Pharmacology

Pharmacology of autonomic nervous system

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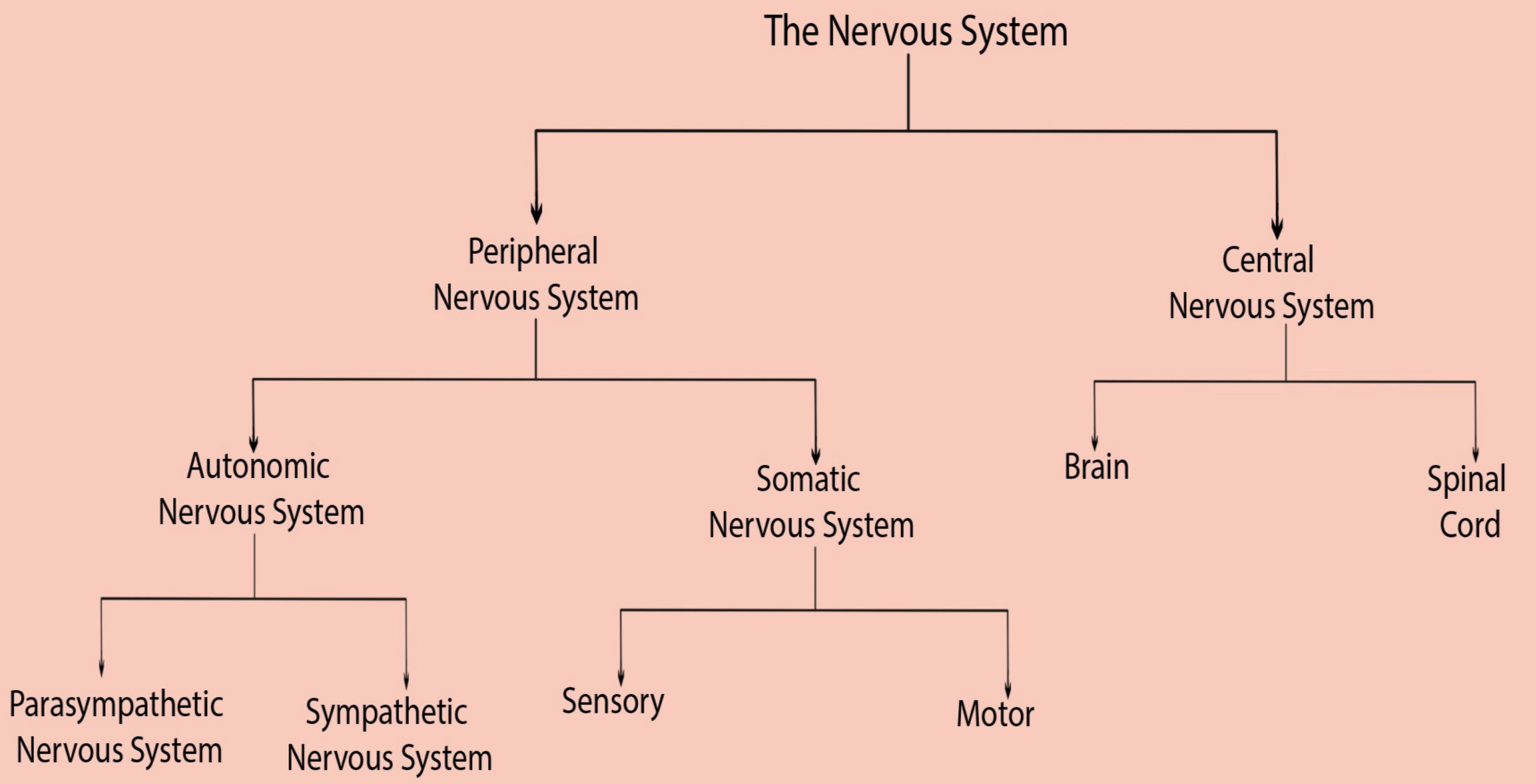
Ph.D Pharmacology

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 (PNS) is further divided into the *afferent* NS bringing information from the periphery to the CNS and *efferent* NS carrying signals away from the CNS to the peripheral tissues.

Organization of the nervous system



What are the functional divisions within the nervous system?

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions:

1- The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion.

2- The ANS regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. Because of the involuntary nature of the ANS as well as its functions, it is also known as the visceral, vegetative, or involuntary nervous system. It is composed of efferent neurons that innervate visceral smooth muscle, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

