Pharmacology I

Drugs Affecting the Autonomic Nervous System
The Autonomic Nervous System

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Lecture No. : 3

I. Chapter Outlines

1. The fundamental physiology of the ANS.
2. Describes the role of **neurotransmitters** in the communication between extracellular events and chemical changes within the cell.

I. Overview

- The autonomic nervous system (ANS), along with the endocrine system, coordinates the **regulation and integration of bodily functions**.
- The **endocrine system** sends **signals** to target tissues by varying the levels of blood-borne **hormones**.
- By contrast, the **nervous system** exerts effects by the rapid transmission of **electrical impulses** over nerve fibers that terminate at **effector cells**, which specifically respond to the release of **neuromediator substances**.

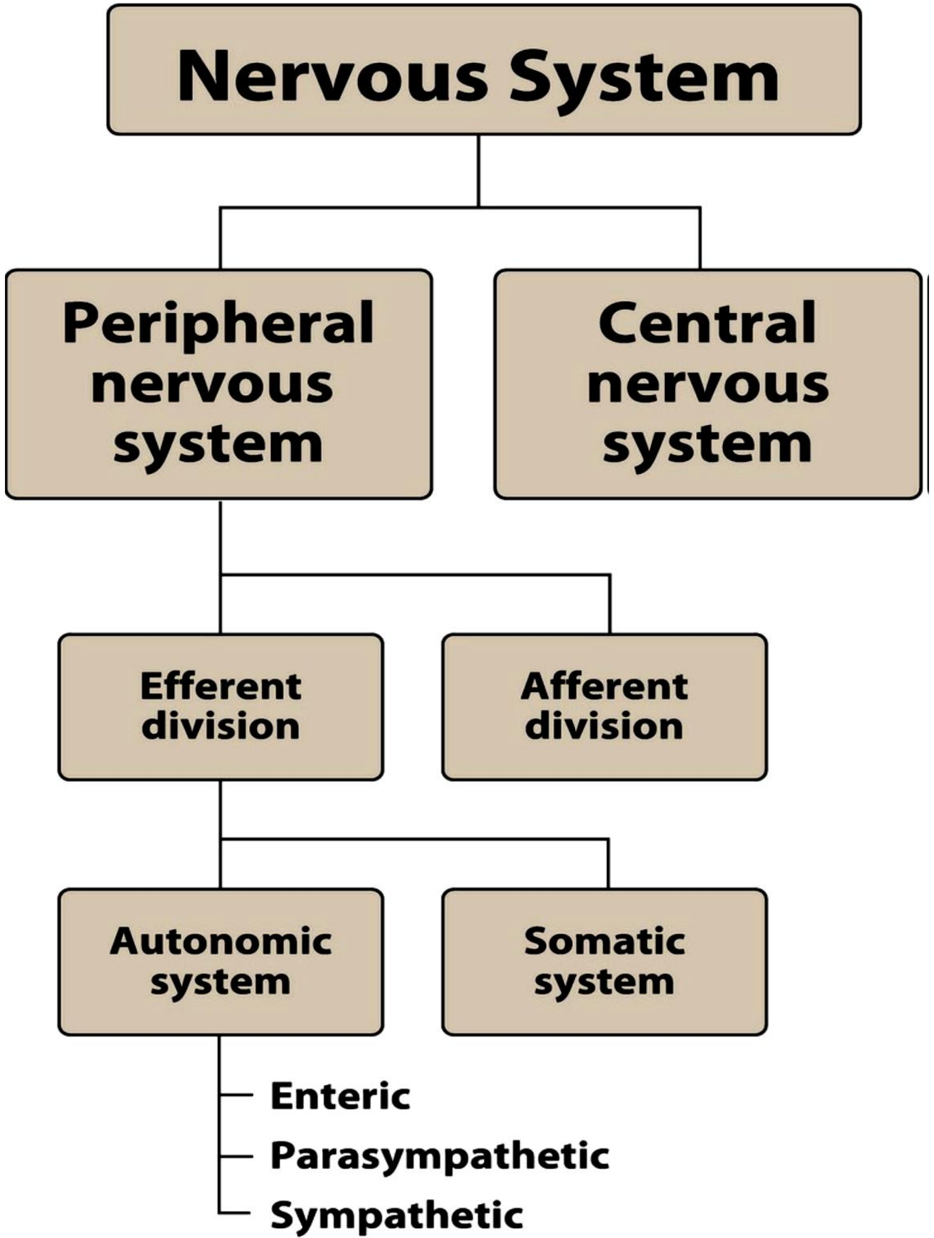
Autonomic drugs

- Drugs that produce their primary therapeutic effect by **mimicking** or **altering** the functions of the autonomic nervous system (ANS) are called **autonomic drugs**.
- The autonomic agents act either by **stimulating** portions of the ANS or by **blocking** the action of the autonomic nerves.

Introduction to the Nervous System

- The **nervous system** is divided into two **anatomical divisions**:

1. **The central nervous system (CNS)**, which is composed of **the brain and spinal cord**
2. **The peripheral nervous system**, which includes neurons located outside the brain and spinal cord—that is, any nerves that enter or leave the CNS .

