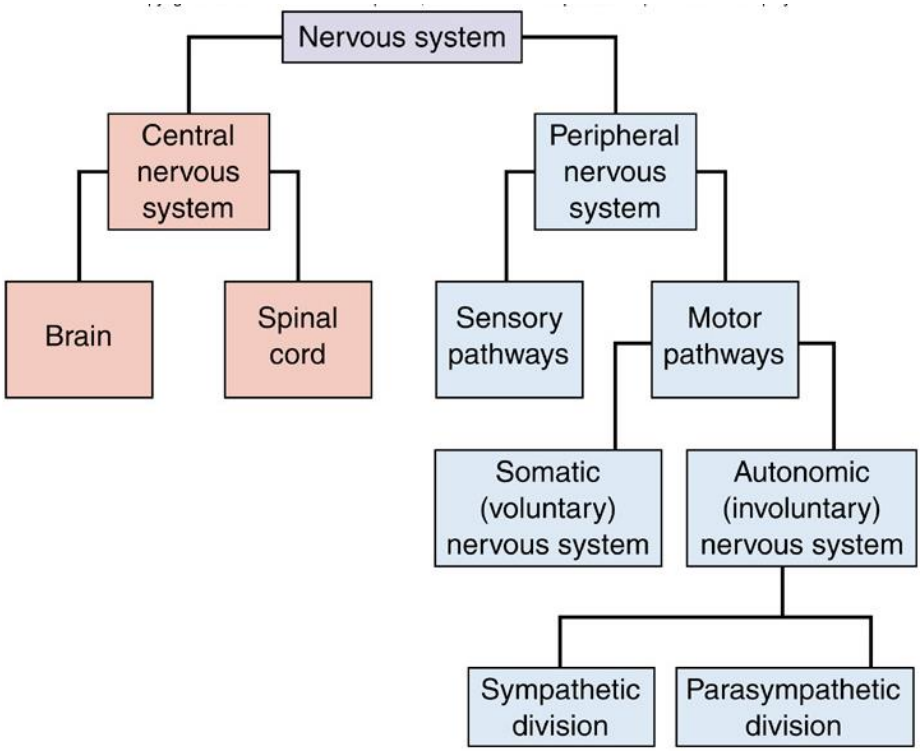
The autonomic nervous system

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord-that is, any nerves that enter or leave the CNS.

The peripheral nervous system is subdivided into the efferent and afferent divisions. The efferent neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent neurons bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action.

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions: the somatic nervous system and the ANS. The autonomic nervous system consists of three main anatomical divisions: sympathetic, parasympathetic and enteric nervous systems.



The sympathetic and parasympathetic systems provide a link between the CNS and peripheral organs.

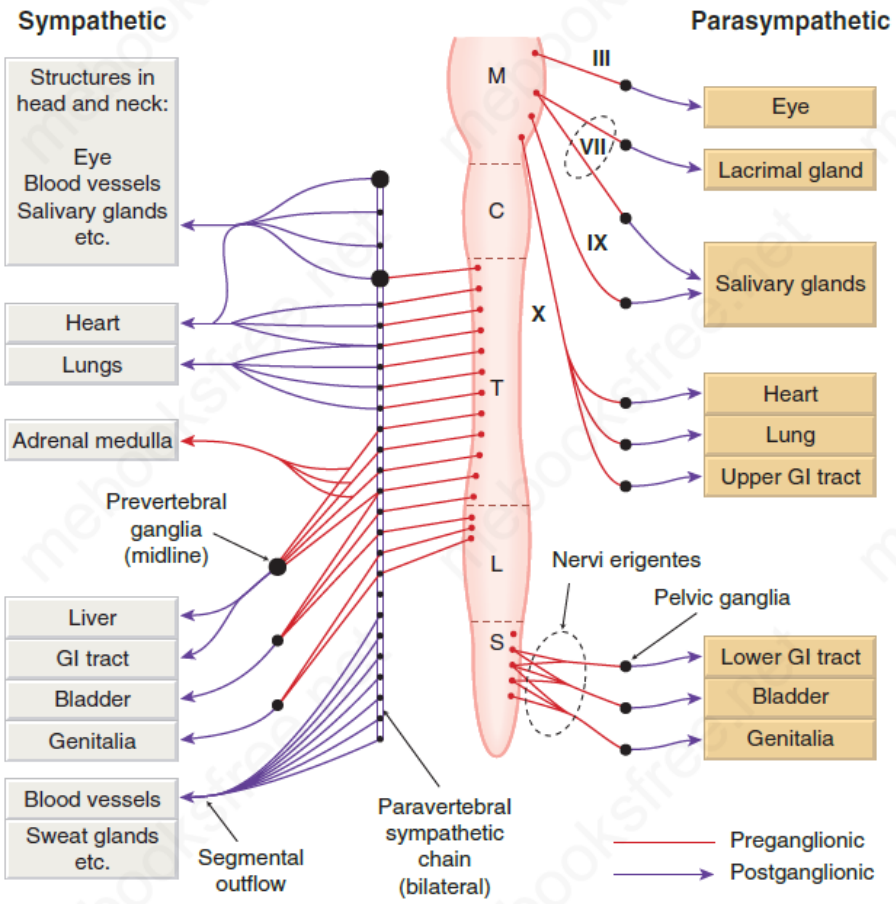
The enteric nervous system comprises the intrinsic nerve plexuses of the gastrointestinal tract, which are closely interconnected with the sympathetic and parasympathetic systems. The autonomic nervous system conveys all the outputs from the CNS to the rest of the body, except for the motor innervation of skeletal muscle. The enteric nervous system has sufficient integrative capabilities to allow it to function independently of the CNS.