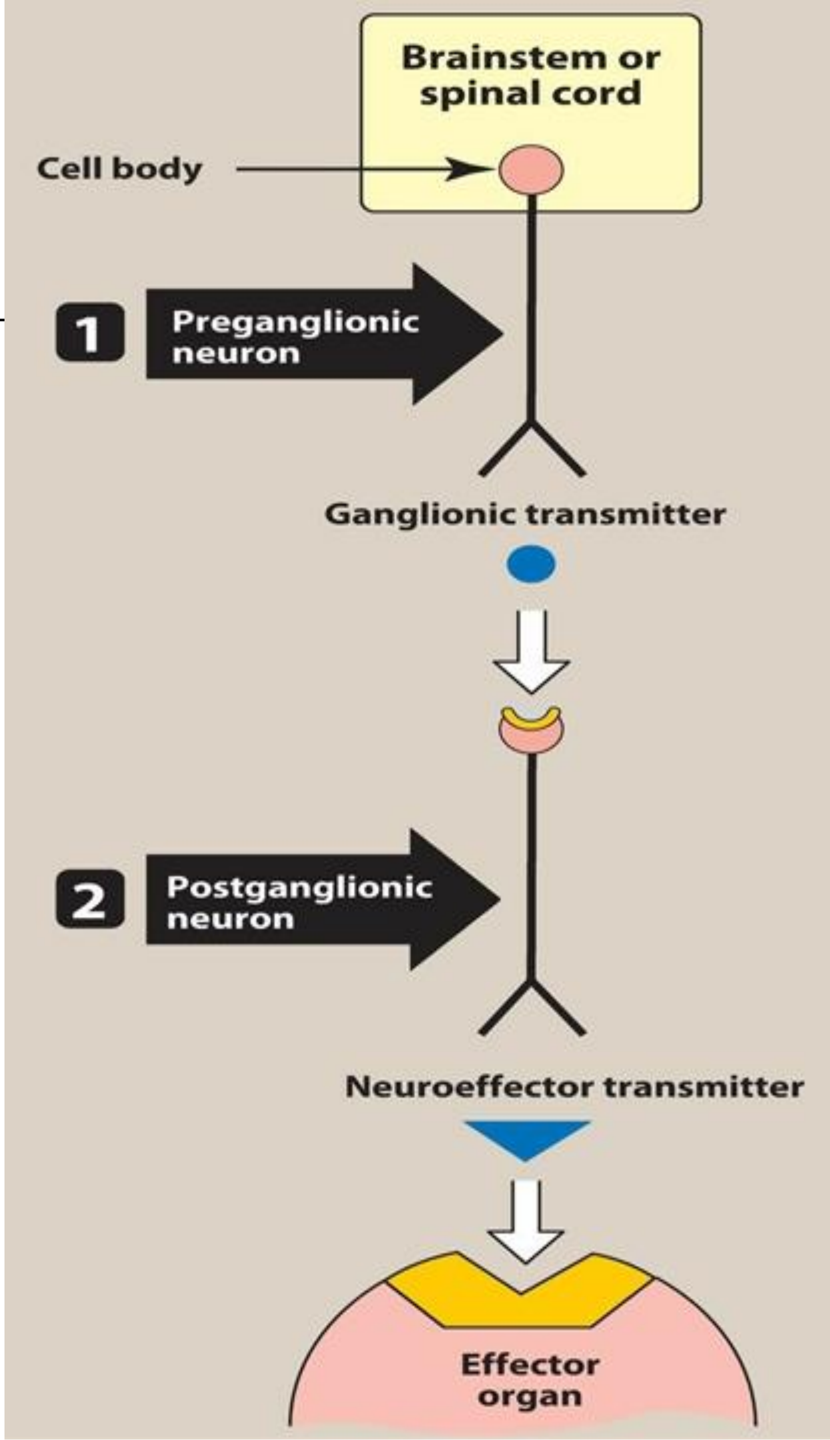
Anatomy of the ANS

1. Efferent neurons (Out put form CNS)

The ANS carries nerve impulses from the CNS to the effector organs through two types of efferent neurons: the preganglionic neurons and the postganglionic neurons (Figure 3.2). The cell body of the first nerve cell, the preganglionic neuron, is located within the CNS. 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 the second nerve cell, the postganglionic neuron. The cell body of the postganglionic neuron originates in the ganglion. It is generally non-myelinated and terminates on effector organs, such as visceral smooth muscle, cardiac muscle, and the exocrine glands.

2-Afferent neurons

The afferent neurons (fibers) of the ANS are important in the reflex regulation of this system (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.



3.Sympathetic neurons

*The efferent ANS is divided into the sympathetic and the parasympathetic nervous systems, as well as the enteric nervous system. 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.

[Note: **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 epinephrine (adrenaline), and lesser amounts of norepinephrine, directly into the blood.]**

