Cholinergic drugs

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Cholinergic drugs

- ❖Cholinergic Agent -A cholinergic drug is a drug that acts on the peripheral nervous system, the central nervous system, or both and enhances the effects that are mediated by acetylcholine.
- ❖Cholinergic medications are a category of pharmaceutical agents that act upon the neurotransmitter acetylcholine, the primary neurotransmitter within the parasympathetic nervous system (PNS).
- ➢**There are two broad categories of cholinergic drugs:**

direct-acting and indirect-acting.

1. The direct-acting cholinergic agonists work by directly binding to and activating the muscarinic receptors. Examples of direct-acting cholinergic agents include

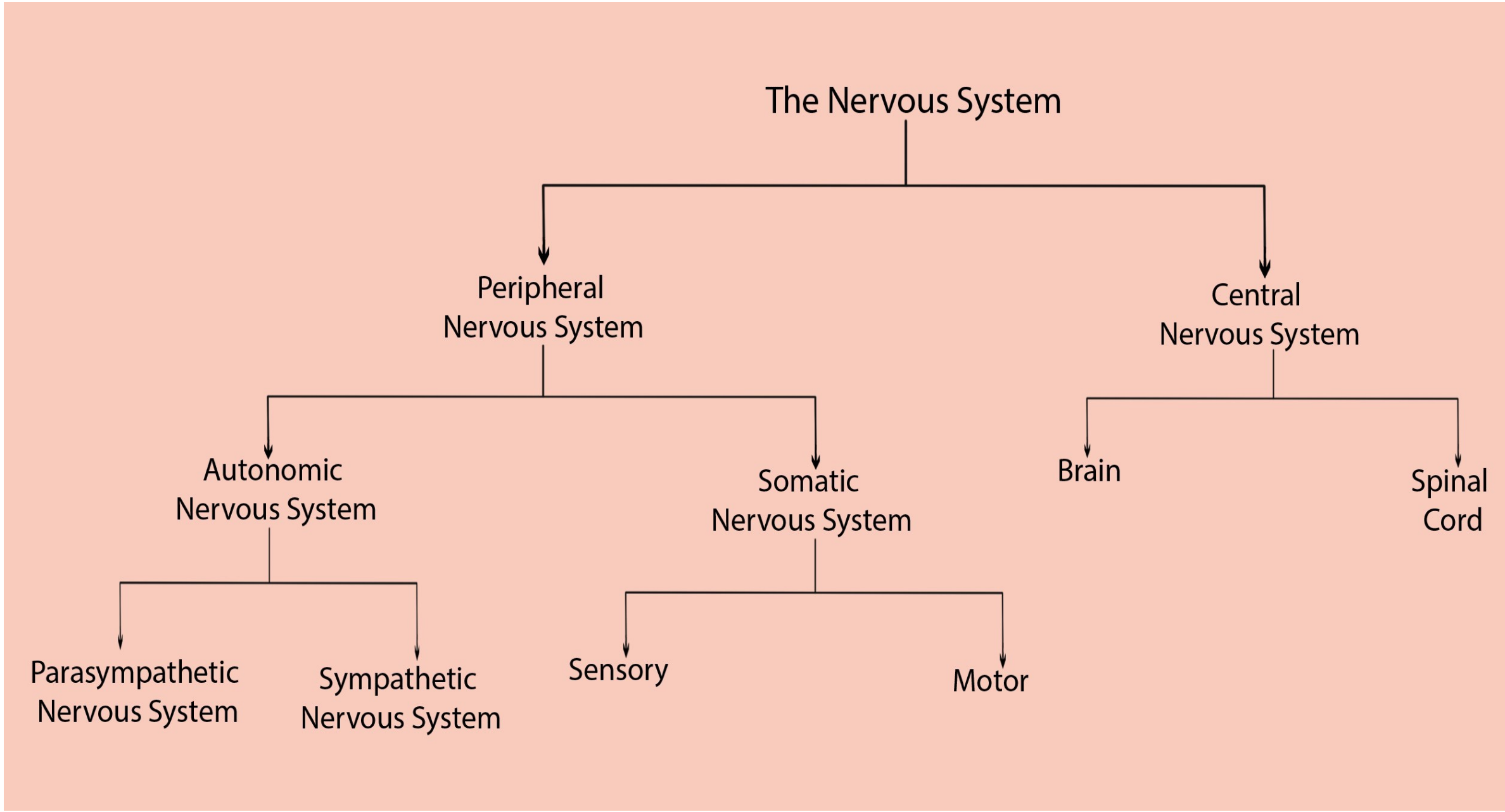
- ○ choline esters (acetylcholine, methacholine, carbachol, bethanechol)
- ○ alkaloids (muscarine, pilocarpine, cevimeline).

2. Indirect-acting cholinergic agents increase the availability of acetylcholine at the cholinergic receptors. These include

- ○ reversible agents (physostigmine, neostigmine, pyridostigmine, edrophonium, rivastigmine, donepezil, galantamine) and
- ○ irreversible agents (echothiophate, parathion, malathion, diazinon, sarin, soman).

Organization of the Nervous System

- The human body is composed of one nervous system that can be subdivided into a **central nervous system** (CNS) and a **peripheral nervous system** (PNS).
- The brain and spinal cord make up the CNS, while the PNS is made up of any nervous tissue outside the brain and spinal cord, including 12 pairs of cranial nerves, 31 pairs of spinal nerves, and peripheral sensory receptors.
- The PNS can be further subdivided into the ANS and the somatic nervous system depending on which type of muscle it innervates and whether or not it is voluntarily controlled.


The Nervous System
Peripheral Nervous System
Central Nervous System
Autonomic Nervous System
Somatic Nervous System
Brain
Spinal Cord
Parasympathetic Nervous System
Sympathetic Nervous System
Sensory
Motor

The ANS

- The ANS can be subdivided into:
- **sympathetic** and **parasympathetic nervous systems**.
- It is the sympathetic branch of the ANS that is responsible for the "fright, flight, or fight" response elicited by the encounter with the bear.
- Another example of a sympathetic response that might be a little closer to home would be your body's reaction after being jilted by your fiancé at the alter.
- You can imagine that your heart rate would increase, you might start to hyperventilate, and you definitely would have no desire to eat.
- A sympathetic response can also occur during illness or physical trauma, from anxiety, or pretty much any stressful situation.
- Such a response is characterized by increased heart rate and blood pressure, goosebumps, pupil (pupil dilation=**mydriasis**), bronchiole dilation, and increased blood flow to cardiac and skeletal muscles.