The main processes that ANS regulates, to a greater or lesser extent, are:
• contraction and relaxation of vascular and visceral smooth muscle
• all exocrine and certain endocrine secretions
• the heartbeat
• energy metabolism, particularly in liver and skeletal muscle

The autonomic efferent pathway consists of two neurons arranged in series, whereas in the somatic motor system a single motor neuron connects the CNS to the skeletal muscle fiber. The two neurons in the autonomic pathway are known, respectively, as preganglionic and postganglionic. In the sympathetic nervous system, the intervening synapses lie in autonomic ganglia, which are outside the CNS, and contain the nerve endings of preganglionic fibers and the cell bodies of postganglionic neurons.

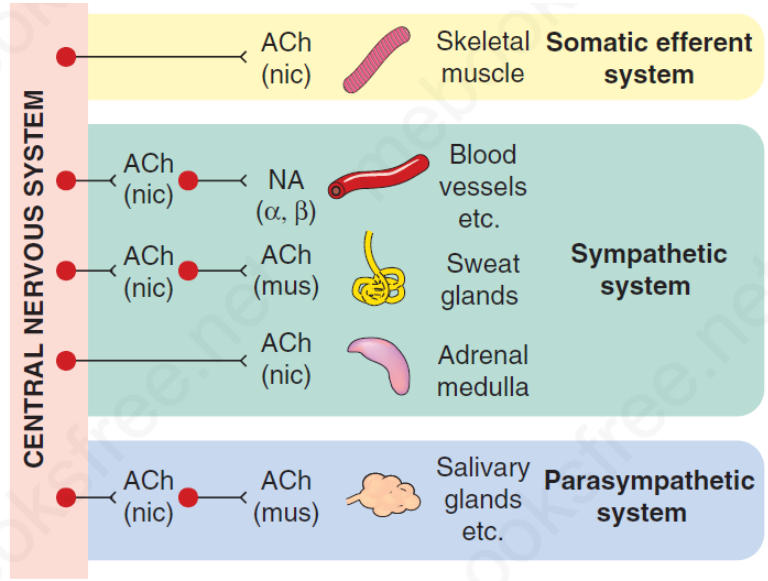
Anatomically, the sympathetic and the parasympathetic neurons originate in the CNS and emerge from two different spinal cord regions. The preganglionic neurons of the sympathetic system come from the thoracic and lumbar regions (T1 to L2) of the spinal cord, and they synapse in two cord-like chains of ganglia that run close to and in parallel on each side of the spinal cord. The preganglionic neurons are short in comparison to the postganglionic ones. Axons of the postganglionic neuron extend from the ganglia to tissues they innervate and regulate.
In most cases, the preganglionic nerve endings of the sympathetic nervous system are highly branched, enabling one preganglionic neuron to interact with many postganglionic neurons. This arrangement enables activation of numerous effector organs at the same time. (The adrenal medulla, like the sympathetic ganglia, receives preganglionic fibers from the sympathetic system. The adrenal medulla, in response to stimulation by the ganglionic neurotransmitter acetylcholine, secretes adrenaline (adrenaline), and lesser amounts of noradrenaline, directly into the blood)

