وَقُل رَّبِّ زِدْنِي عِلْمًا

النادي الطبي

PERIPHERAL NERVOUS SYSTEM

SUBJECT : Pharma

LEC NO. : 1

DONE BY : Rahaf omosh

Peripheral Nervous System (PNS)

Pharmacology (1)

Directly acting cholinergic agonists

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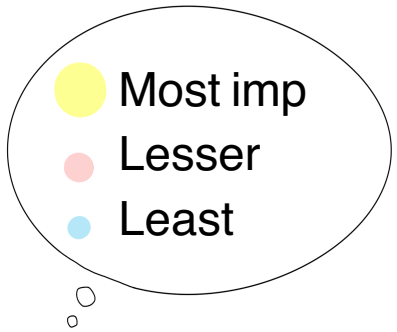


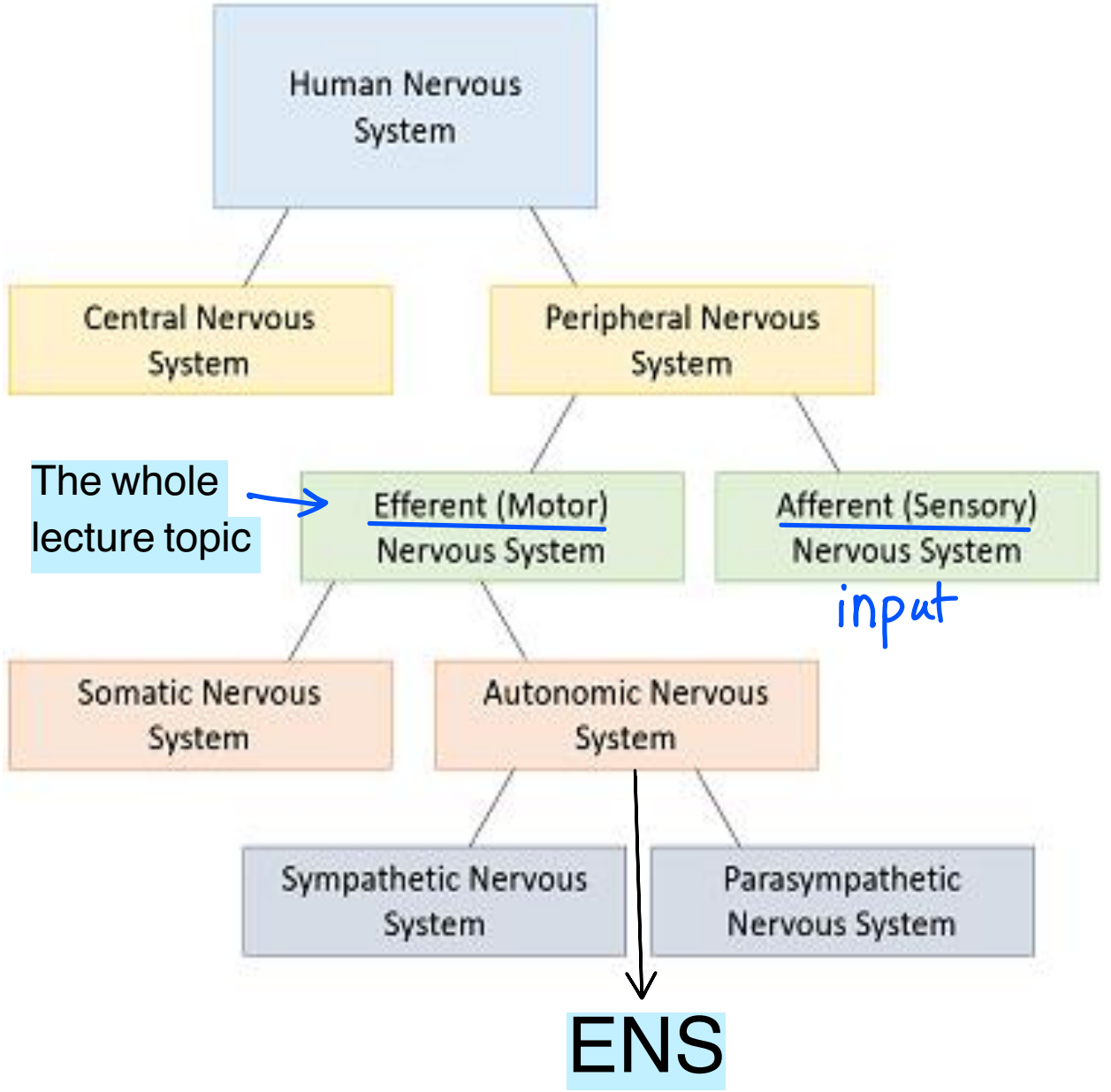
Blue and yellow boxes are imp

Any cat emoji means its v. imp 😻

Introduction to nervous system

It's just an intro

- The nervous system is anatomically divided into the central nervous system (CNS; the brain and spinal cord) and the peripheral nervous system (PNS; neuronal tissues outside the CNS)
- The peripheral nervous system is subdivided into the efferent and afferent divisions. The **effe**rent neurons carry signals **away** from the brain and spinal cord to the peripheral tissues (to **effe**ctor organ), and the **affe**rent neurons bring information from the periphery to the CNS.
- Afferent neurons provide sensory input regarding the internal and external environments and modify motor output through reflex arcs of varying complexity. For example, by sensing pressure in the carotid sinus and aortic arch and in signaling the CNS to influence the efferent branch of the system to respond.