"AUTONOMIC NERVOUS SYSTEM RESPONSE"

Sympathetic Response

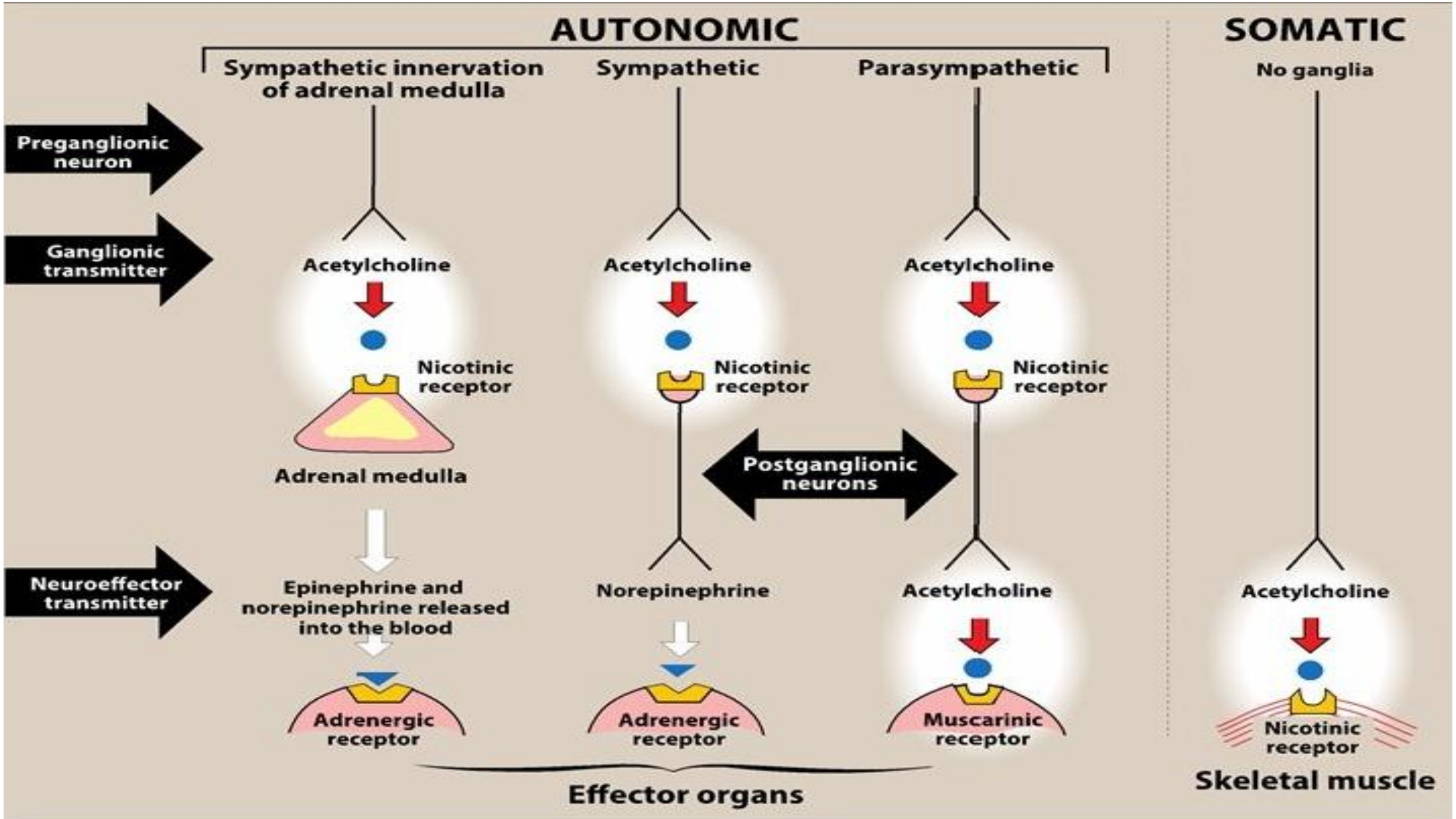
"Fight or Flight"

(Stress)

Parasympathetic Response

"Rest & Digest"

(Peace)


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
No ganglia
Preganglionic neuron
Ganglionic transmitter
Neuroeffector transmitter
Acetylcholine
Acetylcholine
Acetylcholine
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Epinephrine and norepinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Skeletal muscle

Cholinergic Drugs Action

- The parasympathetic division on the other hand, is responsible for energy conserving **("rest and digest")** activities, including decreased heart rate, blood pressure, and respiration; constriction of the pupil (**miosis**); increased secretions and peristalsis of the digestive tract; and increased urination. The acronym **SLUD (S**alivation, **L**acrimation **U**rination, and **D**efecation) may be useful to remember some of the responses caused by the parasympathetic division in certain organs.
- Other than some sweat and salivary glands, most secretions of the body increase when the parasympathetic nervous system is activated.

➢Cholinergic Drugs “rest and digest” system

- **“SLUDGE”**
- Salivation
- Lacrimation
- Urinary incontinence
- Diarrhea
- Gastrointestinal cramps
- Emesis

Action of ANS

- The ANS innervates visceral organs-organs which are unconsciously controlled by the brain.
- Visceral organs contain either smooth or cardiac muscle; respective examples include the intestines and the heart.
- Interestingly, if a visceral organ is removed from the body and placed in an oxygenated Ringer's solution, it will continue to undergo peristalsis (wave-like smooth muscle contractions of the gastrointestinal tract) or beat without even being connected to the ANS. This is called auto rhythmicity.
- Why then, do you ask, is the ANS even necessary for these organs to function? The answer is, it is not. But, the ANS is necessary to regulate the activity of these organs, essentially causing them to speed up or slow down in order to maintain homeostatic conditions in the body.

Action of ANS

- Usually, each visceral organ is innervated by nerves from both sympathetic and parasympathetic divisions, and effects of these divisions are most often in opposition to one another.
- This type of "wiring" is called **dual autonomic innervation.** The heart is a good example of this. It is innervated by fibers from both parasympathetic and sympathetic divisions that oppose one another. Increasing parasympathetic stimulation to the heart will cause decreased heart rate, while increasing sympathetic activity will increase heart rate and force of contraction.