4. Parasympathetic neurons

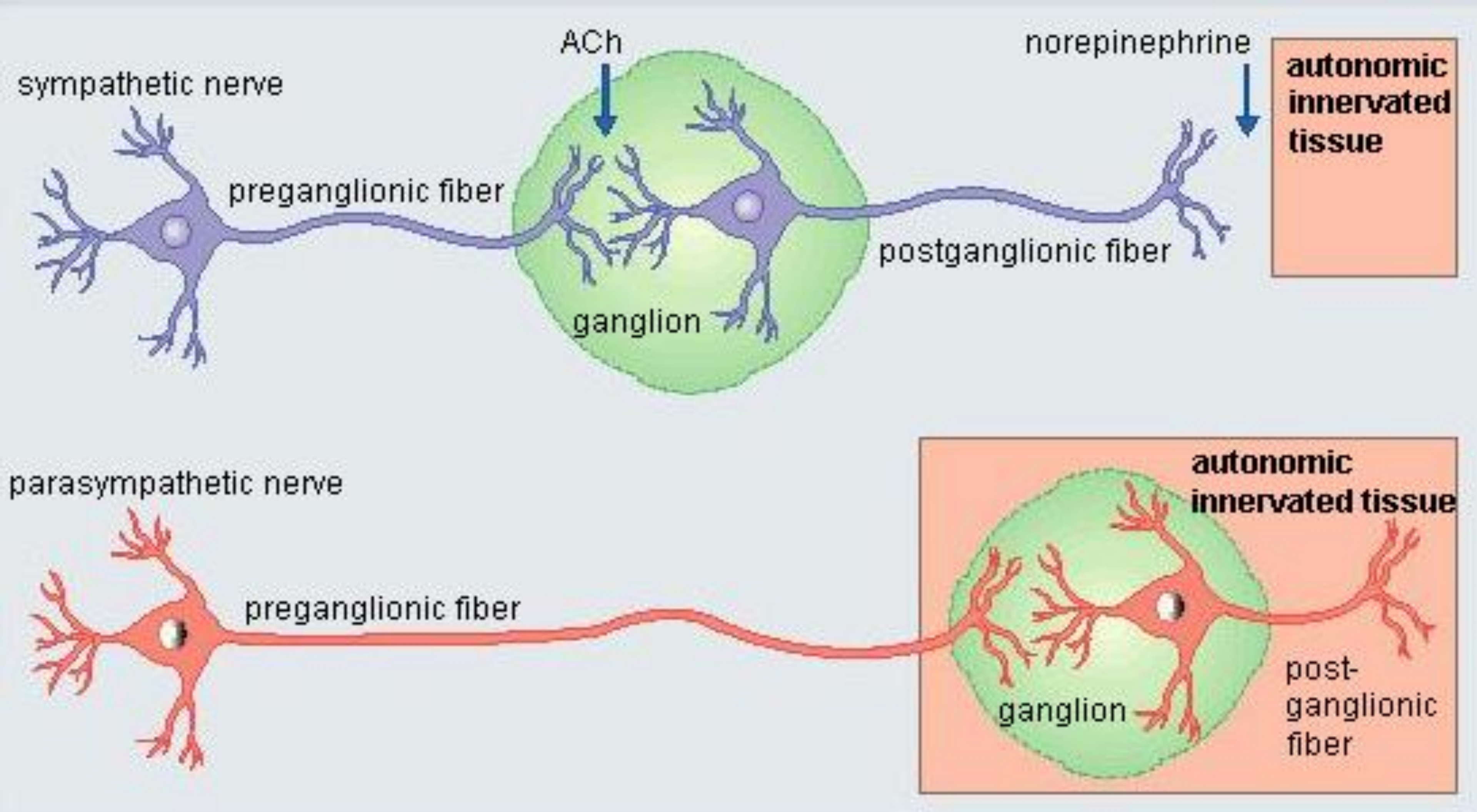
- The parasympathetic preganglionic fibers arise from cranial nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus), as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near or on the effector organs.
- [Note: The vagus nerve accounts for 90% of 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.