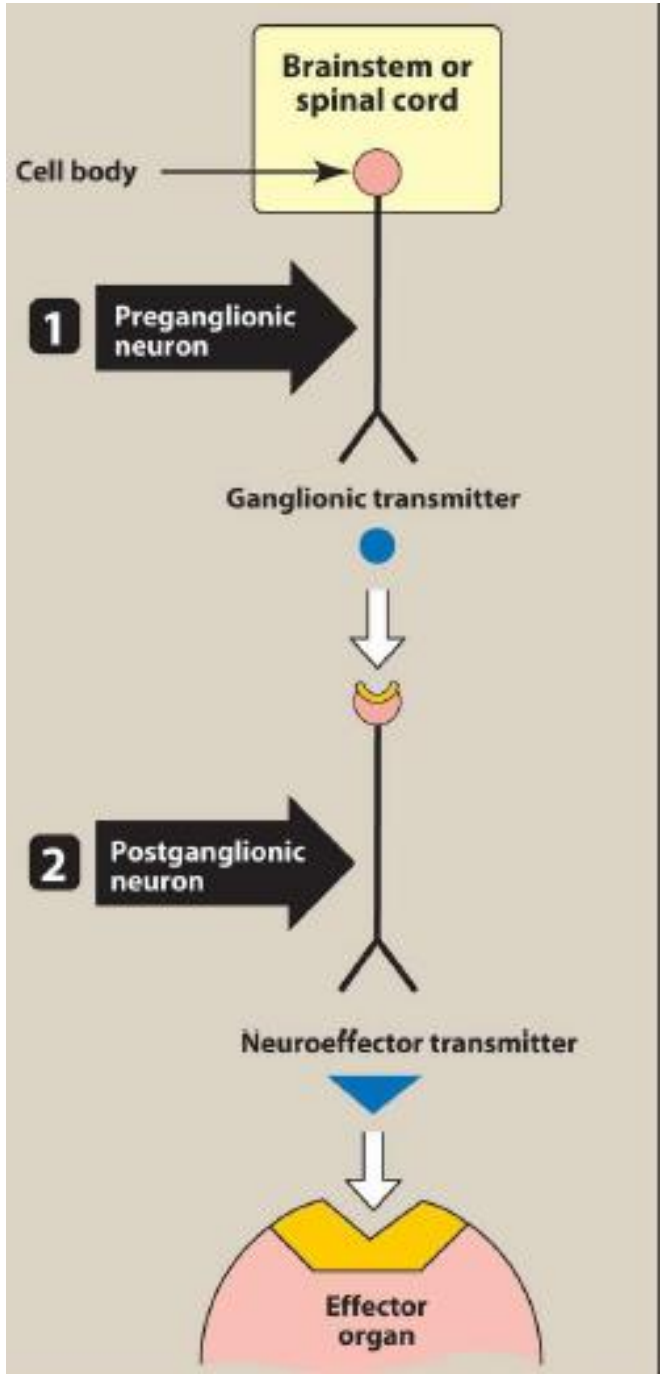
Functional divisions within the nervous system

- The efferent portion of the peripheral nervous system is further divided into the somatic nervous system and the autonomic nervous system (ANS).
- The **somatic** efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion
- The **ANS**, its activities are not under direct conscious control. It regulates vital bodily functions. Through innervation of visceral smooth muscle, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

ANS

The ANS carries nerve impulses from the CNS to the effector organs through two types of efferent neurons.

- the preganglionic : The preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection in
- Ganglia: an aggregation of nerve cell bodies located in the peripheral nervous system. The ganglia function as relay stations between the preganglionic neuron and postganglionic neuron.
- Postganglionic neuron cell bodies originate in the ganglion and terminates on effector organs, such as visceral smooth muscle, cardiac muscle, and the exocrine glands.



Division of ANS

Sympathetic ganglia is closer to the spinal cord
-preganglionic neurons: short
-postganglionic neurons: long

1. Sympathetic nervous system (thoracolumbar): + sacral region

- Preganglionic neurons come from the thoracic and lumbar regions (T1 to L2) of the spinal cord.
- Ganglia are chord-like run close to and in parallel on each side of the spinal cord.
- Preganglionic nerve endings (in most cases) are highly branched; one preganglionic neuron interacts with many postganglionic neurons, Leading to **activation of numerous effector** organs at the same time. That's why the preganglionic neuronal effect is distributed and amplificated.
- The adrenal medulla, receives preganglionic fibers from the sympathetic system.
  Without the need of any postganglionic neurons or even a ganglion, only preganglionic

2. Parasympathetic nervous system 1973

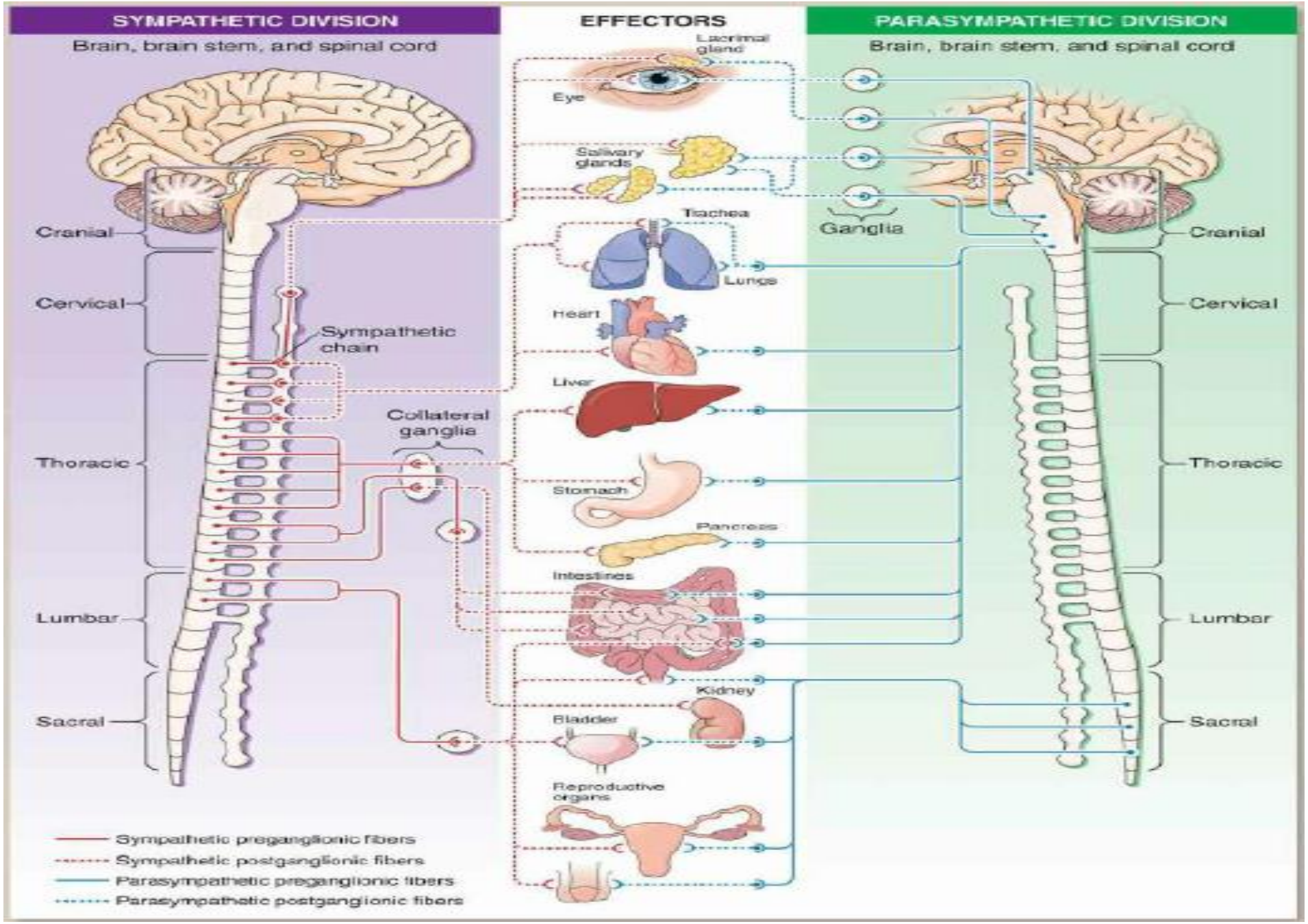
- preganglionic fibers arise from cranial nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus), as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near or on the effector organs.
- The vagus nerve accounts for 90% of preganglionic parasympathetic fibers. Postganglionic neurons from this nerve innervate most organs in the thoracic and abdominal cavity
- Mostly, there is a one-to-one connection between the preganglionic and postganglionic neurons, enabling **discrete** response of this system.