Two neuron system

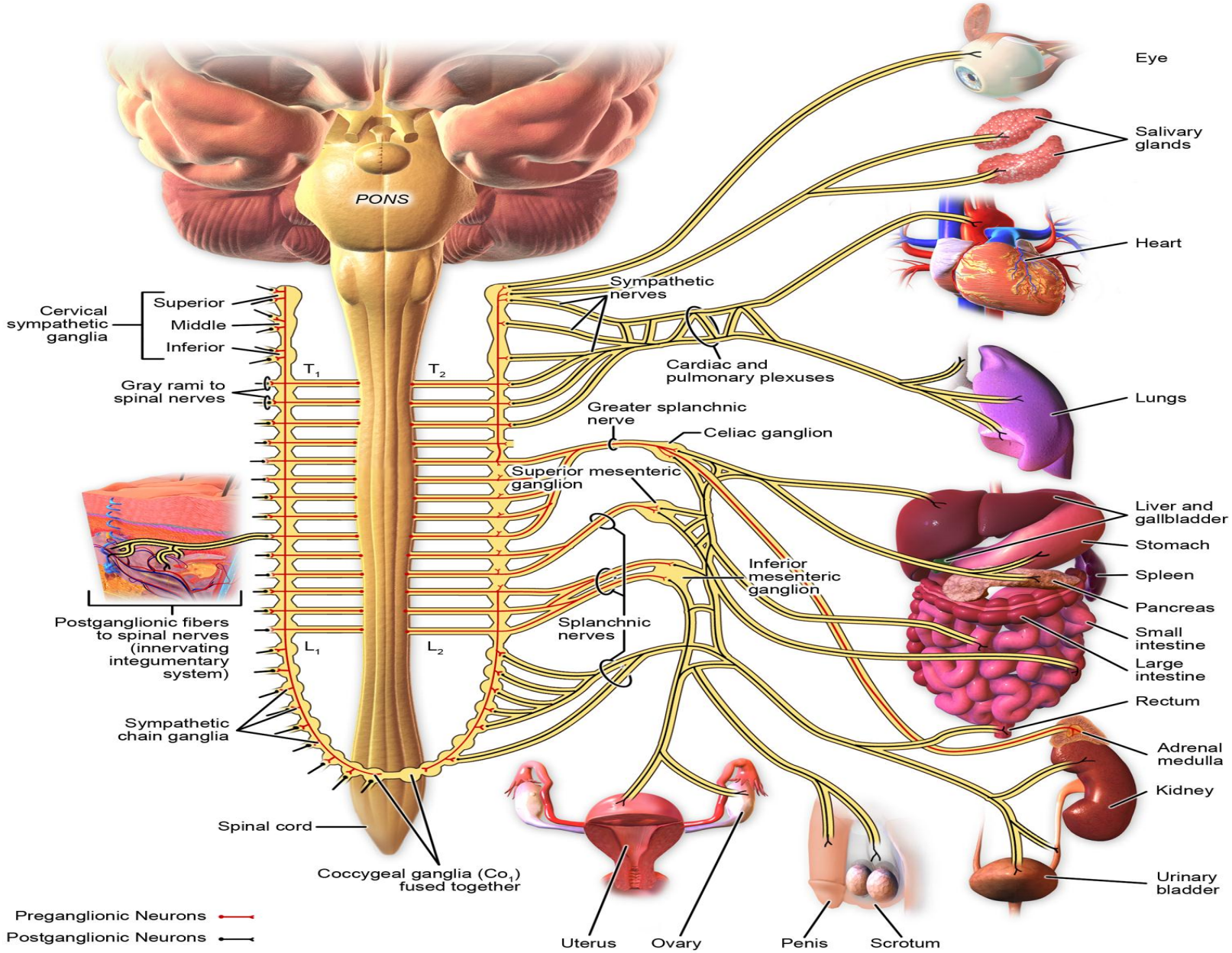
- The ANS uses a “two neuron system” to relay electrical signals from the CNS to **effectors** (organs, glands, and vessels). This is different from the somatic motor division where just one neuron extends from the CNS to skeletal muscle. Parasympathetic and sympathetic divisions are “wired” similarly in that they both have a **preganglionic neuron** and **postganglionic neuron**. (a ganglia is a collection of cell bodies located outside the CNS).

Types of ganglia

- These neurons get their names from their anatomical location in relation to **autonomic ganglia**, or relay centers. Autonomic ganglia for the sympathetic division include -**sympathetic chain ganglia** which are located near the spinal column (labeled at the bottom of the chain in the SNS anatomy) and **collateral ganglia.**
- The collateral ganglia are located further away from the spinal column and are labeled Celiac, Superior mesenteric and Inferior mesenteric. Autonomic ganglia for the parasympathetic division are called **terminal ganglia** and these are located very near the effector they innervate. They are not labeled as there are so many places that parasympathetic neurons synapse with post ganglionic neurons in the very walls of the organs themselves.

Types of ganglia

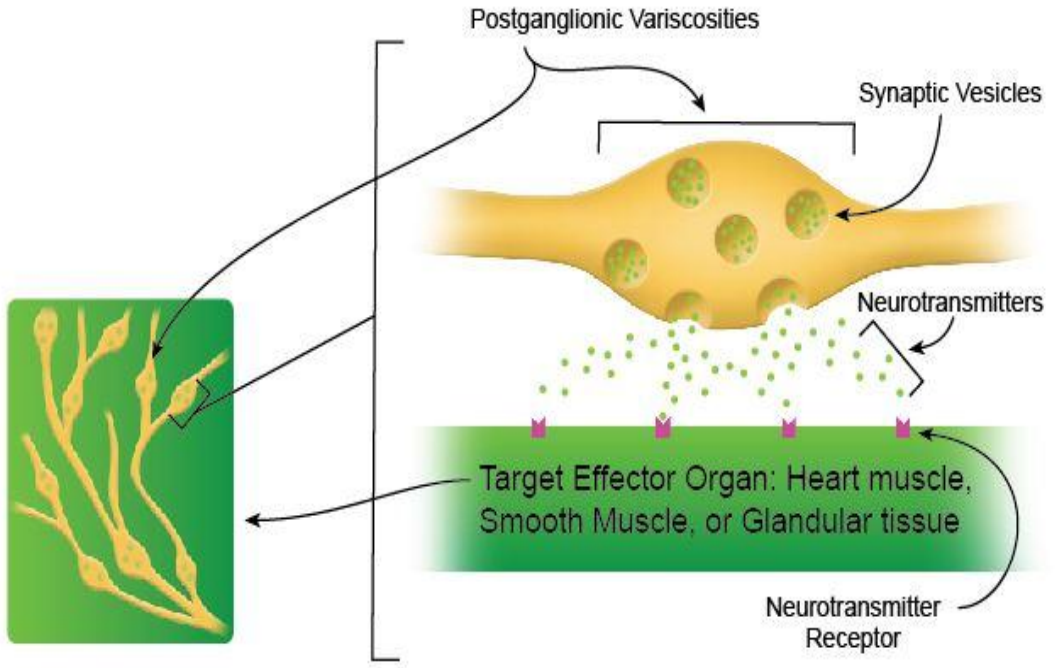
- The cell bodies for preganglionic neurons are located in either the brainstem or spinal cord, and their axon terminals are located in autonomic ganglia.
- In the ganglia, a neuron-to-neuron synapse relays information to the cell body of a postganglionic neuron.
- Postganglionic neurons, also located in the autonomic ganglia, then transmit the signal to effectors.
- The synapse between the postganglionic neuron and the effector is known as a neuroeffector synapse or neuroeffector junction.



Sympathetic Innervation

- In general, the sympathetic division uses shorter preganglionic neurons and longer postganglionic neurons while the parasympathetic division uses long preganglionic neurons and short postganglionic neurons.
- Postganglionic release neurotransmitter onto effector organs.
- However, the synapse is a little unique.
- Rather than forming a nerve terminal at a synaptic juncition, we see many swellings (or variscosities) develop on the most distal segments of the postganglionic neuron and they secrete neurotransmitter onto the effector tissue (see image below).