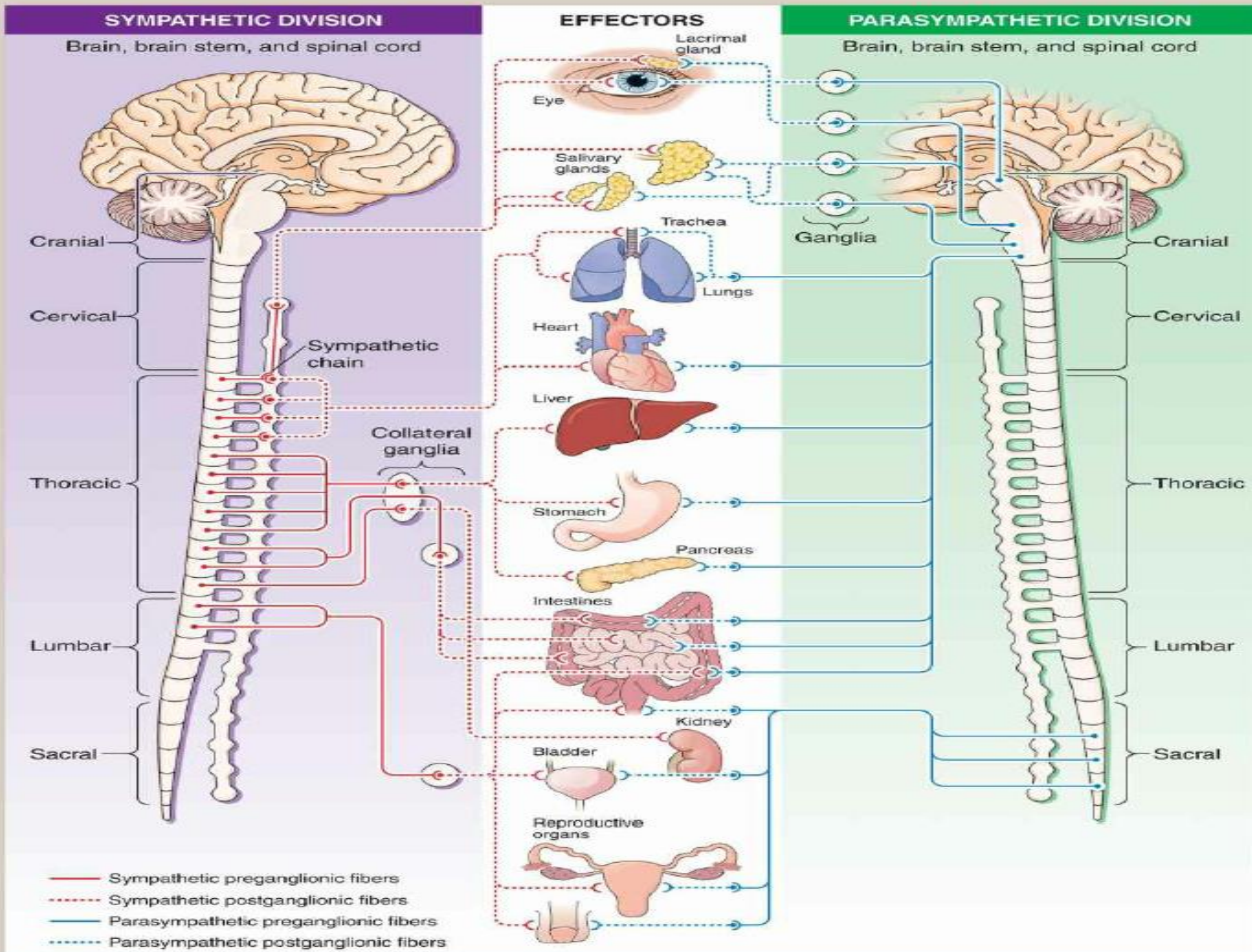
5. Enteric neurons

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 GI tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

There are ganglia between the CNS and the effectors innervated by autonomic nerve system.

Preganglionic fiber, ganglion, postganglionic fiber




SYMPATHETIC DIVISION
Brain, brain stem, and spinal cord
EFFECTORS
PARASYMPATHETIC DIVISION
Brain, brain stem, and spinal cord
Lacrimal gland
Eye
Salivary glands
Trachea
Lungs
Ganglia
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

Functions of the sympathetic nervous system

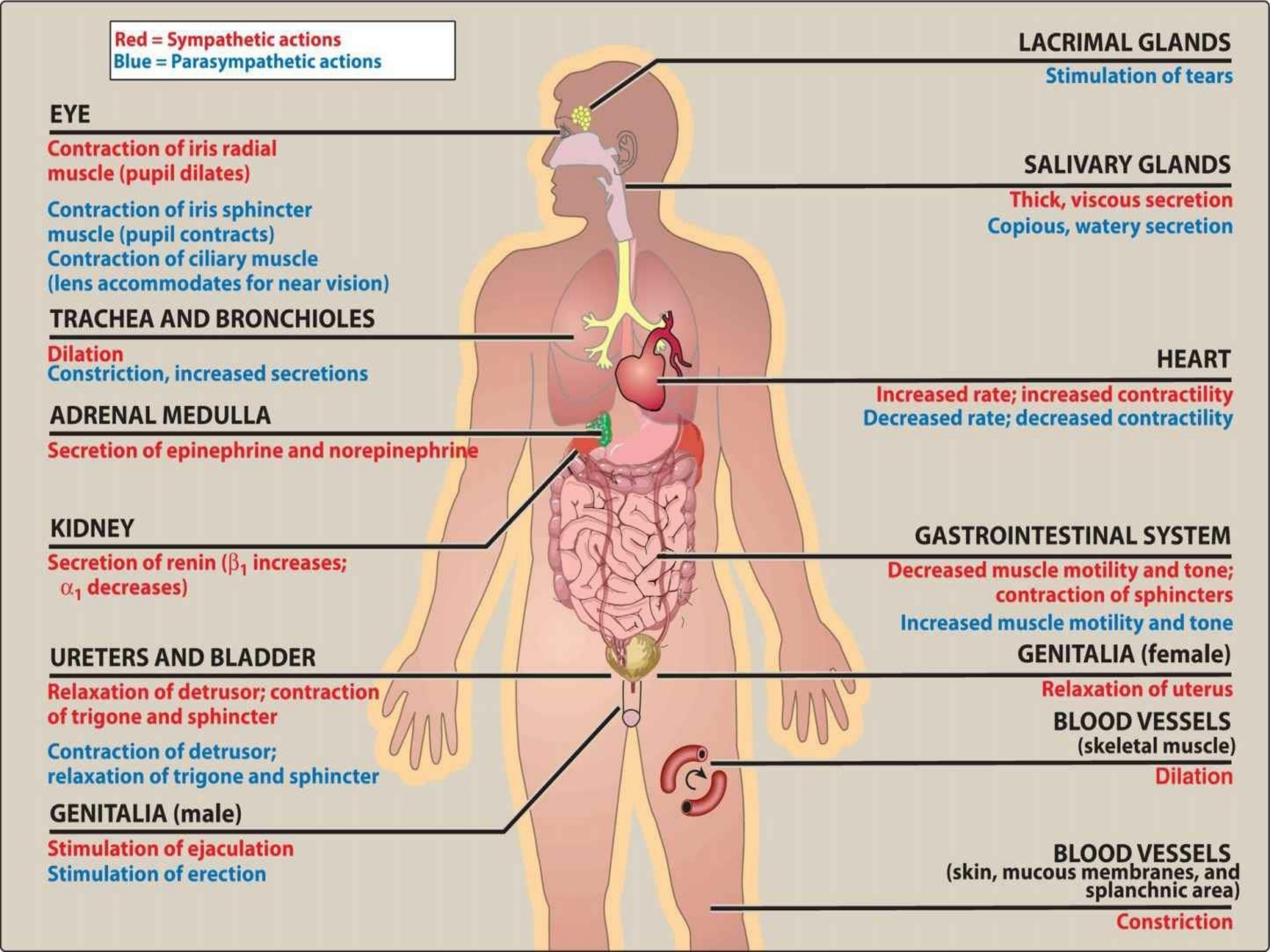
Although continually active to some degree (for example, in maintaining tone of vascular beds), the sympathetic division is responsible for adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise.