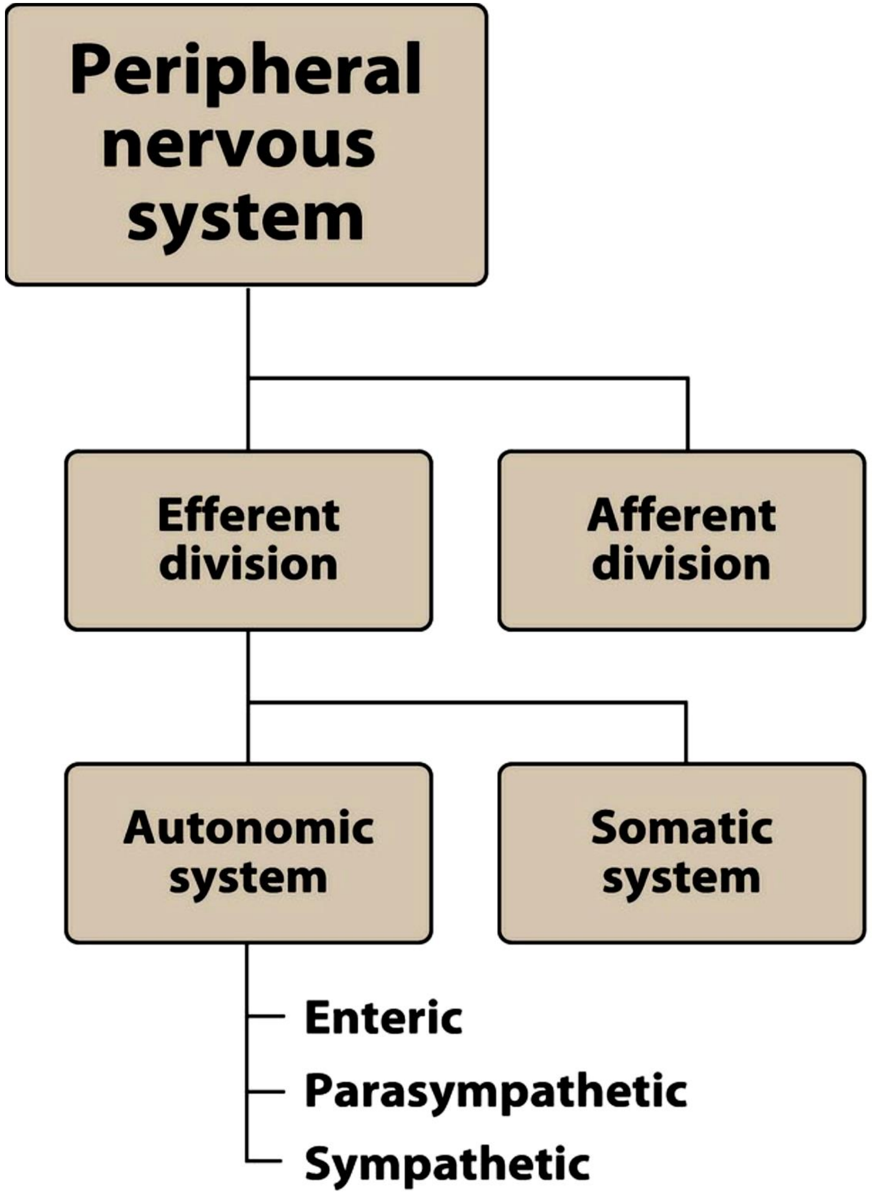


Introduction to the Nervous System

- **The peripheral nervous system is subdivided into:**

1. **The Efferent (motor) neurons** carry signals away from the brain and spinal cord to the peripheral tissues.
2. **The Afferent (sensory) neurons** bring information from the periphery to the CNS.

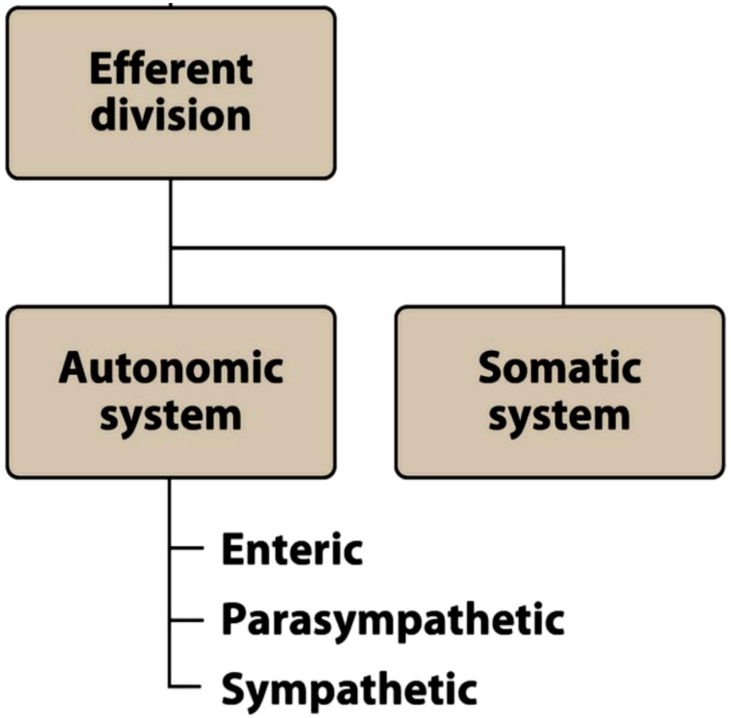
- Afferent neurons provide **sensory input** to modulate the function of the efferent division through **reflex arcs or neural pathways** that mediate a reflex action.



Functional divisions within the nervous system

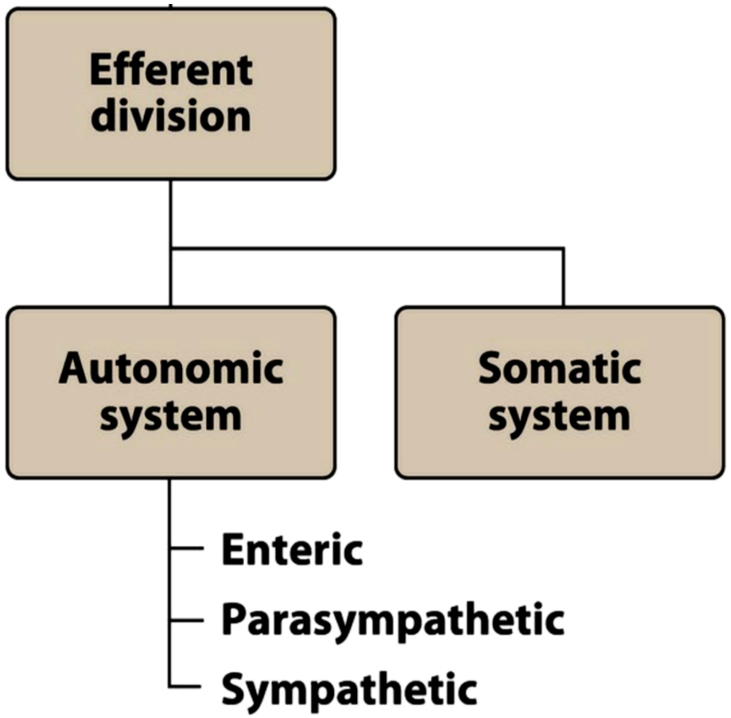
- The efferent portion of the peripheral nervous system is further divided into two subdivisions:

1. The somatic nervous system and
2. The ANS .



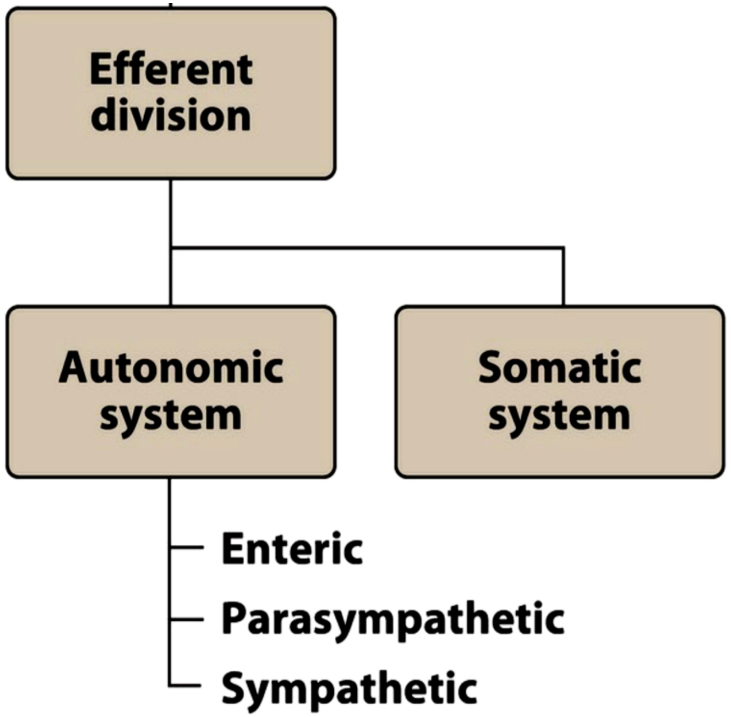
The somatic efferent neurons

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



ANS

- The ANS, conversely, **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.**