Synapses on the effector organs from the autonomic postganglionic neurons occur through variscosities as seen here

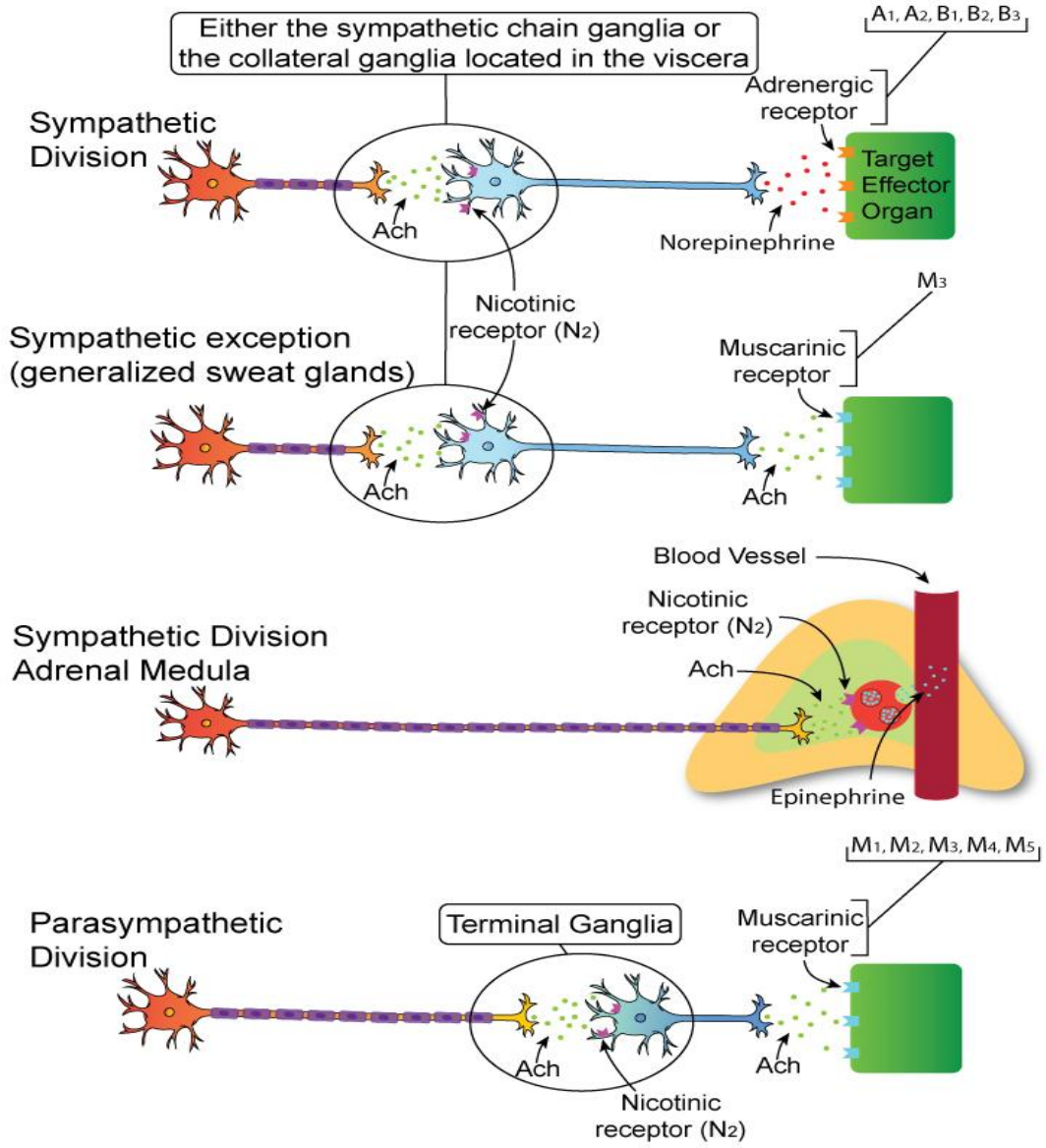


	Sympathetic		Parasympathetic	
	Preganglionic Neuron	**Postganglionic Neuron**	**Preganglionic Neuron**	**Postganglionic Neuron**
Neuron Length	Short to Medium	Medium to Long	Long	Short
Neurotransmitter Released	ACH	NE (except sweat glands and some blood vessels – ACH)	ACH	ACH

Acetylcholine and Norepinephrine are neurotransmitters.

ANS receptors

- ANS preganglionic and postganglionic neurons and locations of ANS receptors.
- Nicotinic receptors are located on the postganglionic neurons of the sympathetic and parasympathetic cell bodies.
- **Nicotinic** receptors respond to the binding of acetylcholine (ACH), **which causes an excitatory effect.**
- Muscarinic receptors are located on all parasympathetic effector cells and some (generalized sweat glands) sympathetic effector cells.
- **Muscarinic** receptors respond to the binding of ACH, and may have **an excitatory or inhibitory effect**. Adrenergic receptors are located on most sympathetic effector cells.
- **Adrenergic receptors respond to the binding of norepinephrine (NE), which may have an excitatory or inhibitory effect.**



Neurotransmitters of the ANS

- Neurotransmitters are chemicals that travel across the synapse connecting two neurons, or between a neuron and an effector.
- For example, when we discussed the neuromuscular junction we were talking about a neuron-effector synapse and the neurotransmitter used was **acetylcholine (ACH)**.
- ACH is also one of the neurotransmitters used by the ANS.
- **Cholinergic neurons** produce ACH and store ACH in their synaptic terminals. The preganglionic neuron for both parasympathetic and sympathetic nervous systems is cholinergic.
- The postganglionic neuron of the parasympathetic division is also cholinergic. The postganglionic neuron for the sympathetic division is usually an **adrenergic neuron** which means that it produces **norepinephrine (NE)** as its neurotransmitter.
- Sympathetic postganglionic neurons innervating sweat glands and some blood vessels are the exception-; they are cholinergic and release ACH.

Neurotransmitters

- Major neurotransmitters of ANS are *acetylcholine* (*ACh*) and *norepinephrine* (*NE*)
  - Ach (same as ACh used by somatic motor neuron) is released by **cholinergic fibers** at:
    - All ANS preganglionic axons and
    - All parasympathetic postganglionic axons
  - NE is released by **adrenergic fibers** at:
    - Almost all sympathetic postganglionic axons, except those at sweat glands (release ACh)
- Effects of neurotransmitter depends on whether it binds to **cholinergic receptor** or **adrenergic receptor**

Acetylcholine Neurotransmission

- Acetylcholine in the Autonomic Nervous System

In the autonomic nervous system, acetylcholine (ACh) is the neurotransmitter in the preganglionic sympathetic and parasympathetic neurons

- ACh in the Peripheral Nervous System

In the peripheral nervous system, ACh is the neurotransmitter at the neuromuscular junction between the motor nerve and skeletal muscle.