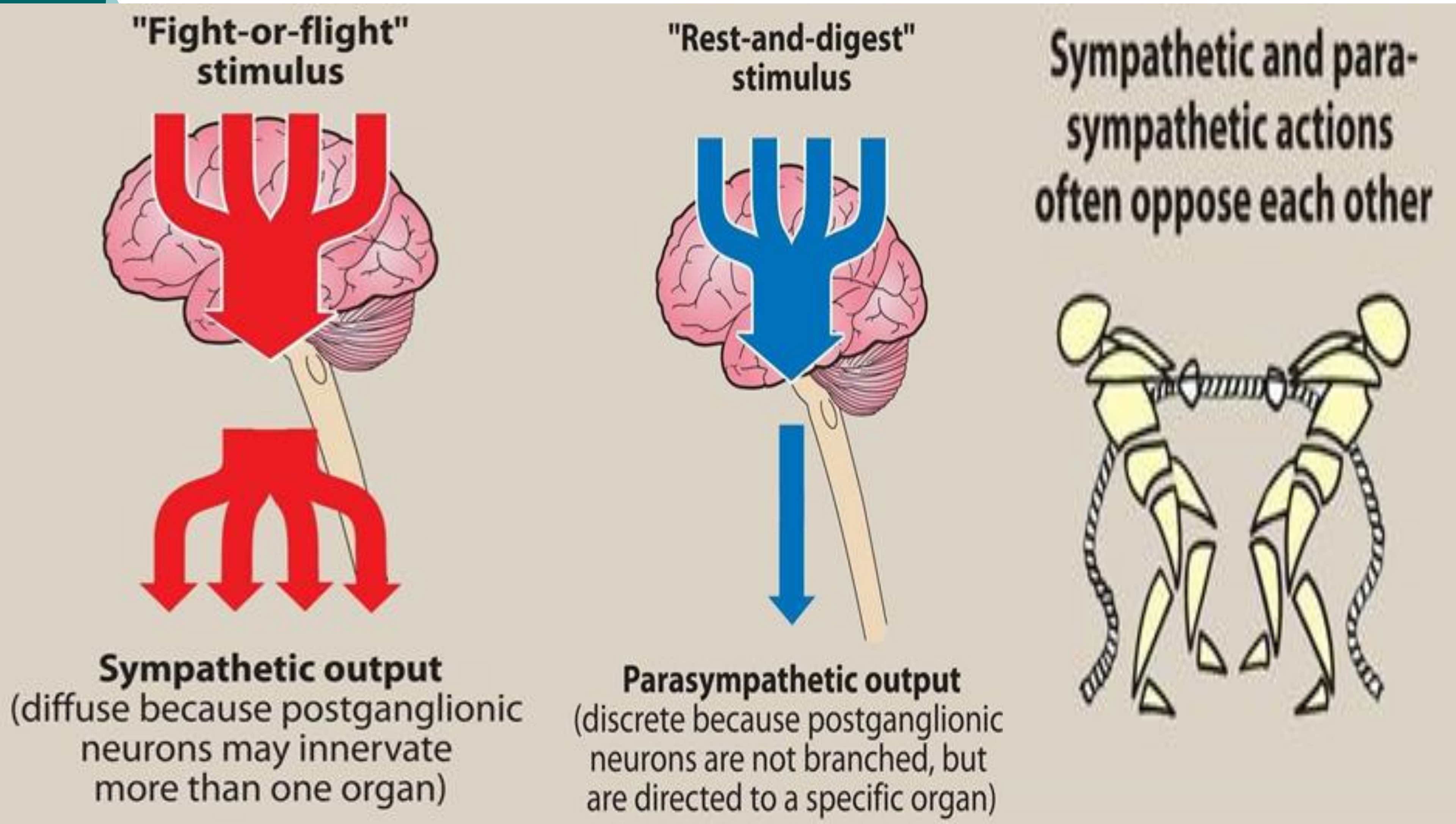
Effects of stimulation of the sympathetic division (fight or flight response)

1. Increase in heart rate and blood pressure
2. Mobilization of energy stores
3. Increase in blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs.
4. Dilation of the pupils and bronchioles.
5. Reduces GI motility and affects function of the bladder and sexual organs.

Functions of the parasympathetic nervous system

- Maintaining homeostasis within the body.
- It is required for life, since it maintains essential bodily functions, such as digestion and elimination.
- It acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in "rest-and-digest" situations.
- 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.
- It is innervating specific organs such as the gut, heart, or eye are activated separately, and the system affects these organs individually.