Parasympathetic neuronal ganglia is closer to the effector organ
- pre : long
- post: short

Division of ANS

3. Enteric nervous system (ENS):

- It is a collection of nerve fibers that innervate the gastrointestinal (GI) tract, pancreas, and gallbladder, and it constitutes the “brain of the gut.”
- Functions independently of the CNS and controls motility, exocrine and endocrine secretions, and microcirculation of the GI
- It is **modulated** by both the sympathetic and parasympathetic nervous systems.


SYMPATHETIC DIVISION
Brain, brain stem, and spinal cord
EFFECTORS
PARASYMPATHETIC DIVISION
Brain, brain stem, and spinal cord
Lacrimal gland
Eye
Salivary glands
Ganglia
Trachea
Lungs
Heart
Liver
Stomach
Pancreas
Intestines
Kidney
Bladder
Reproductive organs
Cranial
Cervical
Thoracic
Lumbar
Sacral
Sympathetic chain
Collateral ganglia
Sympathetic preganglionic fibers
Sympathetic postganglionic fibers
Parasympathetic preganglionic fibers
Parasympathetic postganglionic fibers

Summary

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

Function of sympathetic and parasympathetic nervous system

Sympathetic (Fight or flight response):

- Sympathetic division is responsible for adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and Exercise. The effect of sympathetic stimulation includes:

increase in heart rate and blood pressure, mobilization of energy store, increase in blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs, dilation of the pupils and bronchioles. 

- These reactions are triggered both by direct sympathetic activation of effector organs and by stimulation of the adrenal medulla to release epinephrine and lesser amounts of norepinephrine.

Function of sympathetic and parasympathetic nervous system

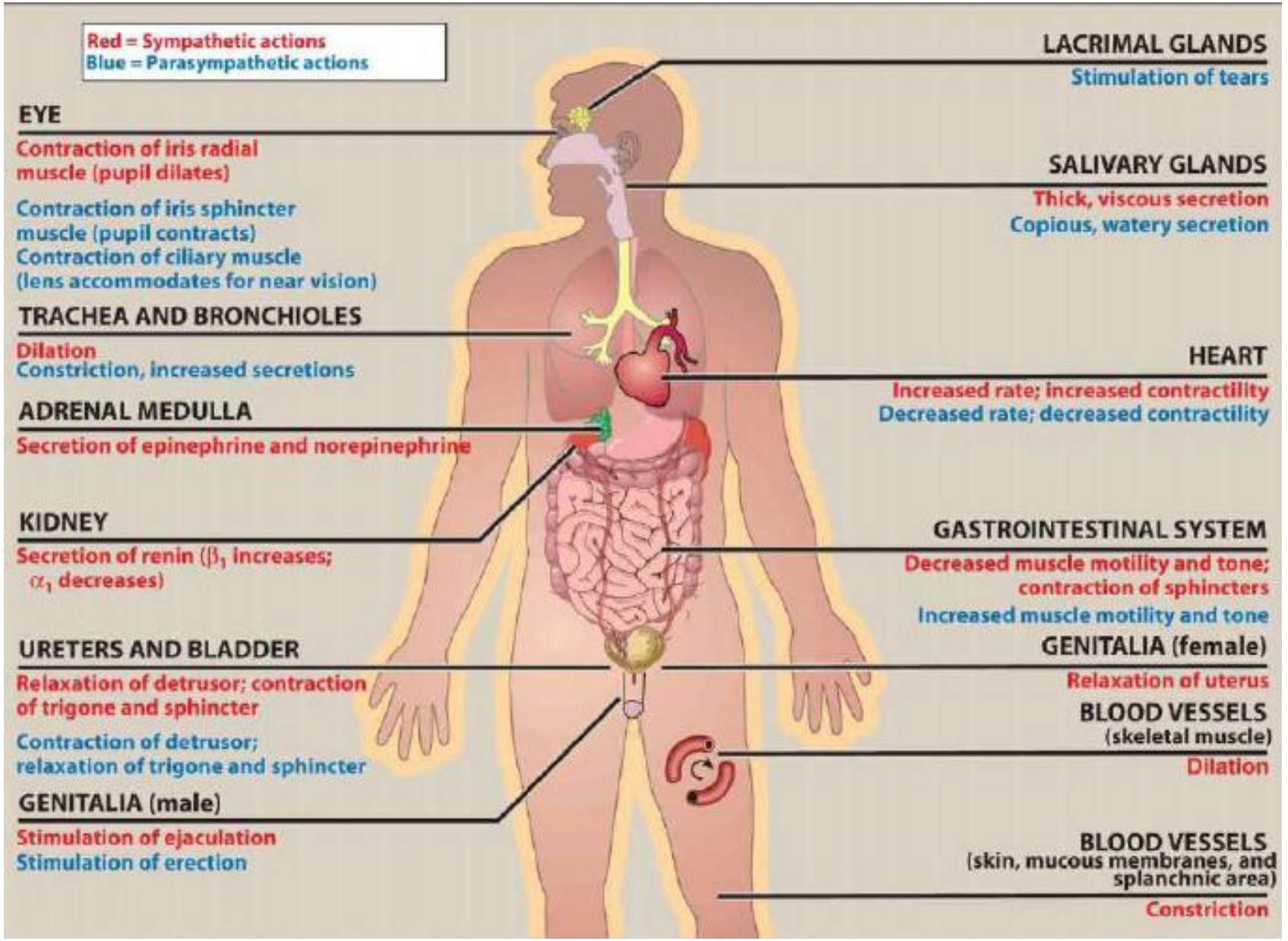
Parasympathetic (rest-and-digest):

- involved with maintaining homeostasis within the body.
- usually acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in“rest-and-digest” situations.
- does not discharge as a complete system (if so, it would produce massive, unpleasant symptoms, such as involuntary urination and defecation).