- ACh in the Central Nervous System

In the central nervous system, ACh is found primarily in interneurons

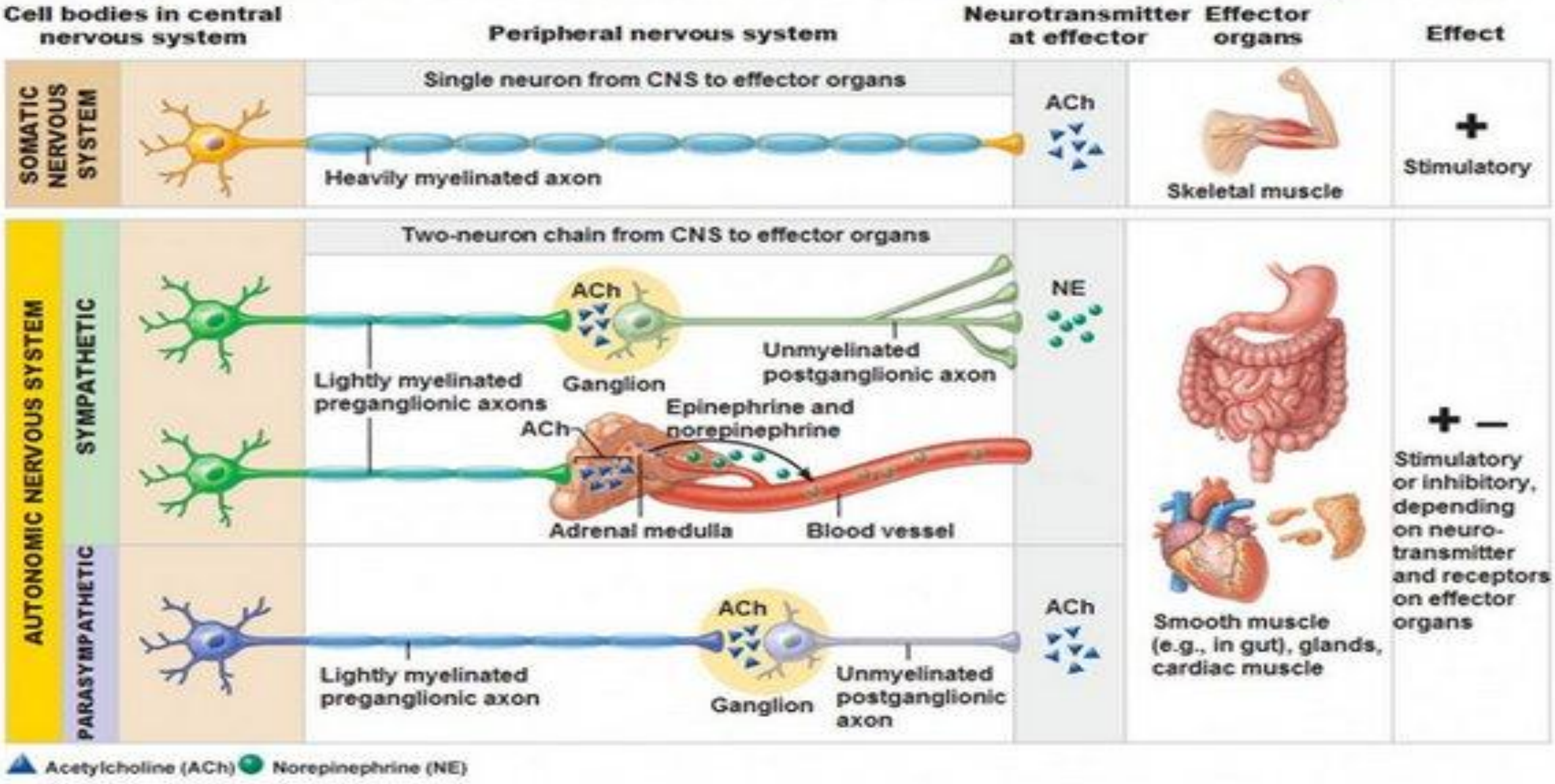
Epinephrine

- **Epinephrine** is a hormone and neurotransmitter used to treat allergic reactions, to restore cardiac rhythm, and to control mucosal congestion, glaucoma, and asthma.
- **Epinephrine, also known as adrenaline,** produced by the adrenal glands that can also be used as a drug due to its various important functions. Though it has long been used in the treatment of hypersensitivity reactions.
- **Epinephrine acts on alpha and beta-adrenergic receptors**. Through its action on alpha-adrenergic receptors, epinephrine minimizes the vasodilation and increased the vascular permeability that occurs during anaphylaxis. Epinephrine relaxes the smooth muscle of the bronchi and iris and is a histamine antagonist

Difference Between Norepinephrine and Epinephrine

- **Definition**
- **Norepinephrine:** Norepinephrine is a hormone which serves as a neurotransmitter.
- **Epinephrine:** Epinephrine is a hormone that increases rates of blood circulation, breathing, and carbohydrate metabolism.
- **Alternative Names**
- **Norepinephrine:** Norepinephrine is also called noradrenaline.
- **Epinephrine:** Epinephrine is also called adrenaline.
- **Production**
- **Norepinephrine:** Norepinephrine is produced in adrenal medulla and sympathetic nerves.
- **Epinephrine:** Epinephrine is exclusively produced in the adrenal medulla.
- **Significance**
- **Norepinephrine:** Norepinephrine is used as a drug to raise blood pressure.
- **Epinephrine**: Epinephrine prepares muscles for exertion.
- **Chemical Structure**
- **Norepinephrine**: Norepinephrine is a catecholamine.
- **Epinephrine:** Epinephrine is structurally similar to norepinephrine, except for the methyl group present in it.
- **Function**
- **Norepinephrine:** Norepinephrine raises the heart rate and modulates bold pressure.
- **Epinephrine:** Epinephrine is an effective antihistamine, which is used in the treatment for shock.

Comparison of Autonomic and Somatic Motor Systems



Cholinergic Receptors

- Preganglionic neurons of both sympathetic and parasympathetic divisions produce and release ACH. The receptors for ACH are known as cholinergic receptors.
- **There are two main subtypes of cholinergic receptors determined by Location and Action once stimulated -: Nicotinic and Muscarinic.**

➢ **Nicotinic receptors located in ganglia of both the PANS and SNS**

- ***Named Nicotinic because they can be stimulated by alkaloid nicotine.***

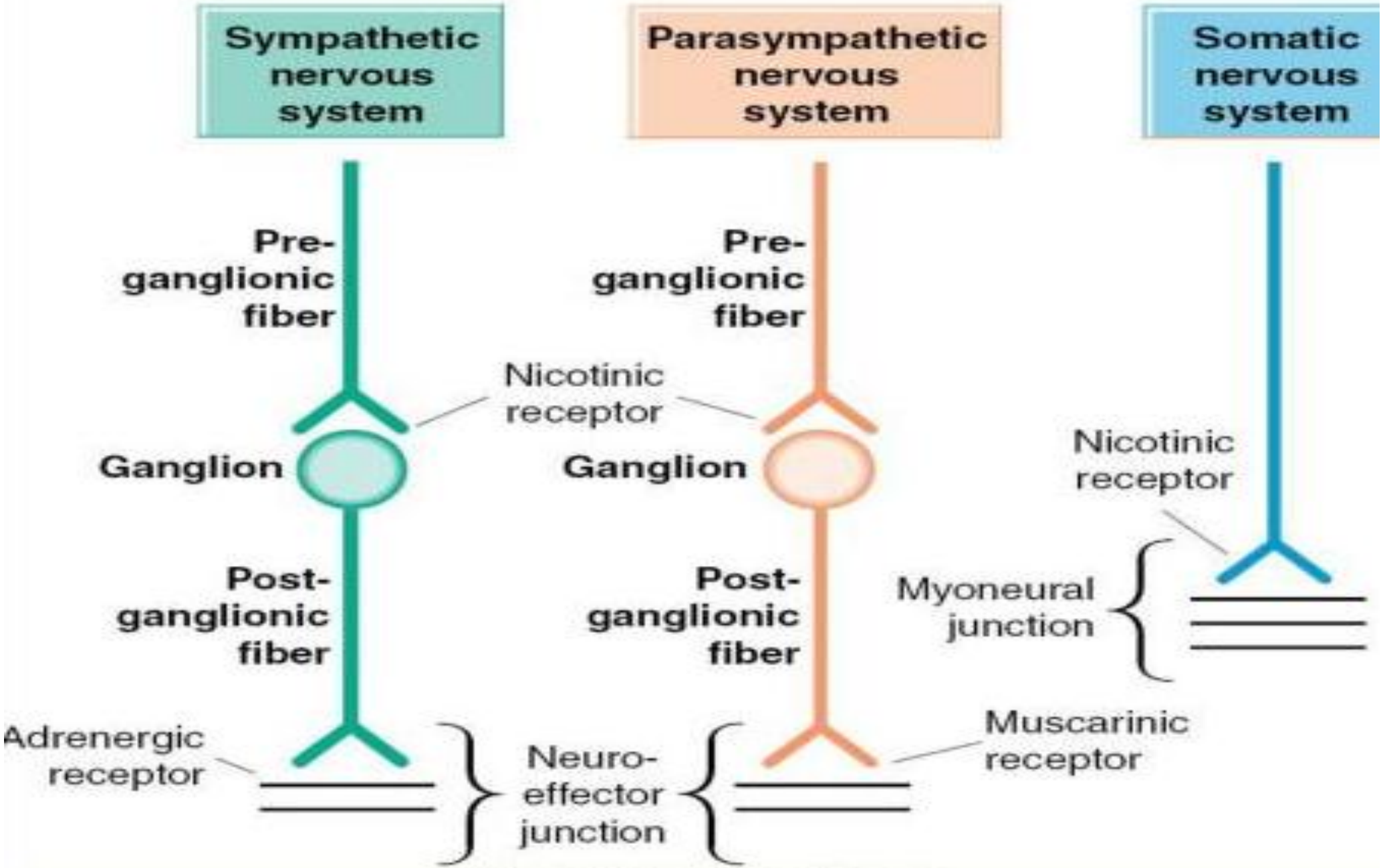
➢ **Muscarinic Receptors located in postsynaptically in the effector organs of the PSNS**