ANS

- **It is composed of efferent neurons that innervate**

1. Visceral smooth muscle,
2. Cardiac muscle,
3. Vasculature,
4. Exocrine glands

- **Thereby controlling**

1. Digestion,
2. Cardiac output,
3. Blood flow,
4. Glandular secretions.

B. Anatomy of the ANS

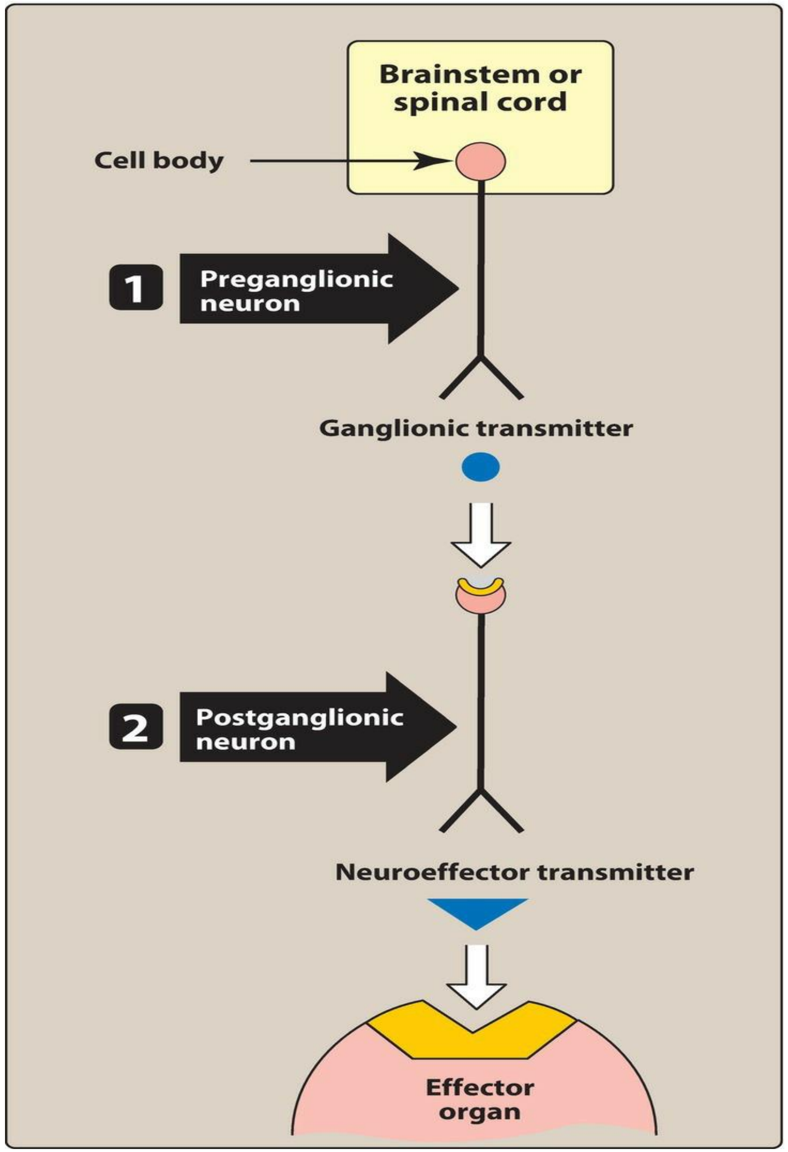
1. Efferent neurons

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

A. **The preganglionic neurons**

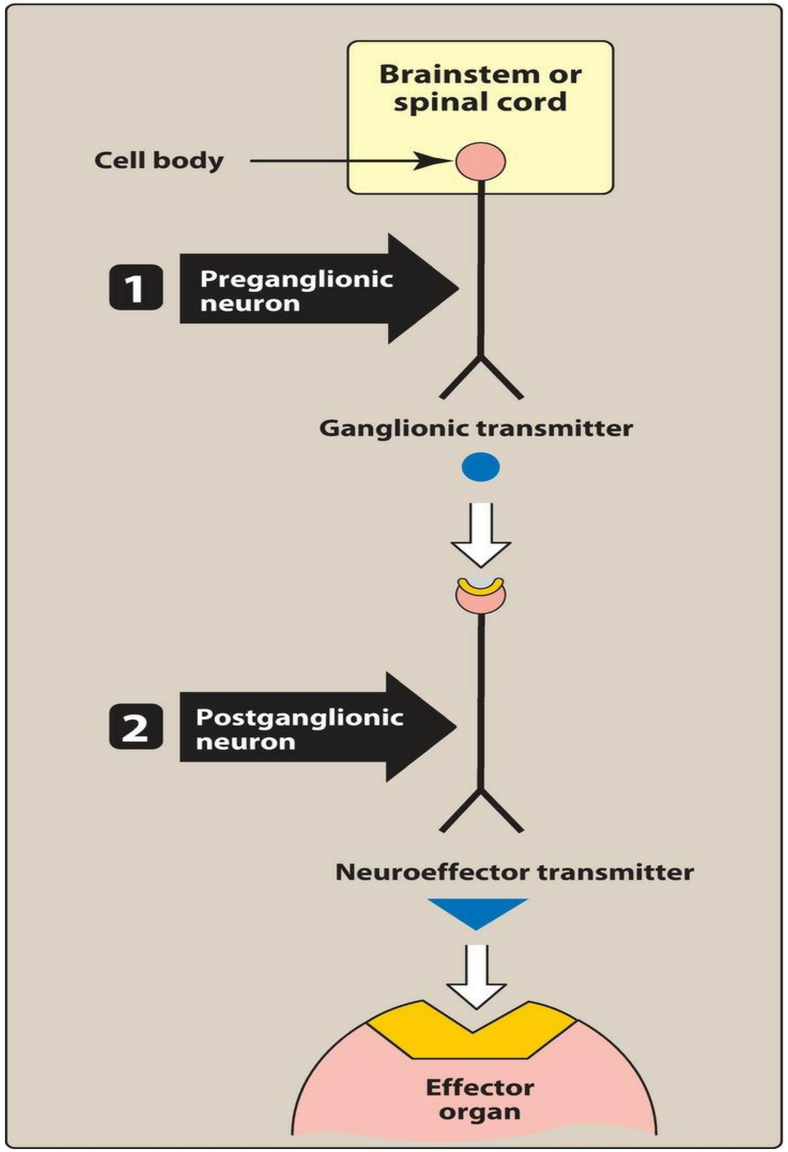
B. **The postganglionic neurons.**

- 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).



Efferent neurons of the autonomic 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 **nonmyelinated and terminates on effector organs**, such as visceral smooth muscle, cardiac muscle, and the exocrine glands.



Efferent neurons of the autonomic nervous system.

2. Afferent neurons

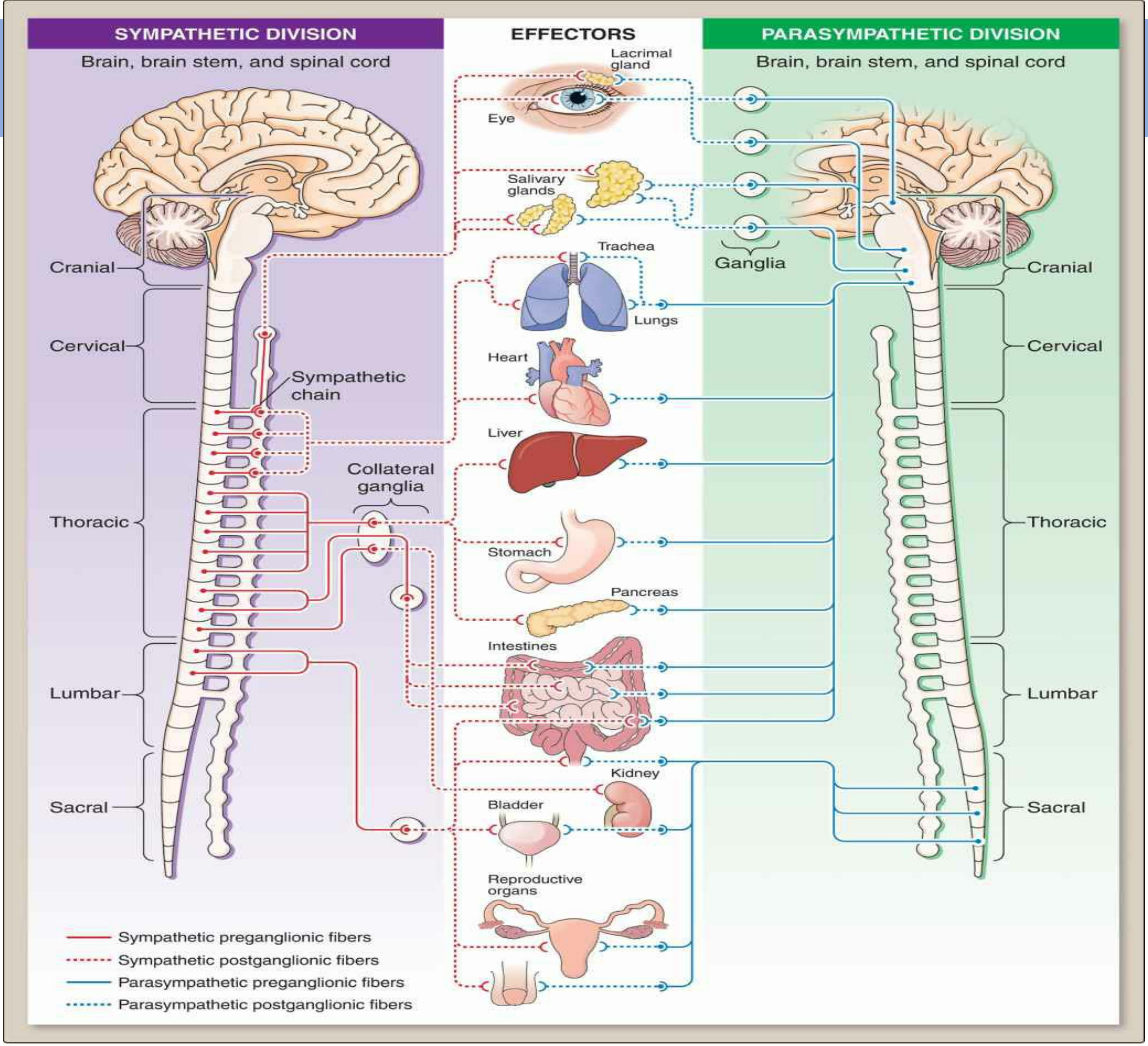
- The afferent neurons (fibers) of the ANS are important in:

1. The **reflex regulation** of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and
2. **In signaling the CNS to influence** the efferent branch of the system to respond.