Most organs are dual innervated. However, one system usually predominates in controlling the activity of a given organ. For example, the vagus nerve (parasympathetic) is the predominant factor for controlling heart rate.

Some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system.

Function of sympathetic and parasympathetic nervous system



Nicotinic / muscarinic a_1, a_2 / B_1, B_2, B_3

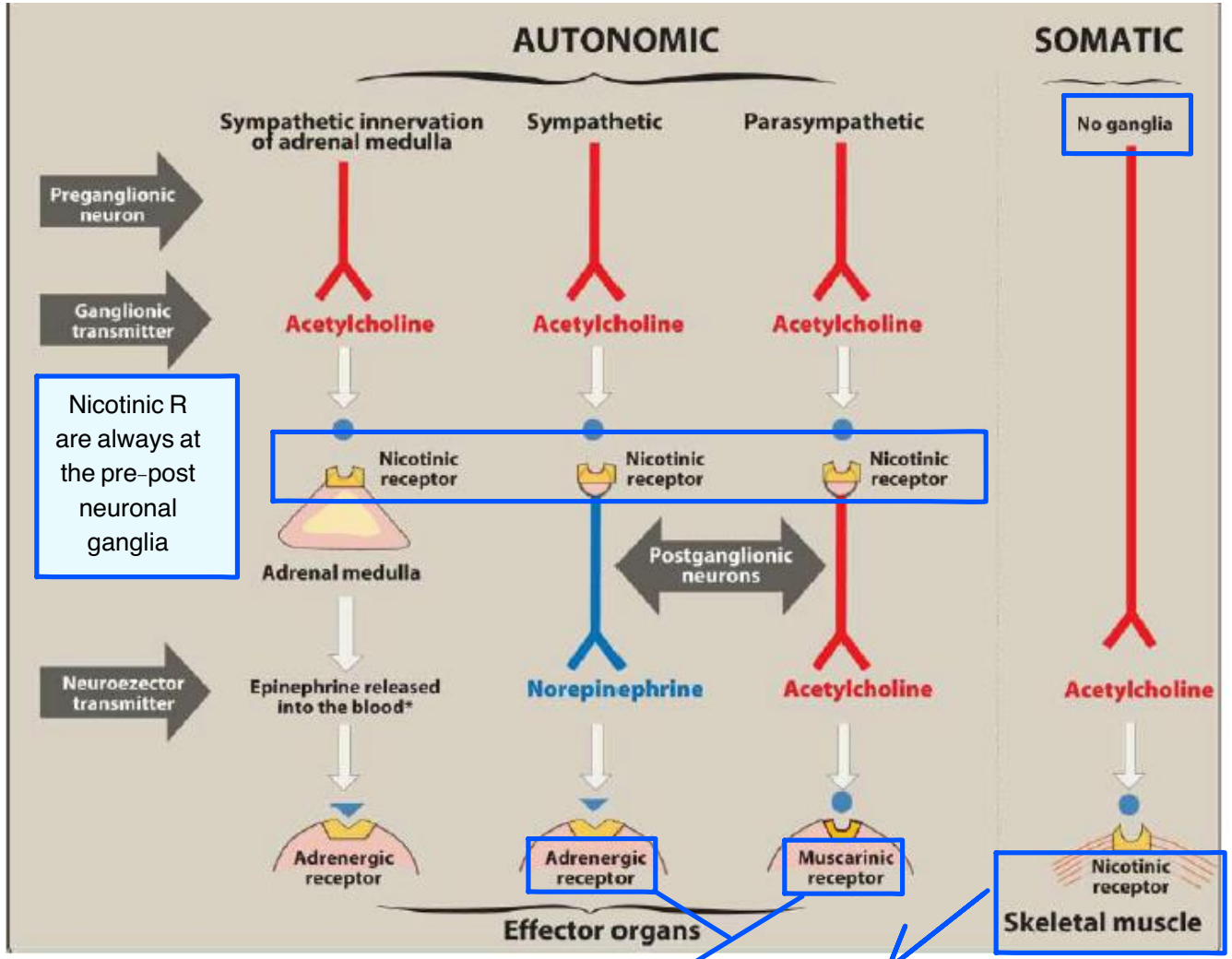
Cholinergic and adrenergic receptors

- The receptors in the ANS effector cells are classified as adrenergic or cholinergic based on the neurotransmitters or hormones that bind to them.
- Adrenergic receptors: bind to epinephrine and norepinephrine
- Cholinergic receptors: bind to Acetylcholine.
- Receptors can also be classified, according to how they mediate ligand effect, into:

1. Ionotropic receptors: directly linked to membrane ion channels and affect ion permeability. Example: postsynaptic cholinergic nicotinic receptors in skeletal muscle cells.
2. G protein–coupled receptors (metabotropic receptors): activate a second messenger system such as adenylyl cyclase system and the calcium/phosphatidylinositol system. Example: all adrenergic receptors and cholinergic muscarinic.

V. impppppppp

- Cholinergic receptors further classified as nicotinic and muscarinic receptors.
- Cholinergic receptors found at sympathetic and parasympathetic **autonomic ganglia**, **adrenal medulla**, effector organs innervated by **para**sympathetic **post**ganglionic nerves, a few sympathetic organs (e.g. **sweat glands**) and at the **neuromuscular junction** (the junction of nerve fibers and voluntary muscles).
- Adrenergic receptors found at effector organs innervated by **sympathetic postganglionic** nerves.