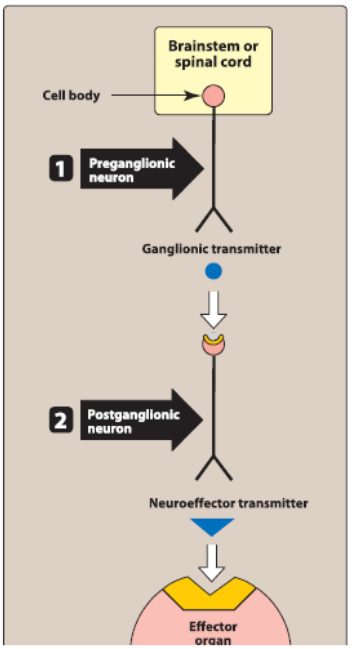
The parasympathetic preganglionic fibers arise from cranial nerves Ill (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus), as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near or on the effector organs. The vagus nerve accounts for 90% of preganglionic parasympathetic fibers. Postganglionic neurons from this nerve innervate most organs in the thoracic and abdominal cavity.
Thus, in contrast to the sympathetic system, the preganglionic fibers are long, and the postganglionic ones are short, with the ganglia close to or within the organ innervated. In most instances, there is a one-to-one connection between the preganglionic and postganglionic neurons, enabling discrete response of this system.



The enteric nervous system is the third division of the ANS. It is a collection of nerve fibers that innervate the gastrointestinal (GI) tract, pancreas, and gallbladder, and it constitutes the "brain of the gut." This system functions independently of the CNS and controls motility, exocrine and endocrine secretions, and microcirculation of the Gl tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

The efferent somatic nervous system differs from the ANS in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the ANS is involuntary. Responses in the somatic division are generally faster than those in the ANS.





Chemical signaling between cells

Neurotransmission in the ANS is an example of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators.

A. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body, exerting effects on broadly distributed target cells.

B. Local mediators

Most cells secrete chemicals that act locally on cells in the immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. Histamine and prostaglandins are examples of local mediators.

C. Neurotransmitters

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals. The release is triggered by arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular Ca2+ initiates fusion of synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell.

All neurotransmitters, and most hormones and local mediators, are too hydrophilic to penetrate the lipid bilayers of target cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs.

Acetylcholine: The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic.

Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs, also involves the release of acetylcholine. In the somatic
nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and voluntary muscles) is also cholinergic.

Noradrenaline: When noradrenaline is the neurotransmitter, the fiber is termed adrenergic.in the sympathetic system, noradrenaline mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs. Adrenaline secreted by the adrenal medulla (not sympathetic neurons) also acts as a chemical messenger in the effector organs. (A few sympathetic fibers, such as those involved in sweating, are cholinergic)

Adrenaline and noradrenaline bind to adrenergic receptors, and acetylcholine binds to cholinergic receptors.
Cholinergic receptors are further classified as nicotinic or muscarinic. Some receptors, such as the postsynaptic cholinergic nicotinic receptors in skeletal muscle cells, are directly linked to membrane ion channels and are known as ionotropic receptors. Binding of neurotransmitter to ionotropic receptors directly affects ion permeability All adrenergic receptors and cholinergic muscarinic receptors are G protein-coupled receptors (metabotropic receptors). Metabotropic receptors mediate the effects of ligands by activating a second messenger system inside the cell. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system.

Transmitters other than noradrenaline and acetylcholine are also abundant in the autonomic nervous system. The main ones are nitric oxide and vasoactive intestinal peptide (parasympathetic), ATP and neuropeptide Y (sympathetic). Others, such as 5-hydroxytryptamine, GABA and dopamine, also play a role.

Cholinergic system

Acetylcholine receptors:

1-Nicotinic ACh receptors (nAChRs) fall into three main classes: the muscle, ganglionic and CNS types.

Muscle receptors are confined to the skeletal neuromuscular junction; ganglionic receptors are responsible for fast transmission at sympathetic and parasympathetic ganglia; and CNS-type receptors are widespread in the brain, and are heterogeneous with respect to their molecular composition and location, Most of the CNS-type nAChRs are located presynaptically.

The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel (ionotropic receptor). Binding of two Ach molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell.