3. Sympathetic neurons (fight and flight):

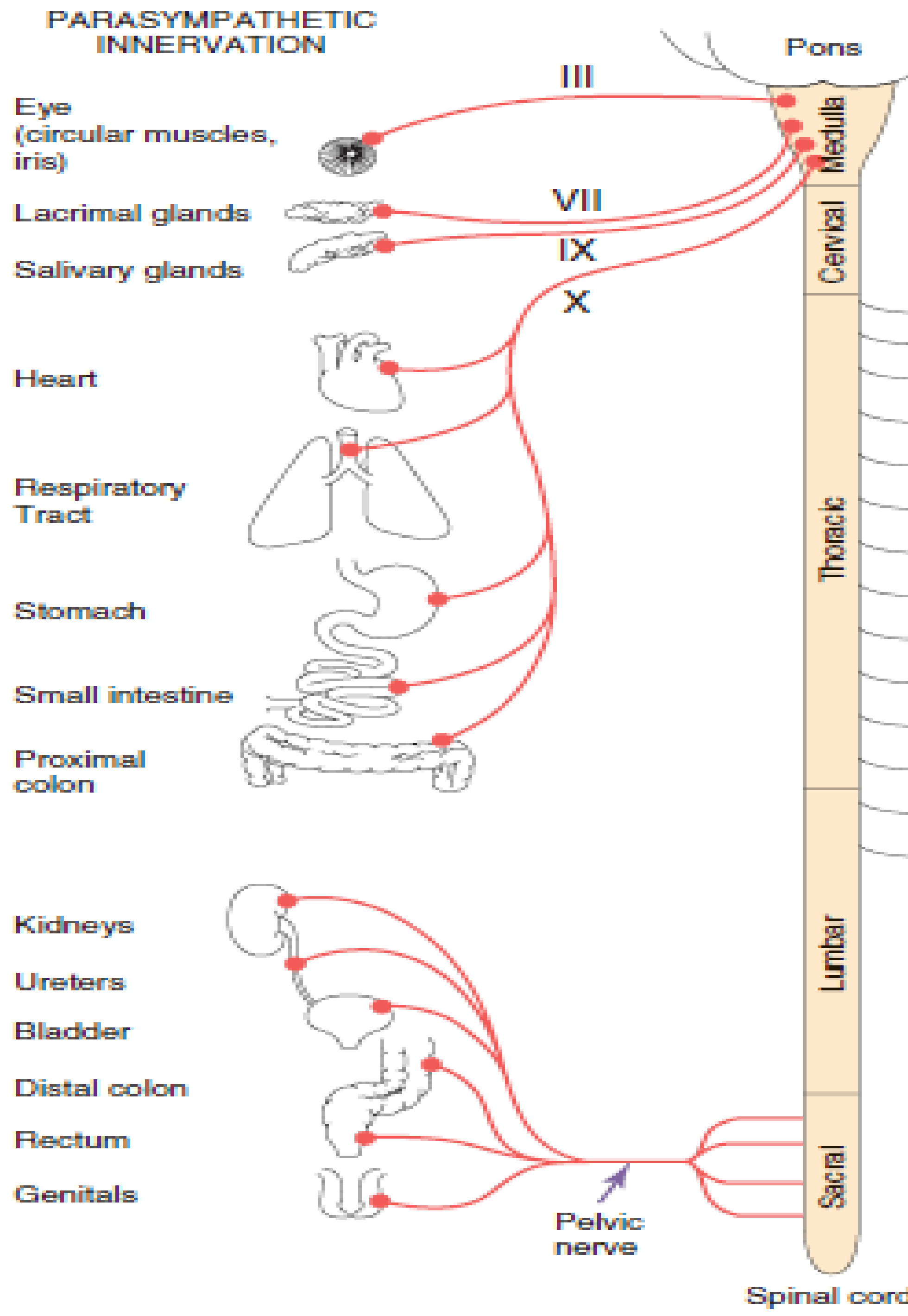
- The efferent ANS is divided into the **sympathetic** and the **parasympathetic** nervous systems, as well as the **enteric nervous system**.
- Anatomically, the sympathetic and the parasympathetic neurons **originate** in the **CNS** and **emerge from two different spinal cord regions**.
- The preganglionic neurons of the **sympathetic** system come from the **thoracic and lumbar regions** (T1 to L2) of the spinal cord.
- **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.]


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

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**.



4. Parasympathetic neurons

- *[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 :

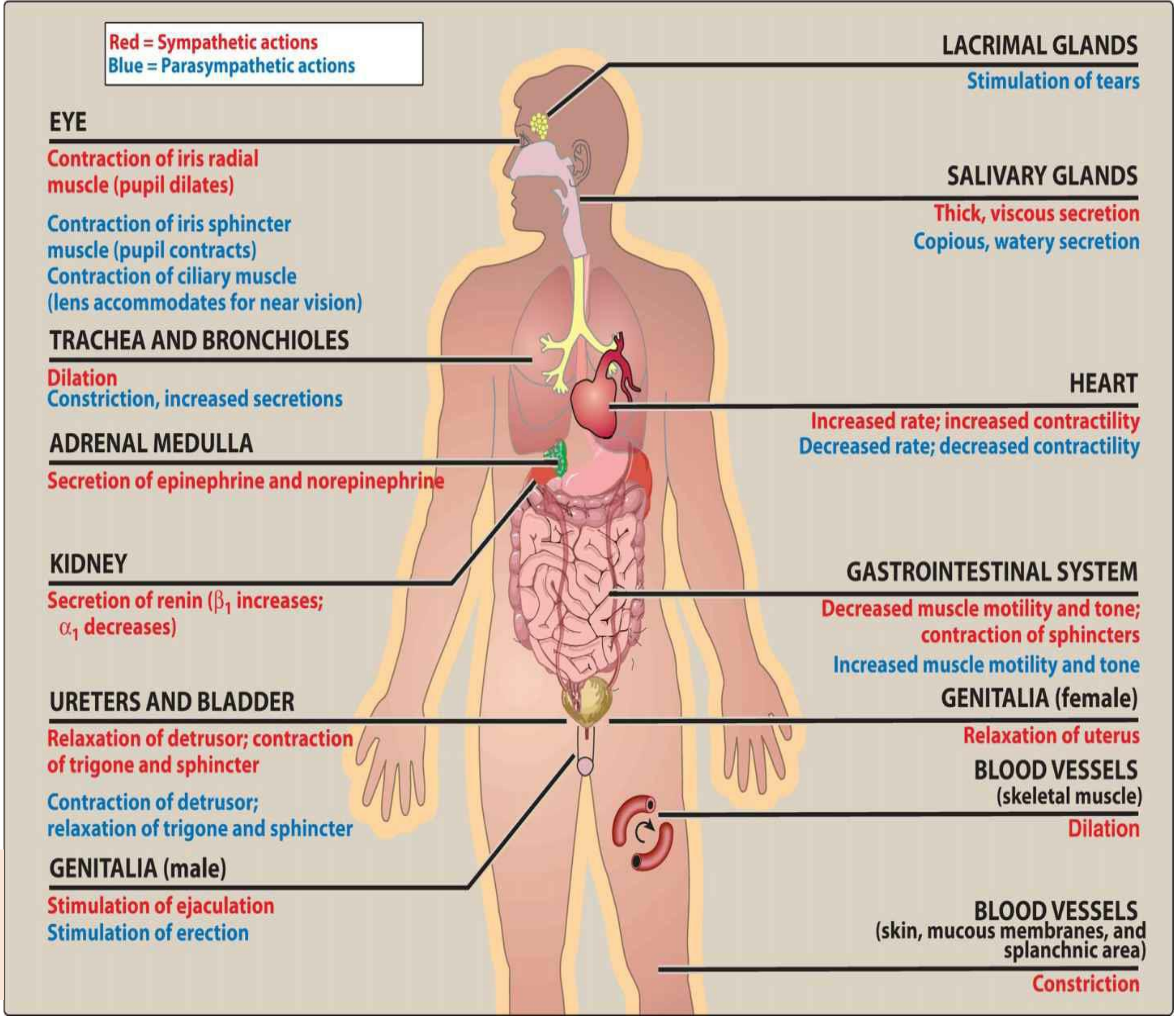
1. The gastrointestinal (GI) tract,
2. Pancreas,
3. Gallbladder,

- 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.