Metabotropic receptors

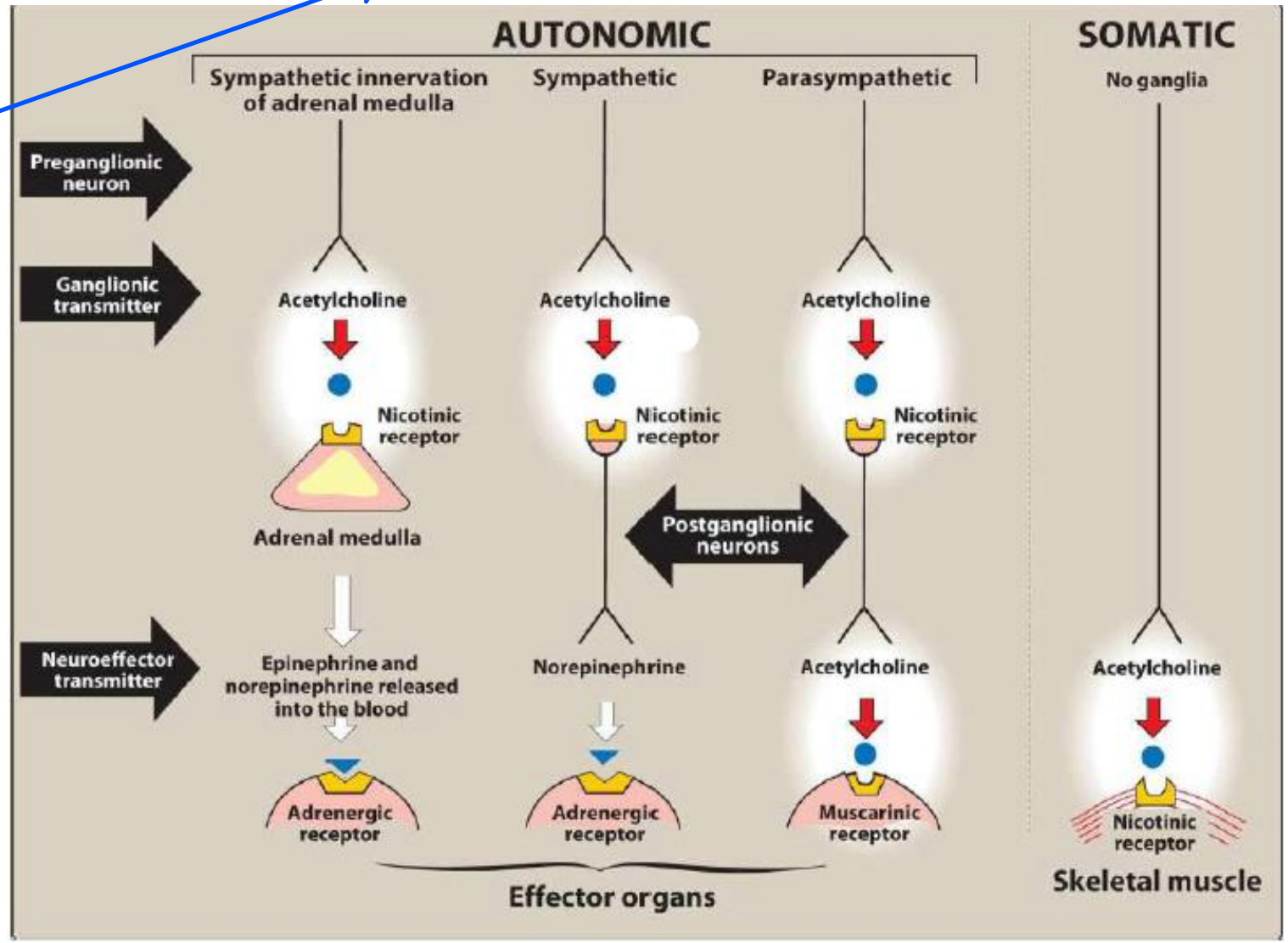
Ionotropic repeptor

Sympathetic postganglionic neurons are always adrenergic except in the SWEAT GLANDS its muscarinic.

The Cholinergic Neuron

Uses only a preganglionic fibers (nicotinic)

- Neurons that use Ach: preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia, the parasympathetic postganglionic fibers and sympathetic postganglionic fibers of sweat glands (muscarinic).
- In addition, cholinergic neurons innervate the muscles of the somatic system and play an important role in CNS (includes cognitive processes such as learning, memory, and attention).



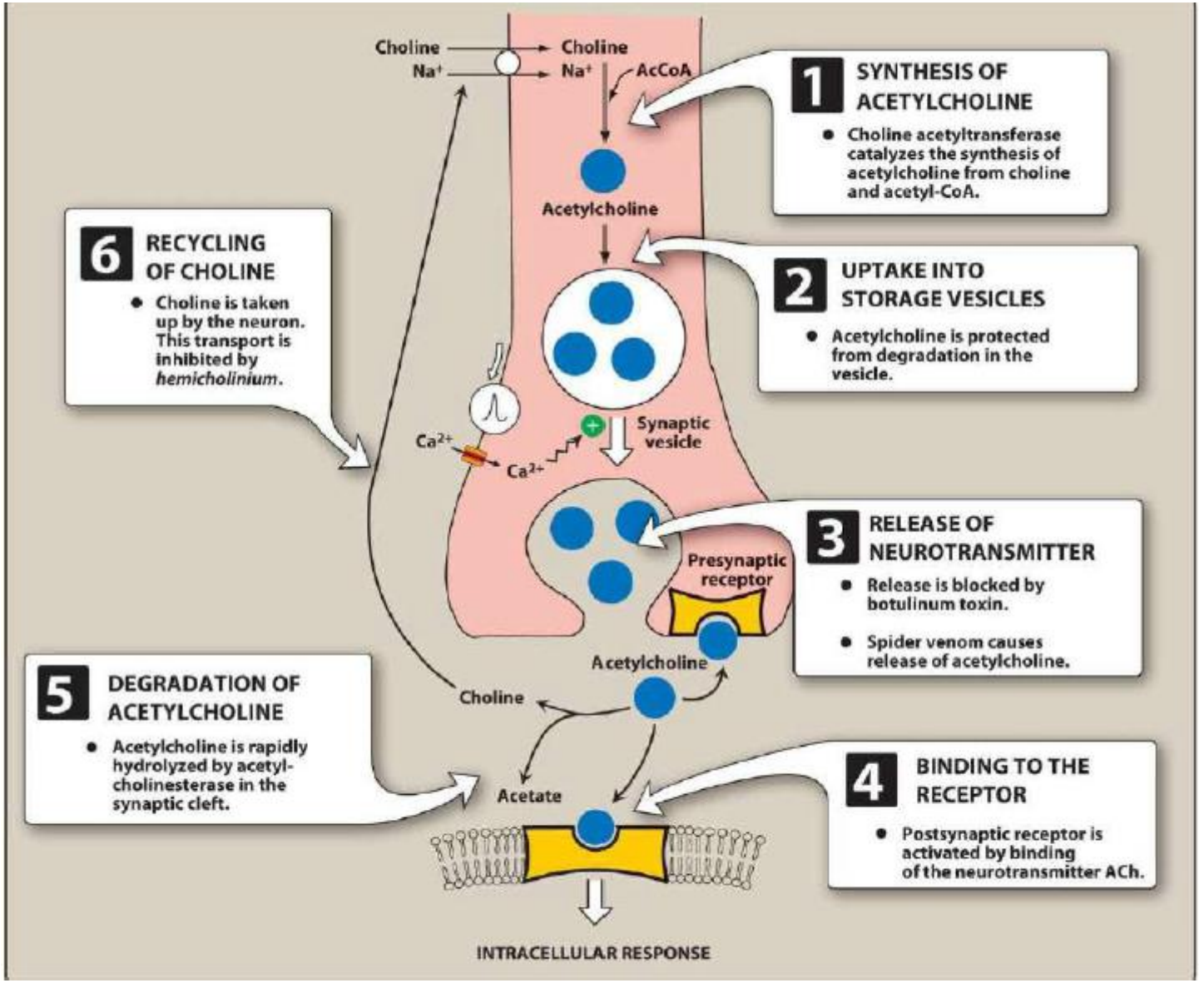
Neurotransmission at cholinergic neurons