Red = Sympathetic actions
Blue = Parasympathetic actions
EYE
Contraction of iris radial muscle (pupil dilates)
Contraction of iris sphincter muscle (pupil contracts)
Contraction of ciliary muscle (lens accommodates for near vision)
TRACHEA AND BRONCHIOLES
Dilation
Constriction, increased secretions
ADRENAL MEDULLA
Secretion of epinephrine and norepinephrine
KIDNEY
Secretion of renin (β_1 increases; α_1 decreases)
URETERS AND BLADDER
Relaxation of detrusor; contraction of trigone and sphincter
Contraction of detrusor; relaxation of trigone and sphincter
GENITALIA (male)
Stimulation of ejaculation
Stimulation of erection
LACRIMAL GLANDS
Stimulation of tears
SALIVARY GLANDS
Thick, viscous secretion
Copious, watery secretion
HEART
Increased rate; increased contractility
Decreased rate; decreased contractility
GASTROINTESTINAL SYSTEM
Decreased muscle motility and tone; contraction of sphincters
Increased muscle motility and tone
GENITALIA (female)
Relaxation of uterus
BLOOD VESSELS (skeletal muscle)
Dilation
BLOOD VESSELS (skin, mucous membranes, and splanchnic area)
Constriction


"Fight-or-flight" stimulus
"Rest-and-digest" stimulus
Sympathetic and para-sympathetic actions often oppose each other
Sympathetic output
(diffuse because postganglionic neurons may innervate more than one organ)
Parasympathetic output
(discrete because postganglionic neurons are not branched, but are directed to a specific organ)

Role of the CNS in the control of autonomic functions

Although the ANS is a motor system, it does require sensory input from peripheral structures to provide information on the current state of the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus, medulla oblongata, and spinal cord. These centers respond to stimuli by sending out efferent reflex impulses via the ANS. Eaxmple Reflex arcs or emotions to ANS

1-Reflex arcs

Most of the afferent impulses are involuntarily translated into reflex responses. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the heart, vena cava, aortic arch, and carotid sinuses) to send fewer impulses to cardiovascular centers in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and heart rate. [Note: In each case, the reflex arcs of the ANS comprise a sensory (afferent) arm and a motor (efferent or effector) arm.]

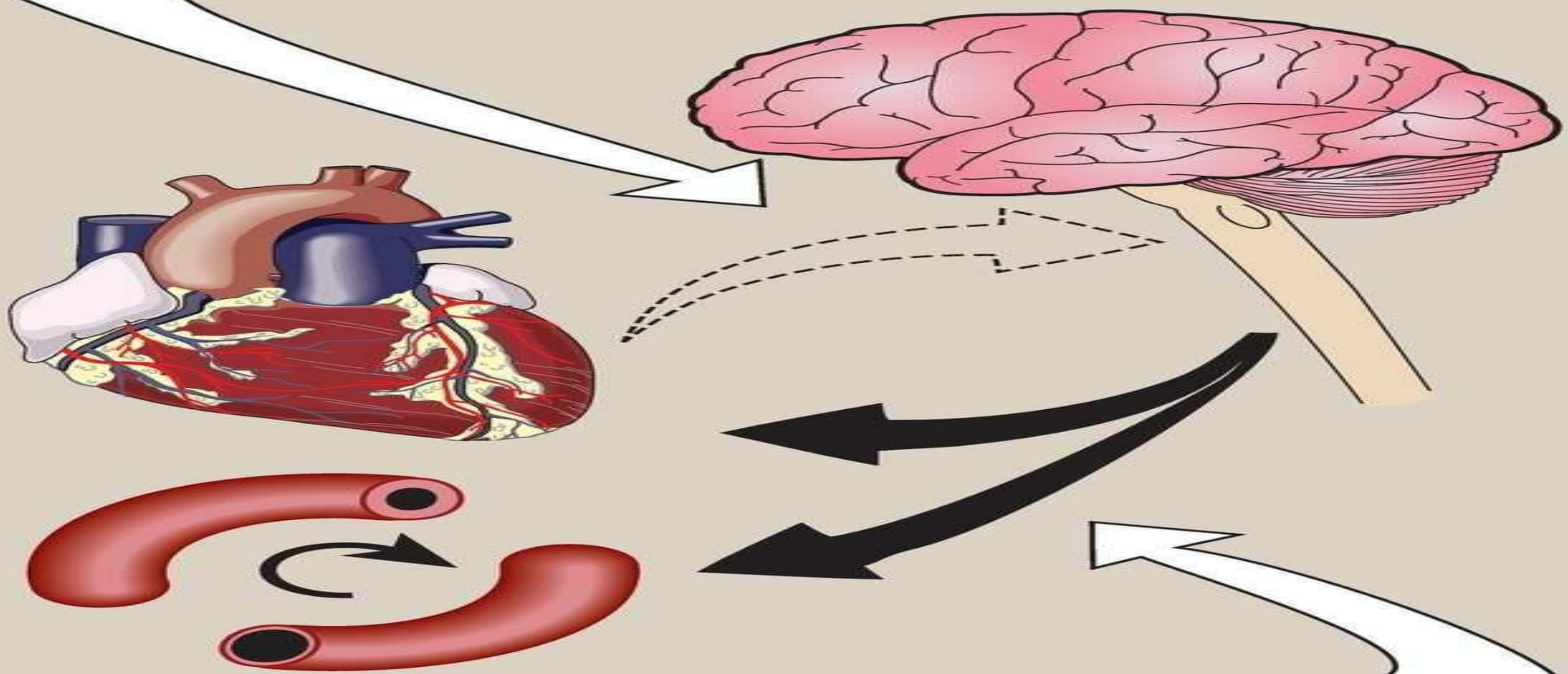
2- Emotions and ANS:

Stimuli that evoke strong feelings, such as rage, fear, and pleasure, can modify activities of the ANS.