C. 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.

C. Functions of the sympathetic nervous system

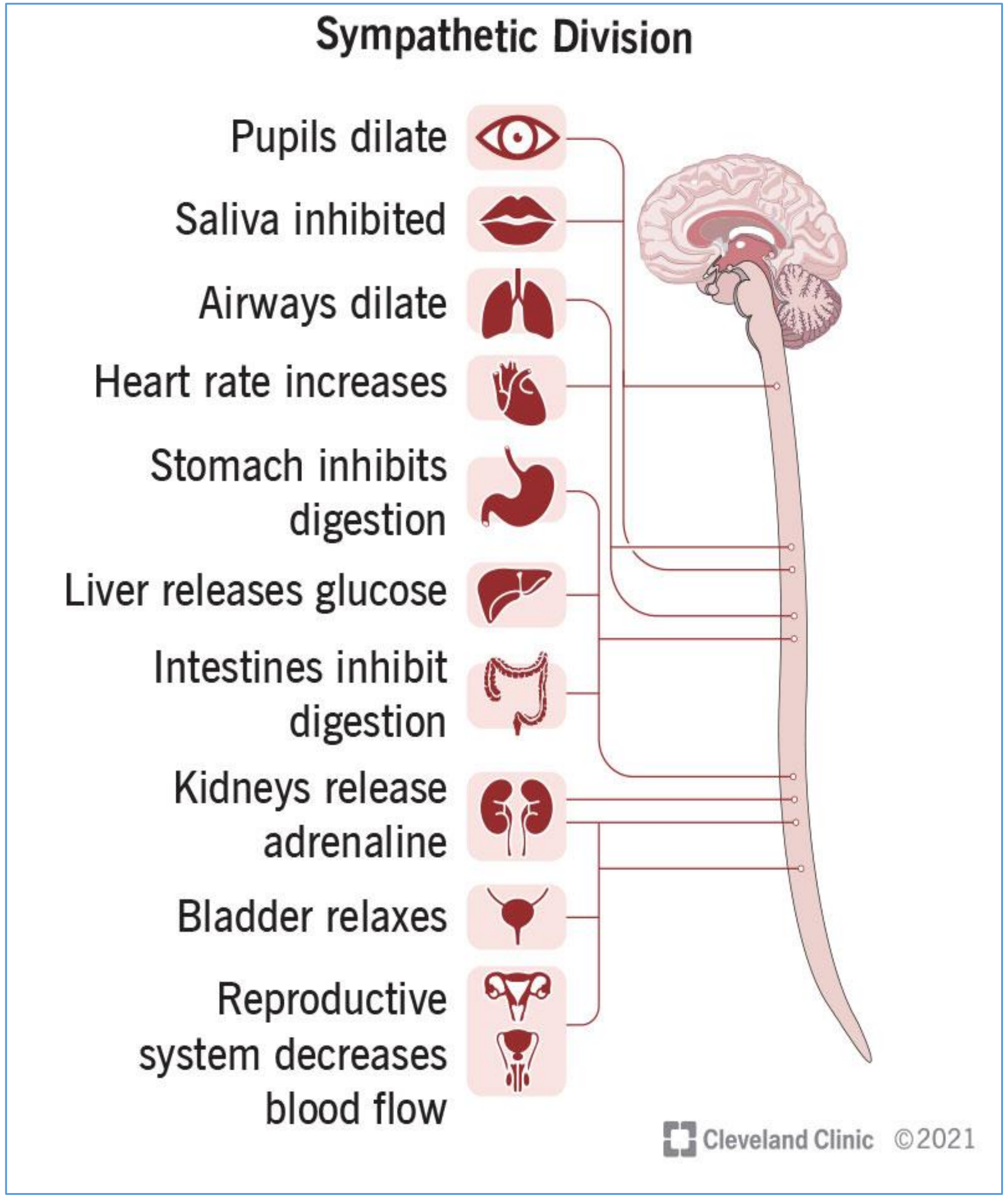


Actions of sympathetic and parasympathetic nervous systems on effector organs.

1. Effects of stimulation of the sympathetic division

- **The effect of sympathetic stimulation is**

1. An increase in **heart rate and blood pressure**,
2. **Mobilization of energy stores**, and
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.



2. Fight or flight response

- The changes experienced by the body **during emergencies** are referred to as the “**fight or flight**” response. These reactions are triggered both

1. By **direct sympathetic activation** of effector organs and
2. **By stimulation of the adrenal medulla** to release epinephrine and lesser amounts of norepinephrine. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain **adrenergic receptors**.