Read

Explained in details in the next slides

Neurotransmission in cholinergic neurons involves six sequential steps:

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



Neurotransmission at cholinergic neurons

1. Synthesis of acetylcholine

- 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 research drug ***hemicholinium***. [Note: Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane.]

no idea if its imp!

- The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA), synthesized in the mitochondria, to form ACh (an ester) in the cytosol.

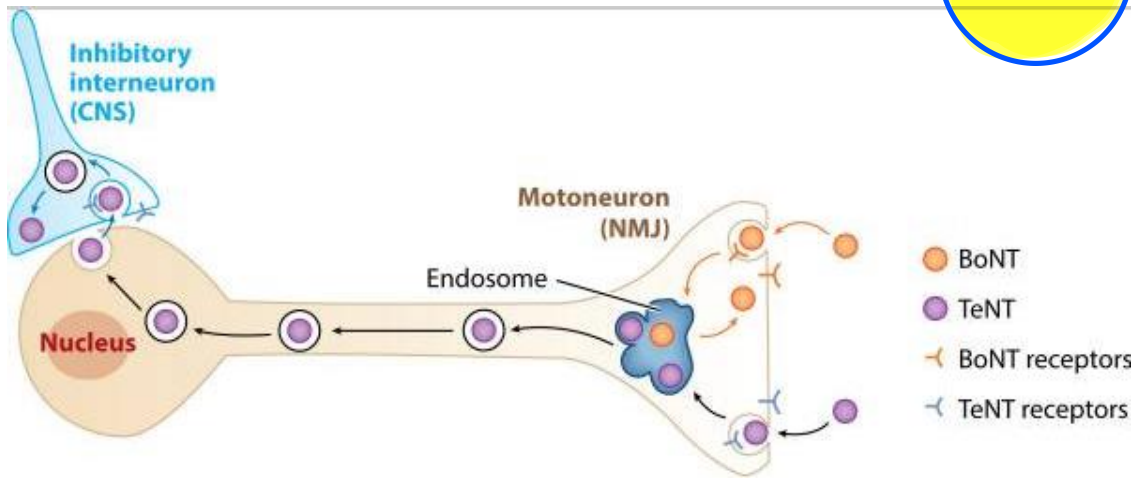
2. Storage of acetylcholine in vesicles

- ACh is packaged and stored into presynaptic vesicles by an active transport process. The mature vesicle contains not only ACh but also ATP as a cotransmitter and proteoglycan (negatively charged molecules).

3. Release of acetylcholine

- Physiologic release of transmitter from the vesicles is dependent on extracellular calcium and occurs when an action potential reaches the terminal and triggers sufficient influx of calcium ions via voltage sensitive calcium channels. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of contents into the synaptic space
- The acetylcholine is blocked by botulinum toxin and tetanus toxin. It blocks the fusion of the vesicle with the membrane
- Tetanospasmin reaches the inhibitory interneurons in the CNS, thus resulting in spasm, rather than paralysis, of skeletal muscle.

bcuz tetanus toxin has the ability to travel through the axon of the nerve ending to reach the CNS to inhibit the inhibitory mechanism so that a spasm occur bcuz of the continuous excitation.



- Black widow spider toxin causes all the ACh stores to empty into the synaptic gap.

Neurotransmission at cholinergic neurons

4. Binding to the receptor

5. Degradation of acetylcholine → Direct / Non direct

The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves Ach to choline and acetate in the synaptic cleft.

6. Recycling of choline

Botulinum Toxin Indication:

1. **Chronic migraine prophylaxis (>= 15 attacks/ month)**
2. **Cervical dystonia (involuntary muscle contraction):** to reduce of neck pain associated with cervical dystonia.
3. **Blepharospasm (**involuntary movements of the eyelids**) and strabismus (crossed eye).**
4. **Primary axillary hyperhidrosis:** for severe primary axillary hyperhidrosis treatment inadequately managed with topical agents.
5. **Adult bladder dysfunction:** For adults who do not respond adequately to or are intolerant of anticholinergic medication
6. **Pediatric detrusor overactivity associated with a neurologic condition: if intolerant or failure of** anticholinergic
7. **Botulinum toxin cosmetic:** used for wrinkles and facial lines.

Involutary blinking

Cholinergic Receptors

A. Muscarinic receptors:

- Have high affinity to muscarine, an alkaloid in certain poisonous mushrooms.
- There are five subclasses of muscarinic receptors M1-M5.
- M1 receptors are also found on gastric parietal cells, M2 receptors on cardiac cells, and M3 receptors on the bladder, exocrine glands, and bronchiolar and GIT wall smooth muscle.