1 AFFERENT INFORMATION

Sensory input from the viscera:

- Drop in blood pressure
- Reduced stretch of baroreceptors in the aortic arch
- Reduced frequency of afferent impulses to the medulla (brainstem)



2 REFLEX RESPONSE

Efferent reflex impulses via the autonomic nervous system cause:

- Inhibition of parasympathetic and activation of sympathetic divisions
- Increased peripheral resistance and cardiac output
- Increased blood pressure

Innervation of organs by ANS

1. Dual innervation

Most organs are innervated by both divisions of the ANS. Thus, vagal parasympathetic innervation slows the heart rate, and sympathetic innervation increases heart rate. Despite this dual innervation, one system usually predominates in controlling the activity of a given organ. For example, the vagus nerve is the predominant factor for controlling heart rate. The dual innervation of organs is dynamic, and fine-tuned continually to maintain homeostasis.

2. Sympathetic innervation

Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system.

Somatic nervous system

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.

Summary of differences between sympathetic, parasympathetic, and motor nerves

	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

Chemical Signaling Between Cells

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.

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 Ca^{2+} 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.

Membrane receptors

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.

Membrane receptors

- **Types of neurotransmitters**
- Although over 50 signal molecules in the nervous system have been identified, norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. ***Acetylcholine and norepinephrine are the primary chemical signals in the ANS, whereas a wide variety of neurotransmitters function in the CNS.***

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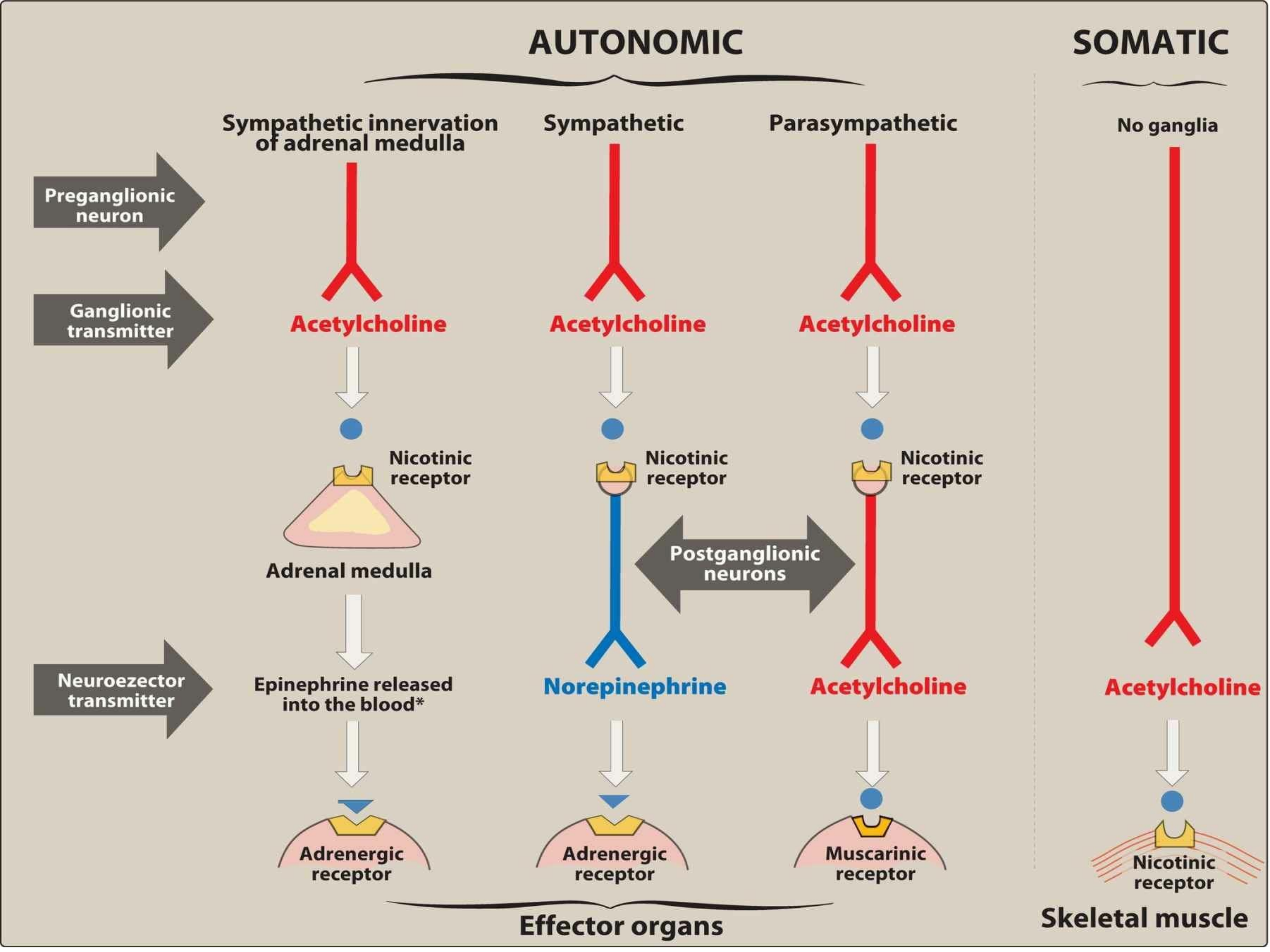
1-Acetylcholine