2-Muscarinic receptors (mAChRs) are typical G protein–coupled receptors, and five molecular subtypes (M1–M5) are known. The odd-numbered members of the group (M1, M3, M5) couple with Gq to activate the inositol phosphate pathway, while the even-numbered receptors (M2, M4) act through Gi to open potassium (K) channels causing membrane hyperpolarization; they also inhibit adenylyl cyclase but intracellular cAMP is usually low.

M1 receptors ('neural') are found mainly on CNS and peripheral neurons and on gastric parietal cells. Its selectively blocked by pirenzepine.

M2 receptors ('cardiac') causing decrease in cardiac rate and force of contraction (mainly of atria). They are selectively blocked by gallamine. M2-receptor activation is responsible for cholinergic inhibition of the heart, as well as presynaptic inhibition in the CNS and periphery.

M3 receptors (glandular/smooth muscle) produce mainly excitatory effects, i.e. stimulation of glandular secretions (salivary, bronchial, sweat, etc.) and contraction of visceral smooth muscle. Also occur in specific locations in the CNS. Darifenacin is an M3-selective receptor antagonist whereas Cevimeline is a selective agonist.

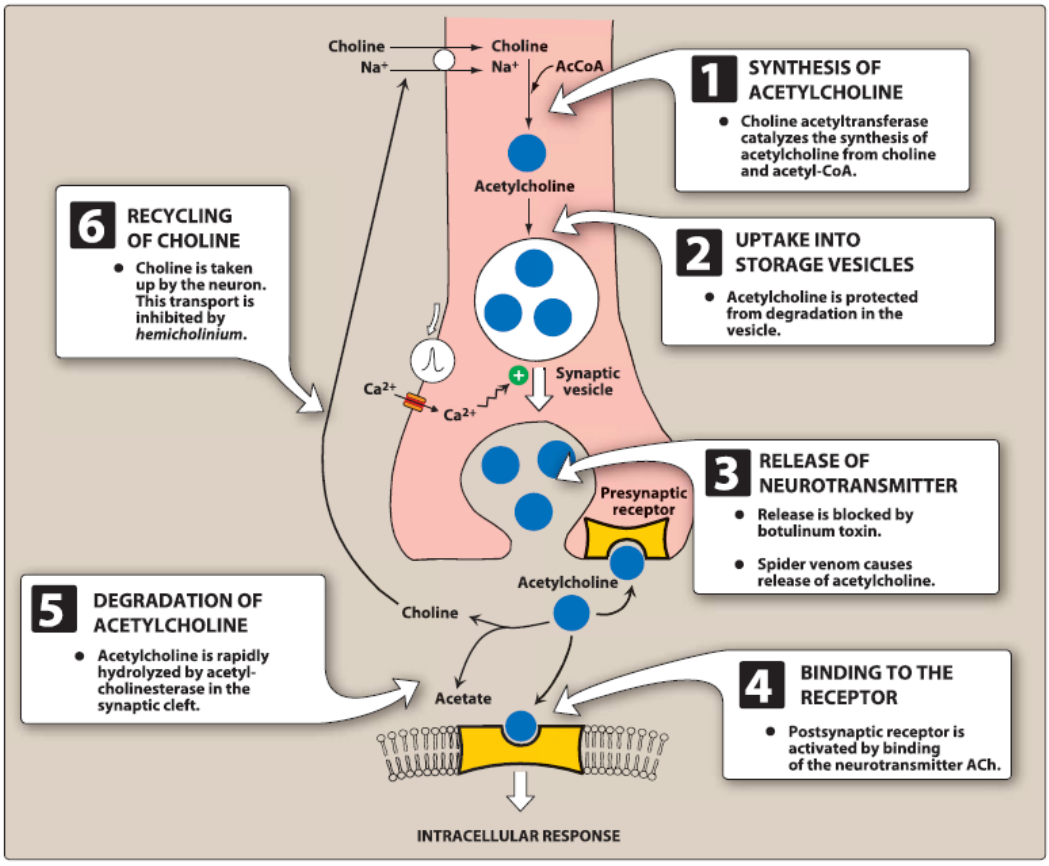
M4 and M5 receptors are largely confined to the CNS, and their functional role is not well understood, although mice lacking these receptors do show behavioural changes. Mamba toxin MT3 is a selective M4 antagonist

All mAChRs are activated by pilocarpine and blocked by atropine.