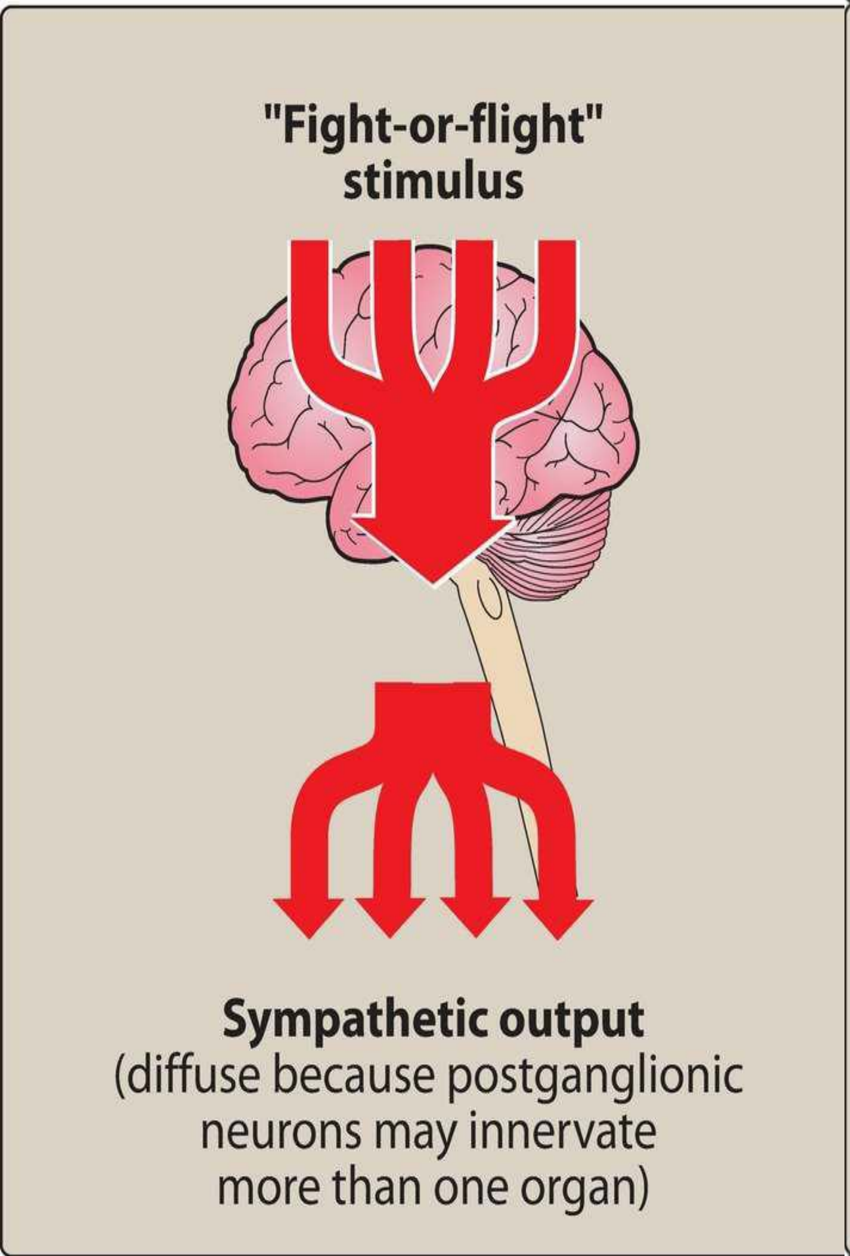
- The sympathetic nervous system tends to **function as a unit** and often **discharges as a complete system**, for example, during severe exercise or in reactions to fear. This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities.
- Although it is not essential for survival, it is essential in preparing the body to handle uncertain situations and unexpected stimuli.

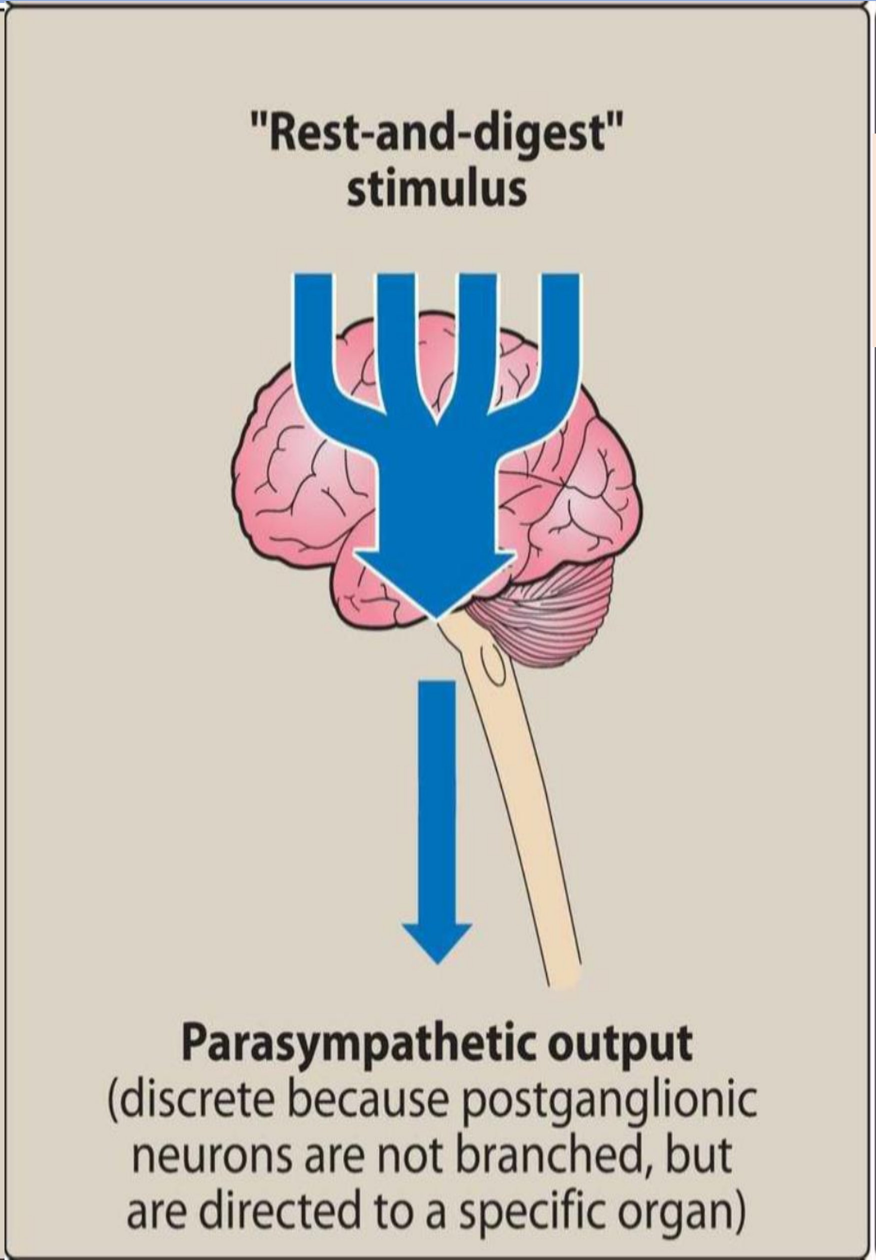
D. Functions of the parasympathetic nervous system

- The parasympathetic division is involved **with maintaining homeostasis within the body.**
- It is required for life, since it maintains essential bodily functions, such as **digestion and elimination**.
- The parasympathetic division usually **acts to oppose or balance the actions** of the sympathetic division and generally predominates the sympathetic system in “rest-and-digest” situations.