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

Norepinephrine and epinephrine

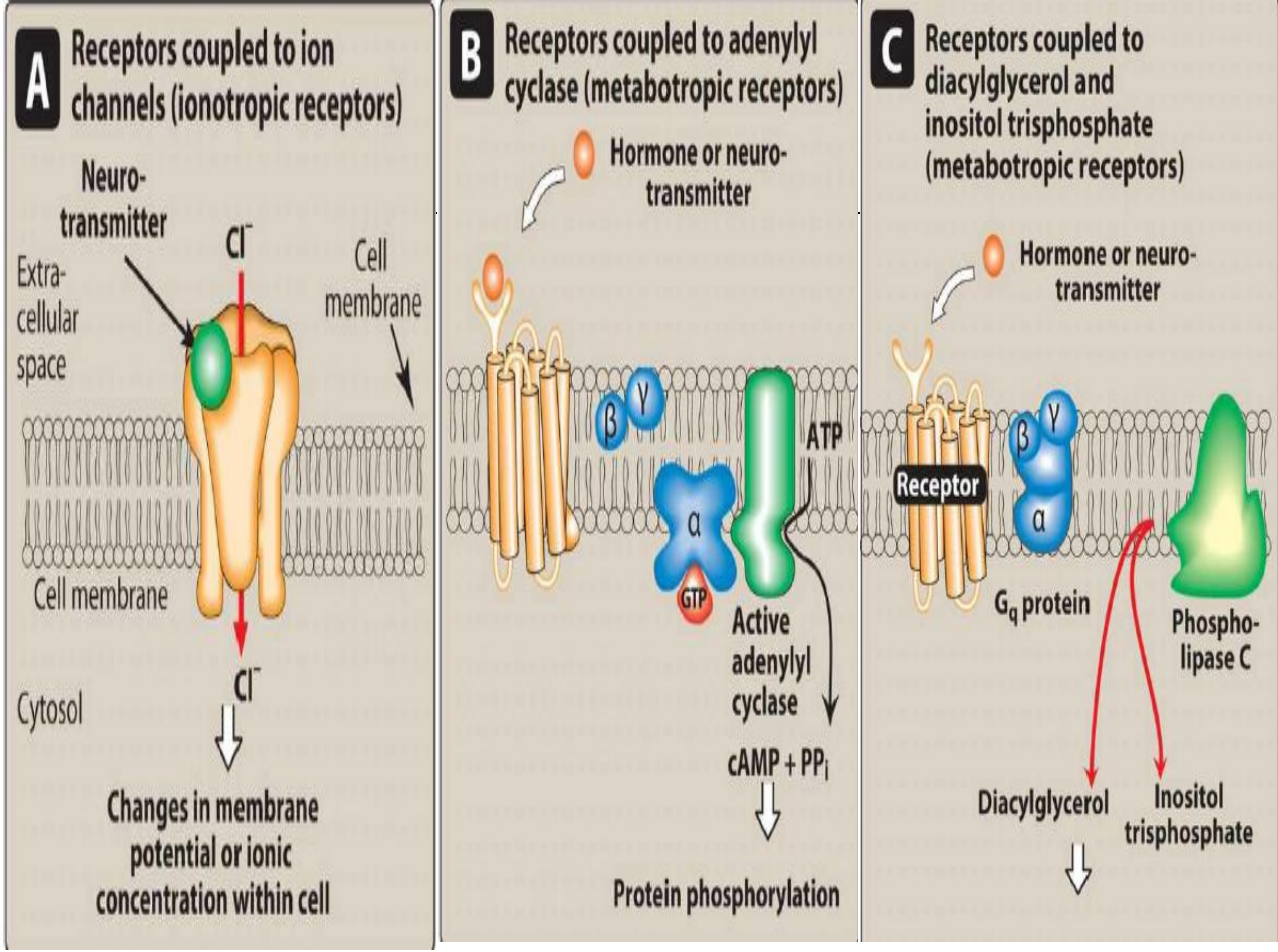
When norepinephrine is the neurotransmitter, the fiber is termed adrenergic. In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs. Epinephrine secreted by the adrenal medulla (not sympathetic neurons) also acts as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



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

Signal Transduction in the Effector Cell

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the phosphorylation of intracellular proteins or changes in the conductivity of ion channels. A neurotransmitter can be thought of as a signal and a receptor as a signal detector and transducer. The receptors in the ANS effector cells are classified as adrenergic or cholinergic based on the neurotransmitters or hormones that bind to them. Epinephrine and norepinephrine bind to adrenergic receptors (alpha and beta receptors, and acetylcholine binds to cholinergic receptors (nicotinic and muscarinic receptors). 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 (see the figure).


A
Receptors coupled to ion channels (ionotropic receptors)
Neuro-transmitter
Cl⁻
Extra-cellular space
Cell membrane
Cell membrane
Cl⁻
Cytosol
Changes in membrane potential or ionic concentration within cell
B
Receptors coupled to adenylyl cyclase (metabotropic receptors)
Hormone or neuro-transmitter
β
γ
ATP
α
GTP
Active adenylyl cyclase
cAMP + PPi
Protein phosphorylation
C
Receptors coupled to diacylglycerol and inositol trisphosphate (metabotropic receptors)
Hormone or neuro-transmitter
β
γ
Receptor
α
Gq protein
Phospho-lipase C
Diacylglycerol
Inositol trisphosphate

Questions & Discussion