- **Smooth muscle**
- **Cardiac muscle**
- **Glands**
- ***Named muscarine because they can be stimulated by the alkaloid muscarine***

- They are named after alkaloids found in tobacco and certain mushrooms respectively.
- The alkaloid nicotine specifically activates nicotinic cholinergic receptors, while muscarine activates muscarinic cholinergic receptors, and ACH activates both types.
- The cell bodies of postganglionic neurons for both sympathetic and parasympathetic nervous systems express nicotinic receptors

Adrenergic Receptors

- Neurons that produce and release the neurotransmitter NE are known as adrenergic neurons.
- NE is secreted by postganglionic neurons of the sympathetic nervous system and binds to **adrenergic receptors** expressed on effector cells.
- Epinephrine (EPI) released by the adrenal gland also binds to adrenergic receptors expressed on effectors .
- There are two main types of adrenergic receptors, namely, alpha and beta which have several subtypes.


Sympathetic nervous system
Parasympathetic nervous system
Somatic nervous system
Pre-ganglionic fiber
Pre-ganglionic fiber
Nicotinic receptor
Ganglion
Ganglion
Nicotinic receptor
Post-ganglionic fiber
Post-ganglionic fiber
Myoneural junction
Adrenergic receptor
Neuro-effector junction
Muscarinic receptor

Cholinergic medications

- Cholinergic medications are a category of pharmaceutical agents that act upon the neurotransmitter acetylcholine, the primary neurotransmitter within the parasympathetic nervous system (PNS).
- There are two broad categories of cholinergic drugs:
- **direct-acting and indirect-acting.**
- **1. The direct-acting cholinergic agonists** work by directly binding to and activating the muscarinic receptors. Examples of direct-acting cholinergic agents include
- **Choline esters** (acetylcholine, methacholine, carbachol, bethanechol).
- **Alkaloids** (muscarine, pilocarpine, cevimeline).
- **2. Indirect-acting cholinergic agents** increase the availability of acetylcholine at the cholinergic receptors. These include:
- **Reversible agents** (physostigmine, neostigmine, pyridostigmine, edrophonium, rivastigmine, donepezil, galantamine).
- **Irreversible agents** (echothiophate, parathion, malathion, diazinon, sarin, soman).

Indications Cholinergic medications

- **Myasthenia gravis:** The initial first-line therapy for most patients is anticholinesterase medication, usually pyridostigmine. Neostigmine is also available but not commonly used.
- **Dementia:** Cholinesterase inhibitors like rivastigmine, donepezil, galantamine are the available medications for cognition and global functioning in patients with dementia of all causes. Their primary use is in mild to moderate Alzheimer disease. These medications have off label use for dementia from Parkinson disease and Lewy body dementia.
- **Ophthalmology:** Pilocarpine and carbachol work by increasing the aqueous outflow and hence decrease the intra-ocular tension in open-angle glaucoma. Miotics are used as an add on therapy and are now third-choice drugs. Carbachol has utility with intraocular use as a miotic in surgery. Sequential use of atropine (mydriatic) and pilocarpine (miotic) is used to break iris-lens adhesions. Pilocarpine is used off label to counter the effects of cycloplegics.
- Reversal of nondepolarizing neuromuscular blockade after surgery: Neostigmine preceded by atropine to block muscarinic effects, rapidly reverses muscle paralysis induced by neuromuscular blockers and is approved by the FDA.

Indications Cholinergic medications

- **Postoperative urinary retention:** For both prevention and treatment of urinary distention and retention, neostigmine is a common option. Bethanechol is the indicated pharmaceutical treatment of acute postoperative and postpartum non-obstructive urinary retention.
- **Neurogenic bladder**: Bethanechol may help complete bladder emptying in those with a hypotonic bladder.
- **Acute colonic pseudo-obstruction**: Off-label use of neostigmine is acute colonic pseudo-obstruction.
- **Xerostomia**: Use of muscarinic agonists in patients with an inadequate response to artificial saliva and mechanical stimulation in Sjogren syndrome or patients post-radiation treatment associated with head and neck cancer. Cevimeline is FDA approved for the treatment of symptoms of dry mouth in Sjogren syndrome.

Indications Cholinergic medications

- **Anticholinergic overdose**: Physostigmine is the specific antidote for poisoning with belladonna or other anticholinergics. It should only be used to reverse toxic, life-threatening delirium caused by an anticholinergic agent (atropine, scopolamine, diphenhydramine).
- **Tensilon test**: Edrophonium was previously a bedside test in patients with suspected myasthenia gravis, has been discontinued and is no longer available in the United States of America.
- **Snakebite:** Neostigmine also has found use in patients with neurotoxic snakebite for who antivenom is not available or is ineffective.

Contraindications

- Pulmonary disease (COPD (Chronic Obstructive Pulmonary Disease) /bronchial asthma)
- Peptic ulcer disease (may use with caution)
- Arrhythmias (atrial fibrillation)
- Coronary vascular disease
- Angle-closure glaucoma
- Hyperthyroidism
- Intestinal resection or anastomosis
- Urinary obstruction
- Orthostatic hypotension
- Severe miosis

What is Botox?