Acetylcholine synthesis and release

Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug hemicholinium. (Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane). The uptake of

choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.
ACh is packaged and stored into presynaptic vesicles by an active transport process.
The mature vesicle contains not only ACh but also adenosine triphosphate (ATP) and proteoglycan.
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.
ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, to presynaptic receptors on the membrane of the neuron that released ACh, or to other targeted presynaptic receptors.
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, as mediated by second messenger molecules.
The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft.



Cholinergic agonists

1-Direct-acting cholinergic agonists:

Cholinergic agonists mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic) Like pilocarpine and bethanecol. All direct-acting cholinergic drugs have a longer duration of action than ACh. The direct acting agonists show little specificity in their actions, which limits clinical usefulness.

Acetylcholine is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases.
Its actions include the following:
1. Decrease in heart rate and cardiac output: ACh IV produces a brief decrease in cardiac rate (bradycardia) and cardiac output (M2), mainly because of a reduction in the rate of firing at the sinoatrial (SA) node as normal vagal activity regulates the heart by the release of ACh at the SA node.

2. Decrease in blood pressure: Injection of ACh causes vasodilation and lowering of blood pressure. ACh activates M3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine.
3- Non vascular smooth muscle: Smooth muscle generally contracts in direct response to muscarinic agonists, in contrast to their indirect effect via NO on vascular smooth muscle. Peristaltic activity of the gastrointestinal tract is increased, which can cause colicky pain, and the bladder and bronchial smooth muscle also contract. Contraction of airway smooth muscle is mediated by M3 muscarinic receptors.
4-Sweating, lacrimation, salivation (M3) and bronchial secretion. Muscarinic agonists stimulate exocrine glands. The combined effect of bronchial secretion and constriction can interfere with breathing.
5-Effects on the eye. Ocular effects of muscarinic agents are clinically important. The parasympathetic nerves to the eye supply the constrictor pupillae muscle (Miosis), which runs circumferentially in the iris, and the ciliary muscle, which adjusts the curvature of the lens (accommodation of vision, mainly M3).
6- In addition to these peripheral effects, muscarinic agonists that penetrate the blood–brain barrier produce marked central effects due to activation of muscarinic (mainly M1) receptors in the brain. These include tremor, hypothermia and increased locomotor activity (and cognition)

Generally, adverse effects include blurred vision, cramps and diarrhea, low blood pressure and decreased heart rate, nausea and vomiting, salivation and sweating, shortness of breath, and increased urinary frequency.

-Currently there are few important uses for muscarinic agonists

Bethanechol

Bethanechol is an unsubstituted carbamyl ester, structurally related to Ach. It is not hydrolyzed by AChE due to the esterification of carbamic acid, although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions but does have strong muscarinic activity.

Bethanechol directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the sphincter muscles is relaxed. These effects stimulate urination that's why bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.

Carbachol (carbamylcholine)

Carbachol has both muscarinic and nicotinic actions. like bethanechol, carbachol is an ester of carbamic acid and a poor substrate for AChE. It is biotransformed by other esterases, but at a much slower rate.

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.

Pilocarpine

The alkaloid pilocarpine is a tertiary amine and is stable to hydrolysis by AChE , Compared with ACh and its derivatives, it is far less potent but is uncharged and can penetrate the CNS at therapeutic doses. Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

Applied topically to the eye, pilocarpine produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation.

Pilocarpine is used to treat glaucoma and is the drug of choice for emergency lowering of intraocular

pressure 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.

Pilocarpine or cevimeline, a selective M3 agonist, can be used to increase salivation and lacrimal secretion in patients with dry mouth or dry eyes Xerostomia (e.g. following irradiation, or in patients with autoimmune, damage to the salivary or lacrimal glands as in Sjögren's syndrome).

2-Indirect-acting cholinergic agonists: Anticholinesterase agents

A-Reversible

AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound.

Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) indirectly provide cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space.
Therefore, these drugs can provoke a response at all cholinoceptors, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain.

Edrophonium
Edrophonium is the prototype short-acting AChE inhibitor. Edrophonium binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It has a short duration of action of 10 to 20 minutes due to rapid renal elimination. Edrophonium is a quaternary amine, and its actions are limited to the periphery. It is used in the diagnosis of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes the degradation of the nicotinic receptors, making fewer receptors available for interaction with ACh.