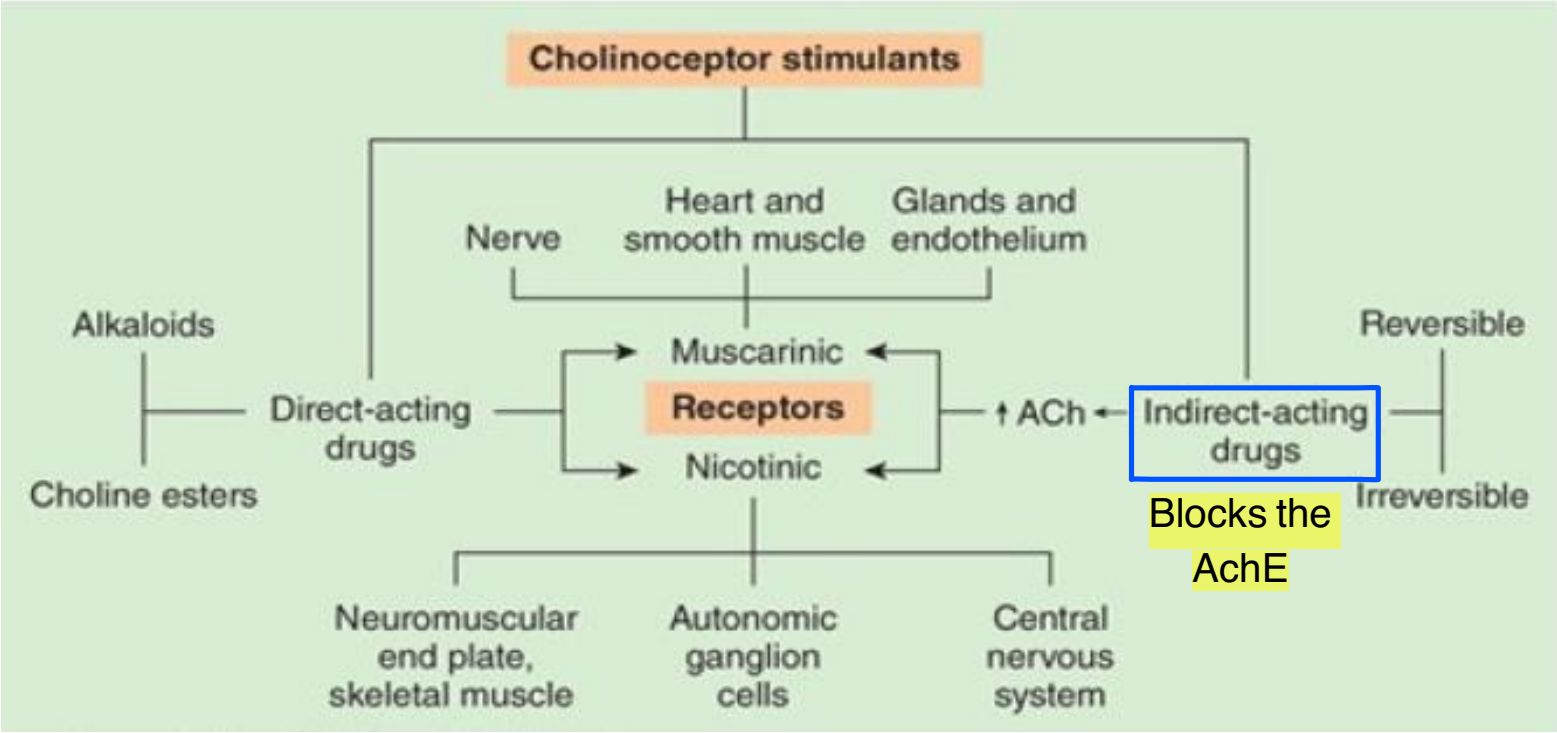
B. Nicotinic receptors

- Bind to *nicotine* an alkaloid found in tobacco and other plants but show only a weak affinity for muscarine
- *Nicotine* at low concentration stimulates the receptor, whereas *nicotine* at high concentration blocks the receptor. Nicotinic receptors are located in the CNS, the adrenal, medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.
- The nicotinic receptors of autonomic ganglia (N_N) differ from those of the NMJ (N_M). For example, ganglionic receptors are selectively blocked by *mecamylamine*, whereas NMJ receptors are specifically blocked by *atracurium*

Cholinomimetics

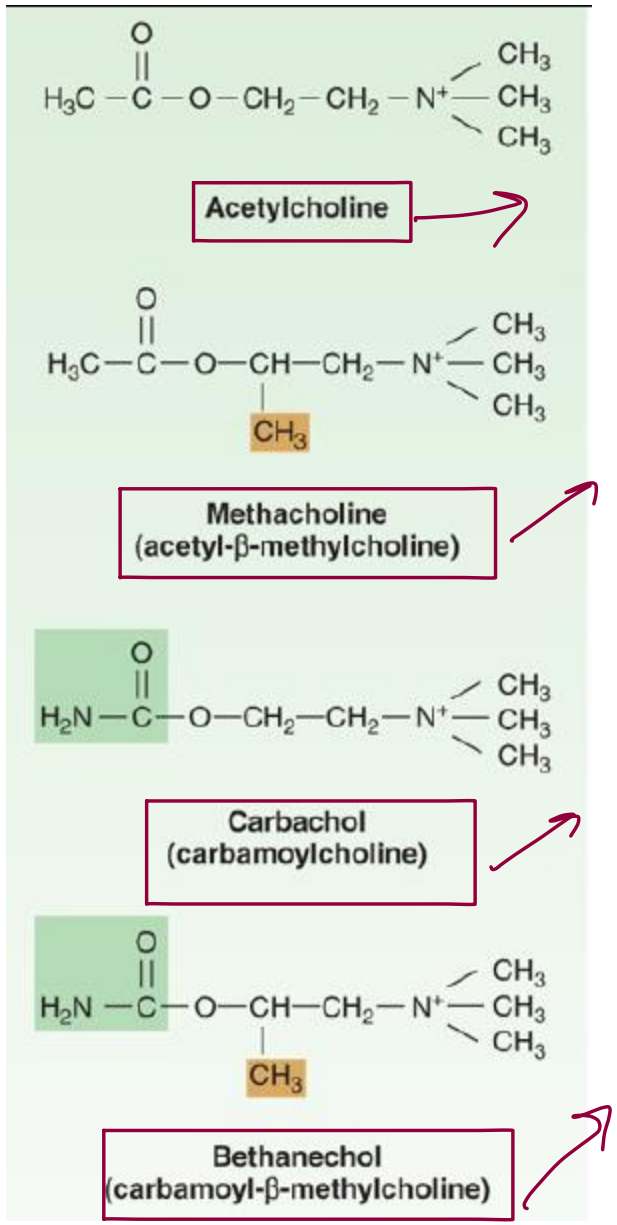
Cholinoceptor stimulants, mimmics Ach, and classified pharmacologically:

- by their spectrum of action, depending on the type of receptor—muscarinic or nicotinic—that is activated.
- by their mechanism of action because some bind directly to (and activate) cholinoceptors, whereas others act indirectly by inhibiting the hydrolysis of endogenous ACh.