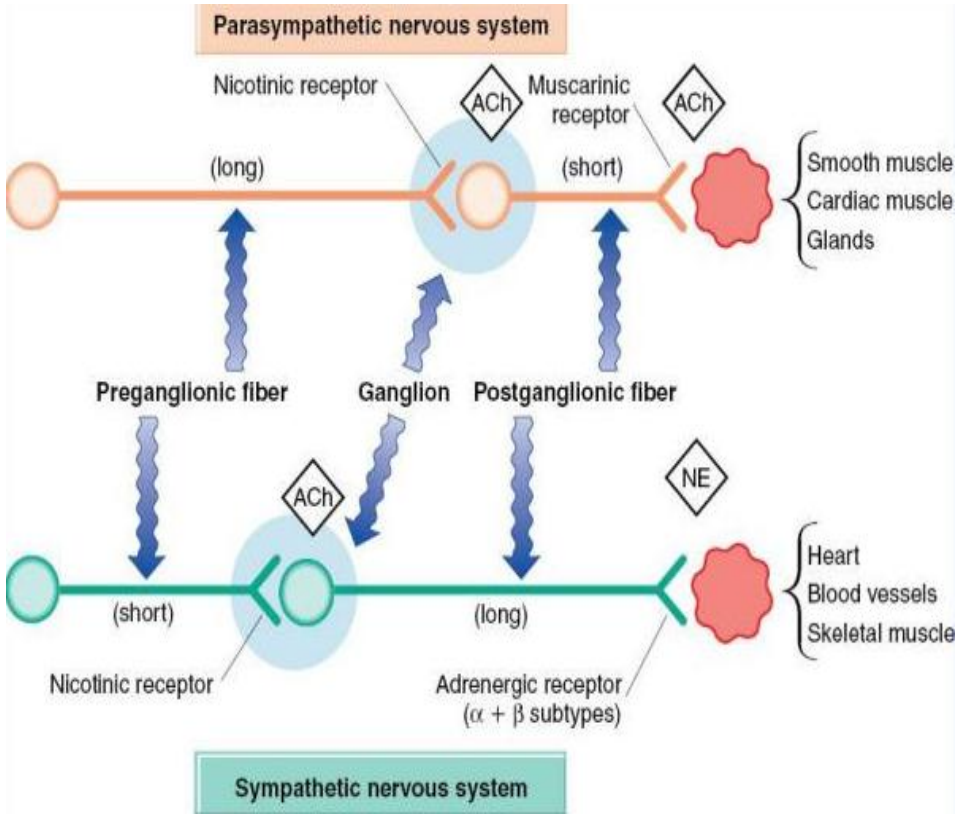
- Botulinum toxin, sometimes referred to as miracle poison or Botox, is the most poisonous neurotoxin. It blocks the neurotransmitter acetylcholine causing muscle paralysis. This neurotoxin is primarily produced by Clostridium botulinum bacteria and has multiple uses in the medical and cosmetic sectors. Most of us know botulinum toxin in the form of Botox injections, used in an extremely diluted form to combat the signs of aging.
- Botox® is one of the most widely known brands of botulinum toxin injections.
- Botulinum toxins are neurotoxins that affect nerves and cause muscle weakening. You might get a botulinum toxin injection for cosmetic or medical reasons. Healthcare providers inject small amounts of Botox into specific muscles to smooth wrinkles, prevent migraine headaches and treat a wide range of other health conditions.
- Botox blocks nerve signals to muscles. As a result, injected muscles can't contract (tense up). These effects are always temporary, but can last for several months. The muscle injected depends on the primary area of concern. Several areas can be treated in one session.

Cholinergic Drugs

- **Cholinergic Drugs** Drugs that stimulate the parasympathetic nervous system (PSNS) The PSNS is the opposing system to the SNS
- Also known as cholinergic agonists or parasympathomimetics Mimic effects of the PSNS neurotransmitter acetylcholine (ACh).

- Cholinergic drugs Cholinomimetics or Parasympathomimetics Drugs: which produce actions similar to that of ACh either by directly interacting with cholinergic receptors or by increasing the availability of ACh at these sites

- Eg:
- **1. Cholinergic agonists**
- **2. Anticholinesterases**



1. Cholinergic agonists

❑ 1. Cholinergic agonists

- **A. Choline esters:**
- Acetyl choline
- Methacholine
- Carbachol
- Bethanechol.

B. Alkaloids:

- Muscarine
- Pilocarpine
- Arecoline

❑Pharmacological actions of Choline esters

- Muscarinic actions
- Nicotinic actions
- CNS actions

Mechanism of Action

Mechanism of Action

- **Direct-acting** cholinergic agonists Bind to cholinergic receptors, activating them
- **Indirect-acting** cholinergic agonists Inhibit the enzyme acetylcholinesterase, which breaks down ACh Results in more ACh available at the receptors

- **Indirect-Acting (Cholinesterase Inhibitors)**
  - **Reversible** Bind to cholinesterase for a period of minutes to hours.
  - **Irreversible** Bind to cholinesterase and form a permanent covalent bond. The body must make new cholinesterase to break these bonds

Drug Effects of Cholinergic Agents

❑**Drug Effects of Cholinergic Agents**

1. Effects seen when the PSNS is stimulated.

2. Stimulate intestine and bladder

- Increased gastric secretions
- Increased gastrointestinal motility
- Increased urinary frequency
- 3. Stimulate pupil
- Constriction (miosis)
- Reduced intraocular pressure

4. Increased salivation and sweating.

5. Cardiovascular effects

-Decreased heart rate

-Vasodilation

6. Respiratory effects

-Bronchial constriction, narrowed airways.

7. At recommended doses, the cholinergics primarily affect the MUSCARINIC receptors.

8. At high doses, cholinergics stimulate the NICOTINIC receptors.

Cholinergic Agents: Side Effects

❑Cholinergic Agents:

❖Side Effects Side effects are a result of overstimulation of the PSNS.

❖ Cardiovascular: -Bradycardia, hypotension, conduction abnormalities (AV block and cardiac arrest)

❖CNS: -Headache, dizziness, convulsions

❖Gastrointestinal: -Abdominal cramps, increased secretions, nausea, vomiting.

❖ Respiratory: -Increased bronchial secretions, bronchospasms

❖ Other: -Lacrimation, sweating, salivation, loss of binocular accommodation, miosis

Cholinergic Agonists: Generic and Brand Names

Classification	Generic Name	Brand Name
Direct-Acting Cholinergic Agonists	bethanechol	Duvoid, Urecholine
	carbachol	Miostat
	cevimeline	Evoxac
	pilocarpine	Salagen
Indirect-Acting Cholinergic Agonists		
Agents of Myasthenia Gravis	ambenonium	Mytelase
	edrophonium	Reversal
	neostigmine	Prostigmin
	pyridostigmine	Mestinon
Agents for Alzheimer's Disease	donepezil	Aricept
	galantamine	Razadyne
	rivastigmine	Exelon
	tacrine	Cognex

Direct-acting Cholinergic Agonists

❑**Direct-acting cholinergic agonists** are similar to Ach and react directly with receptor sites to cause the same reaction if Ach has stimulated the receptor sites.

- Common examples include bethanechol and pilocarpine.

❑**Therapeutic Action**

- The desired and beneficial actions of direct-acting cholinergic agonists are as follows:
- **Direct-acting cholinergic agonists** occupy receptor sites for ACh on the membranes of the effector cells causing increased stimulation.
- Effects include slowed heart rate and decreased myocardial contractility, vasodilation, bronchoconstriction and increased bronchial mucus secretion, increased GI activity and secretions, increased bladder tone, relaxation of GI and bladder sphincters, and pupil constriction.