Physostigmine
Physostigmine is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.
Physostigmine stimulates not only the muscarinic and nicotinic sites of the ANS, but also the nicotinic receptors of the NMJ. Muscarinic stimulation can cause contraction of Gl smooth muscles, miosis bradycardia, and hypotension. Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses). Its duration of action is about 30 minutes to 2 hours.
Physostigmine is used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, and to reverse the effects of NMBs.

Neostigmine
Neostigmineis a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits AChE in a manner similar to physostigmine. Unlike physostigmine, neostigmine has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the Gl tract, and does not enter the CNS. Its effect on skeletal muscle
is greater than physostigmine, and it can stimulate contractility before it paralyzes. Neostigmine has an intermediate duration of action, usually 30 minutes to 2 hours.
It is used to stimulate the bladder and Gl tract and as an antidote for competitive neuromuscular-blocking agents. Neostigmine is also used to manage symptoms of myasthenia gravis.
Pyridostigmine is another cholinesterase inhibitor used in the chronic management of myasthenia gravis. Its duration of action is intermediate (3 to 6 hours) but longer than that of neostigmine. Adverse effects are similar to those of neostigmine.

Tacrine, donepezil, rivastigmine, and galantamine
Patients with Alzheimer disease have a deficiency of cholinergic neurons and therefore lower levels of ACh in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function.

B-Irreversible
Echothiophate is an organophosphate that covalently binds via its phosphate group at the active site of AChE. Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl groups. The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as pralidoxime, to break the bond between the remaining drug and the enzyme.
Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties}, and convulsions. Echothiophate produces intense miosis and, thus, has found therapeutic use. Atropine in high dosages can reverse many of the peripheral and some of the central muscarinic effects of echothiophate.
A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma. However,
echothiophate is rarely used due to its side effect profile, which includes the risk of cataracts.

Cholinergic Antagonists

1-Antimuscarinic agents
Commonly known as anticholinergic drugs, these agents (for example, atropine and scopolamine) block muscarinic receptors causing inhibition of muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia.

Atropine
Atropine is a tertiary amine and has a high affinity for muscarinic receptors and binds competitively to prevent ACh from binding. Atropine acts both centrally and peripherally. General actions last about 4 hours; however, effects of topical administration in the eye may persist for days.

a-Eye: Atropine blocks muscarinic activity in the eye, resulting in mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). intraocular pressure may rise dangerously.

b. Gastrointestinal (GI): Atropine (as the active isomer,L-hyoscyamine) can be used as an antispasmodic to reduce activity of the Gl tract. Atropine and scopolamine) are probably the most potent antispasmodic drugs available. Although gastric motility is reduced, hydrochloric acid production is not significantly affected.
Doses of atropine that reduce spasms also reduce saliva secretion, and urination.
c. Cardiovascular: At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of atropine cause a progressive increase in heart rate by blocking M2 receptors on the sinoatrial node.
d. Secretions: Atropine blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). Sweat and lacrimal glands are similarly affected.

Therapeutic uses
a- 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. Shorter-acting antimuscarinics (cyclopentolate and tropicamide have largely replaced atropine due to prolonged mydriasis observed with atropine (days vs. hours with other agents).
b. Antispasmodic
c. To treat bradycardia of varying etiologies.
d. Antisecretory: Atropine is sometimes used as an antisecretory agent to block secretions in the respiratory tract prior to surgery.
e. Antidote for cholinergic agonists: Atropine is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as physostigmine, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances
that block cholinesterases).

Adverse effects: Depending on the dose, atropine may cause dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium

Scopolamine
Scopolamine, another tertiary amine plant alkaloid, produces peripheral effects similar to those of atropine. However, scopolamine has greater action on the CNS and a longer duration of action as compared to atropine.
Scopolamine is used for the prevention of motion sickness and postoperative nausea and vomiting. For
motion sickness, it is available as a topical patch that provides effects for up to 3 days.

Aclidinium, glycopyrrolate, ipratropium, and tiotropium
lpratropium and tiotropium are quaternary derivatives of atropine, and glycopyrrolate and aclidinium synthetic quaternary compounds.

lpratropium is classified as a short-acting muscarinic antagonist, while glycopyrrolate, tiotropium, and aclidinium are classified as long-acting muscarinic antagonists based on the duration of action.
These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease.
lpratropium and tiotropium are also used in the acute management of bronchospasm in asthma and chronic management of asthma, respectively. All of these agents are delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

Tropicamide and cyclopentolate
These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of atropine. Tropicamide produces mydriasis for 6 hours and cyclopentolate for 24 hours.