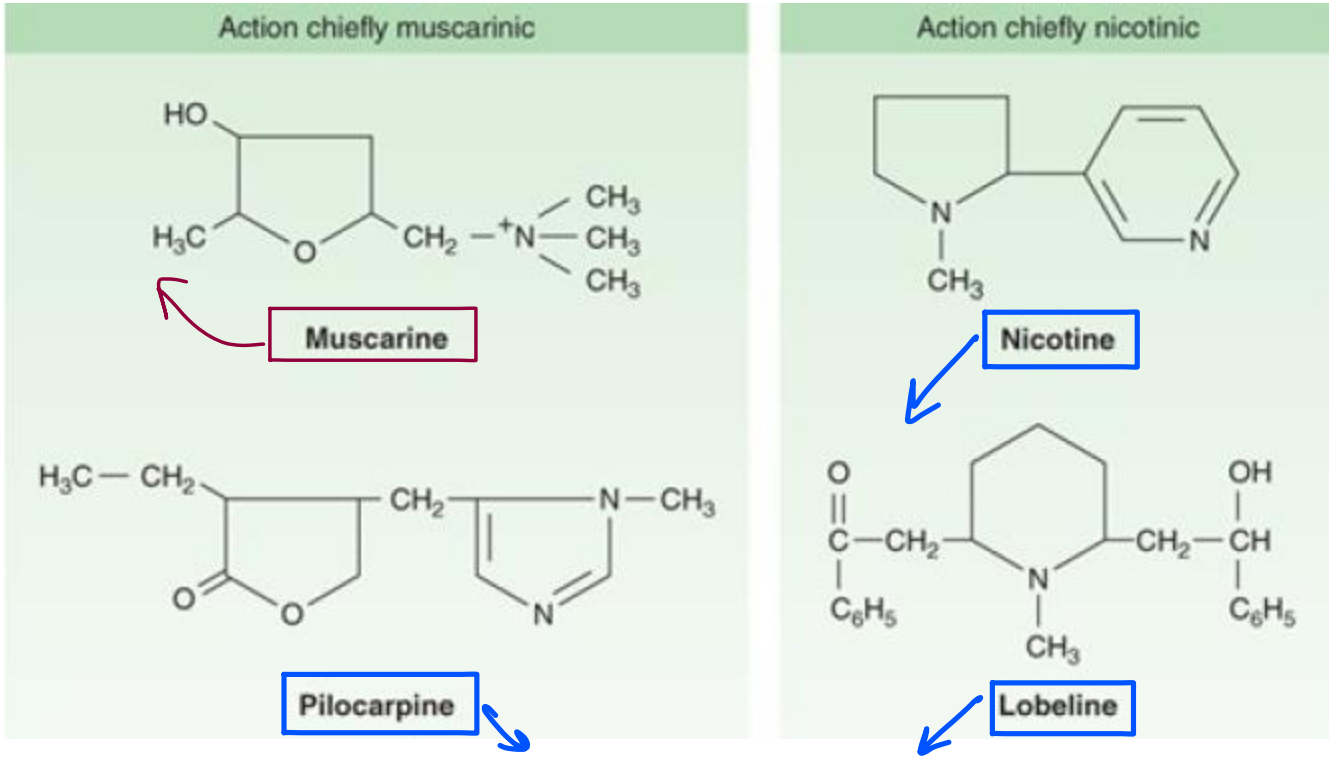
Direct-Acting Cholinergic Agonists

- Divided on the basis of chemical structure into 1) esters of choline, including acetylcholine and synthetic esters of choline, such as *carbachol* and *bethanechol* and 2) alkaloids muscarine, nicotine and pilocarpine
- All direct-acting cholinergic drugs have a longer duration of action than ACh. The more
- *pilocarpine* and *bethanechol* preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents.
- None of the clinically useful drugs is selective for receptor subtypes within either class.



has quaternary ammonium

so it can't reach CNS



has Tertiary ammonium so it can reach CNS

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Acetylcholine

- Has very limited therapeutic importance because of its diffuse effects and its rapid inactivation by the cholinesterase. (used as eye-drops to constrict the pupil during cataract surgery).
- Its actions include the following:

Cardiovascular: Decreases heart rate and cardiac output (mimic effect of vagal nerve stimulation) and reduction in blood pressure (indirect effect through activation of M3 of blood vessels smooth muscles which results in NO production and eventually muscle relaxation and vasodilatation)

GI tract: increases salivary secretion, gastric acid secretion, and stimulates intestinal secretions and motility.

Airways: enhances bronchiolar secretions and bronchoconstriction. *Methacholine*, a direct-acting cholinergic agonist, is used to diagnosis of asthma.

Genitourinary tract: increases the tone of the detrusor muscle, causing urination.

Eye: contraction of ciliary muscle for near vision and constriction of the pupillae sphincter muscle, causing miosis.

Bethanechol

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. Its major actions are on the smooth musculature of the bladder and GI tract. It has about a 1-hour duration.

➢ Actions

Bethanechol directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed. These effects stimulate urination.

➢ Therapeutic uses

1

Bethanechol is the indicated pharmaceutical treatment of acute postoperative and

2 postpartum non-obstructive urinary retention. Neurogenic bladder: Bethanechol may help complete bladder emptying in those with a hypotonic bladder. 3

➢ Adverse effects

Bethanechol can cause generalized cholinergic stimulation, with sweating, salivation, flushing, decreased blood pressure (with reflex tachycardia), nausea, abdominal pain, diarrhea, and bronchospasm. *Atropine sulfate* may be administered to overcome severe cardiovascular or bronchoconstrictor responses

Carbachol (carbamylcholine)

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.

➢ Actions

Carbachol has profound effects on both the cardiovascular and GI systems because of its ganglion-stimulating activity. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, causes miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction. The vision becomes fixed at a particular distance, making it impossible to focus.

➢ Therapeutic uses

Because of its high potency, receptor non selectivity, 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.

➢ Adverse effects

With ophthalmologic use, few adverse effects occur due to lack of systemic penetration (quaternary amine). (Tertiary amines have systemic effects)

Pilocarpine

Naturally occurring alkaloid containing a tertiary amine. it is stable to hydrolysis by AChE but less potent. Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

➢ Actions

Applied topically to the eye, pilocarpine produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation. Pilocarpine is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity.

➢ Therapeutic uses

- 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 causes an immediate drop in intraocular pressure because of the increased drainage of aqueous humor. This action occurs within a few minutes, lasts 4 to 8 hours, and can be repeated. Pilocarpine useful in reversing mydriasis due to atropine.
- The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and **cevimeline**, a cholinergic drug that also has the drawback of being nonspecific.

➢ Adverse effects

Pilocarpine can cause blurred vision, night blindness, and brow ache. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating and salivation. Parenteral atropine, at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of pilocarpine.

Atropine is an anticholinergic that can reverse the pilocarpine toxicity/overdose