Indications / Direct-acting cholinergic agonists

- Direct-acting cholinergic agonists are indicated for the following medical conditions:
- Direct-acting cholinergic agonists are systematically used as agents to increase bladder tone, urinary excretion, and GI secretions. As ophthalmic agents, they can induce miosis to relieve increased intraocular pressure in patients with glaucoma.
- **Bethanechol** has specific affinity for the cholinergic receptors in the urinary bladder and is used to treat non-obstructive postoperative and postpartum urinary retention to treat neurogenic bladder atony. It directly increases detrusor muscle tone and relaxes the sphincters to improve bladder emptying.
- **Carbachol** is an ophthalmic agent used to induce miosis or pupil constriction. It can relieve the increased intraocular pressure of glaucoma.
- **Cevimeline** and **pilocarpine** bind to muscarinic receptors throughout the body and are used to increase secretions in the mouth and GI tract and relieve symptoms of dry mouth. They are approved for use in adults and are given three times a day, often with meals.

- Here are some important aspects to remember for indication of cholinergic agonists in different age groups:

❑Children

- They are at greater risk for complications related to use of these drugs, i.e. GI upset, diarrhea, increased salivation (leading to choking), and loss of bowel and bladder control.
- **Bethanechol** is approved for treatment of neurogenic bladder in children older than 8 years of age.
- **Neostigmine and pyridostigmine** are used in the control of myasthenia gravis and for reversal of neuromuscular junction blocker effects in children. **Edrophonium** is used for diagnosis of myasthenia gravis only.

❑Adults

- Adults should be cautioned of these drugs' adverse effects (e.g. dizziness, GI upset, urinary urgency). They should not be allowed to operate machines.
- Use of these drugs among pregnant and lactating women is only justified if benefits outweigh the risks.

❑Older adults

- Dose adjustment is needed as this age group is also more susceptible to drug side effects.
- They are more likely to have toxic levels of the drug because of renal or hepatic impairments.

Pharmacokinetics

- Here are the characteristic interactions of direct-acting cholinergic agonists and the body in terms of absorption, distribution, metabolism, and excretion:

Route	Onset	Peak	Duration
Oral	30-90 min	60-90 min	1-6 h

Contraindications and Cautions

- The following are contraindications and cautions for the use of **direct-acting cholinergic agonists:**
- **Allergy to any component of the drug.** To prevent hypersensitivity reaction
- **Bradycardia, hypotension, vasomotor instability, and coronary artery disease.** Can be made worse by the cardiac- and cardiovascular-suppressing effects of the parasympathetic system.
- **Peptic ulcer, intestinal obstruction, or recent GI surgery.** Can be negatively affected by the GI-stimulating effects of the parasympathetic nervous system.
- **Bladder obstruction.** Aggravated by the stimulatory effects on the bladder.
- **Epilepsy and parkinsonism.** Affected by the stimulation of ACh receptors in the brain.
- **Hepatic or renal dysfunction.** Drugs used to treat Alzheimer's are metabolized in the liver.
- **Pregnancy and lactation.** Potential adverse effects on the fetus or neonate.

Adverse Effects

- Use of direct-acting cholinergic agonists may result to these adverse effects:
- CV: bradycardia, heart block, hypotension, cardiac arrest
- GI: nausea, vomiting, cramps, diarrhea, increased salivation
- GU: urinary urgency
- Others: flushing, increased sweating
- **WARNING Pilocarpine and cevimeline** may cause swallowing difficulties.

Interactions

- The following are drug-drug interactions involved in the use of direct-acting cholinergic agonists:
- **Acetylcholinesterase inhibitors.** Increased risk of cholinergic effects.
- **NSAIDs.** Increased risk of GI bleeding

Indirect-acting Cholinergic Agonists

- **Indirect-acting cholinergic agonists** do not react directly with ACh receptor sites; instead, they react chemically with **acetylcholinesterase** (enzyme breaking down acetylcholine) in the synaptic cleft to prevent it from breaking down ACh.
- These drugs can irreversibly or reversibly bind to acetylcholinesterase. The ones that bind irreversibly are not used therapeutically; they are being developed as nerve gas to be used as weapons. The antidote is pralidoxime.
- The **reversible indirect-acting cholinergic agonists** fall into two main categories: agents used to **treat myasthenia gravis**; and agents used to treat **Alzheimer's disease**.

Therapeutic Action

- The desired and beneficial actions of indirect-acting cholinergic agonists are as follows:
- **Indirect-acting cholinergic agonists** react with the enzyme **acetylcholinesterase** to increase the stimulation of the ACh receptor sites. Consequently, ACh remains the area and accumulates, stimulating ACh receptors for a longer period of time than normally expected.

- **Agents for myasthenia gravis** increase the levels of ACh, facilitating transmission at the neuromuscular junction.
- **Agents for Alzheimer's disease** cause elevated ACh levels in the cortex, which slows the neuronal degradation of Alzheimer's disease.

Indications

- Indirect-acting cholinergic agonists are indicated for the following medical conditions:
- Treatment of myasthenia gravis, antidote for nondepolarizing neuromuscular junction blockers, increased survival after exposure to nerve gas
- Treatment of mild to moderate Alzheimer's disease

Pharmacokinetics

The characteristic interactions of agents for myasthenia gravis and the body in terms of absorption, distribution, metabolism, and excretion:

Route	Onset	Peak	Duration
Oral	35-45 min	–	3-6 h
IM	15 min	–	3-6 h
IV	5 min	–	3-6 h
T1/2: 1.9-3.7 h Metabolism: liver Excretion: urine			

Pharmacokinetics

- The characteristic interactions of agents for Alzheimer's disease and the body in terms of absorption, distribution, metabolism, and excretion:

Route	**Onset**	**Peak**	**Duration**
Oral	Varies	2-4 h	–
T1/2: 70 h Metabolism: liver Excretion: urine			

Contraindications and Cautions

- The following are contraindications and cautions for the use of **indirect-acting cholinergic agonists:**
- **Allergy to any component of the drug.** To prevent hypersensitivity reaction
- **Bradycardia, intestinal/urinary tract obstruction.** Can be exacerbated by the stimulation of cholinergic receptors
- **Pregnancy.** Uterus could be stimulated and labor induced
- **Asthma, coronary disease, peptic ulcer, arrhythmias, epilepsy, parkinsonism.** Can be exacerbated by effects of parasympathetic stimulation
- **Hepatic or renal dysfunction.** Can interfere with metabolism and excretion of drugs

Adverse Effects

- Use of indirect-acting cholinergic agonists may result to these adverse effects:
- CNS: miosis, blurred vision, headaches, dizziness, drowsiness
- CV: bradycardia, heart block, hypotension, **cardiac arrest**
- GI: nausea, vomiting, cramps, diarrhea, increased salivation, involuntary defecation
- GU: urinary urgency
- Others: flushing, increased sweating

Interactions

- The following are drug-drug interactions involved in the use of indirect-acting cholinergic agonists:
- **NSAIDs.** Increased risk of GI bleeding
- **Theophylline.** Increased levels if combined with tacrine (oral acetylcholinesterase inhibitor previously used for therapy of Alzheimer disease).