Benztropine and trihexyphenidyl
Benztropine and trihexyphenidyl are useful as adjuncts with other antiparkinson agents to treat Parkinson disease and other types of parkinsonian syndromes, including antipsychotic induced extrapyramidal symptoms.

Oxybutynin and other anti muscarinic agents for overactive bladder
Oxybutynin, darifenacin, fesoterodine, solifenacin, tolterodine, and trospium are synthetic atropine-like drugs with antimuscarinic actions.
By competitively blocking muscarinic (M3) receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced.
Darifenacin and solifenacin are relatively more selective M3 muscarinic receptor antagonists; however, the other drugs are mainly nonselective muscarinic antagonists, and binding to another muscarinic receptor subtypes may contribute to adverse effects.
These agents are used for management of overactive bladder and urinary incontinence. Oxybutynin is also
used in patients with neurogenic bladder. Trospium is a quaternary compound that minimally crosses the blood-brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with
dementia.
Adverse effects include dry mouth, constipation, and blurred vision.

2-Ganglionic blockers, e.g Mecamylamine
Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. Except for nicotine,

the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses of the nondepolarizing blockers are complex and mostly unpredictable.
Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.
Nicotine is a component of cigarette smoke and a prototype nicotinic agonist; it is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitters, due to effects on both sympathetic and parasympathetic ganglia.

3-Neuromuscular blocking agents
These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscle. They possess some chemical similarities to ACh and act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ.
Neuromuscular blockers (NMBs) are clinically useful to facilitate rapid intubation when needed due to respiratory failure. During surgery, they are used to facilitate endotracheal intubation and provide complete muscle relaxation at lower anesthetic doses.

A-Non-depolarizing (competitive) blockers
D-Tubocurarine, cisatracurium, mivacurium, pancuronium, vecuronium

Mechanism of action
a. At low doses: NMBs competitively block ACh at the nicotinic receptors. They compete with ACh at the receptor without stimulating it, thus preventing depolarization of the muscle cell membrane and inhibiting muscular contraction. Their competitive action can be overcome by administration of cholinesterase inhibitors, such as neostigmine and edrophonium, which increase the concentration of ACh in the NMJ.

b. At high doses: Nondepolarizing agents can block the ion channels of the motor end plate. This leads to further weakening of neuromuscular transmission, reducing the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers.

All NMBs are injected intravenously or occasionally intramuscularly. These agents possess two or more quaternary amines in their bulky ring structure that prevent absorption from the gut. They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Drug action is terminated in a variety of ways. Pancuronium is excreted unchanged in urine. Cisatracurium undergoes organ-independent metabolism (via Hofmann elimination) to laudanosine, which is further metabolized and renally excreted. The amino steroid drugs vecuronium and rocuronium are deacetylated in the liver and excreted unchanged in bile. Mivacurium is eliminated by plasma cholinesterase. Adverse effects: In general, these agents are safe with minimal side effects.

Drugs such as gentamicin and tobramycin inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with competitive blockers, enhancing neuromuscular blockade.
Calcium channel blockers may increase the neuromuscular blockade of competitive blockers.

B-Depolarizing agents
Succinylcholine is the only depolarizing muscle relaxant in use today.
Succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarize the junction. Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a longer time and providing sustained depolarization of the muscle cell.
Duration of action is dependent on diffusion from the motor end plate and hydrolysis by plasma cholinesterase also called butyrylcholinesterase or pseudocholinesterase. Genetic variants in which plasma cholinesterase levels are low or absent lead to prolonged neuromuscular paralysis. The depolarizing agent first causes opening of the sodium channel associated with nicotinic receptors, which results in depolarization of the receptor . This leads to a transient twitching of the muscle (fasciculations) Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (phase II) and flaccid paralysis.

Succinylcholine is useful when rapid endotracheal intubation is required. It is also used during electroconvulsive shock treatment.

Adverse effects: Hyperthermia, Apnea, Hyperkalemia.

Reference:
Lippincott illustrated review Pharmacology, P70 Chapter 5, Seventh edition 2017.
@Rojgar Hamed, 4th September 2022