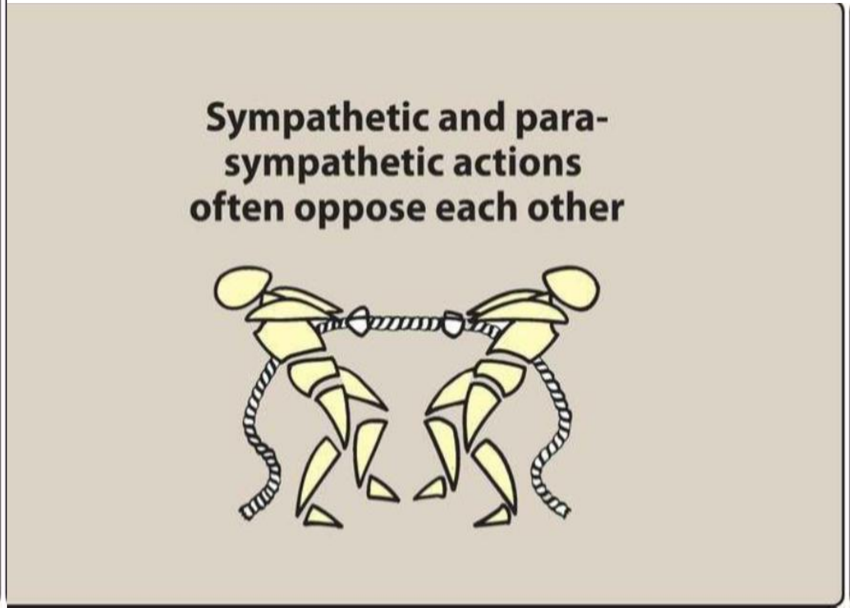
D. Functions of the parasympathetic nervous system

- Unlike the sympathetic system, **the parasympathetic system never discharges as a complete system**. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation.
- Instead, parasympathetic fibers innervating specific organs such as the gut, heart, or eye **are activated separately,** and the system affects these organs **individually**.





Sympathetic and parasympathetic actions are elicited by different stimuli.



E. 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.

F. Innervation by the 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.
- This type of antagonism is considered to be dynamic and is fine-tuned continually to **control homeostatic organ functions**.

F. Innervation by the ANS

2. Sympathetic innervation

- Although most tissues receive dual innervation, some effector organs, such as:

1. The **adrenal medulla,**
2. **Kidney,**
3. **Pilomotor muscles, and**
4. **Sweat glands**, receive innervation only from the **sympathetic system**.

G. 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.

H. Summary of differences between sympathetic, parasympathetic, and motor nerves

- Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division.
- The **sympathetic** nervous system is widely **distributed**, innervating practically **all effector systems** in the body.
- By contrast, the distribution of the **parasympathetic** division is more **limited**.

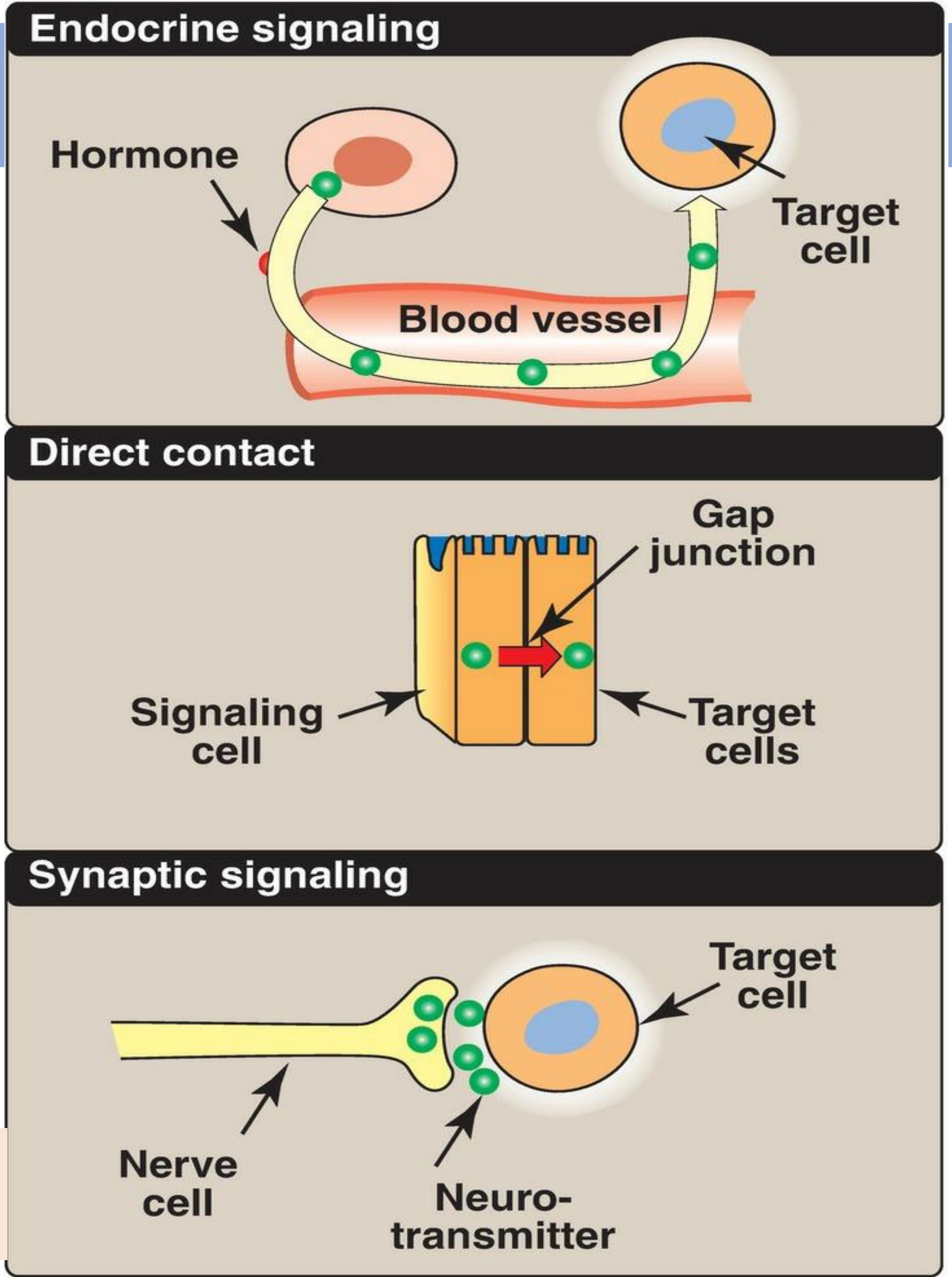
H. Summary of differences between sympathetic, parasympathetic, and motor nerves

- The **sympathetic preganglionic fibers** have a much broader influence than the **parasympathetic** fibers and synapse with a larger number of postganglionic fibers.
- This type of organization permits a **diffuse discharge of the sympathetic nervous** system.
- The parasympathetic division is **more circumscribed**, with **mostly one-to-one interactions**, and the **ganglia are also close to, or within, organs** they innervate. This limits the amount of branching that can be done by this division.

	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

III. Chemical Signalling 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**.



Some commonly used mechanisms for transmission of regulatory signal between cells.

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

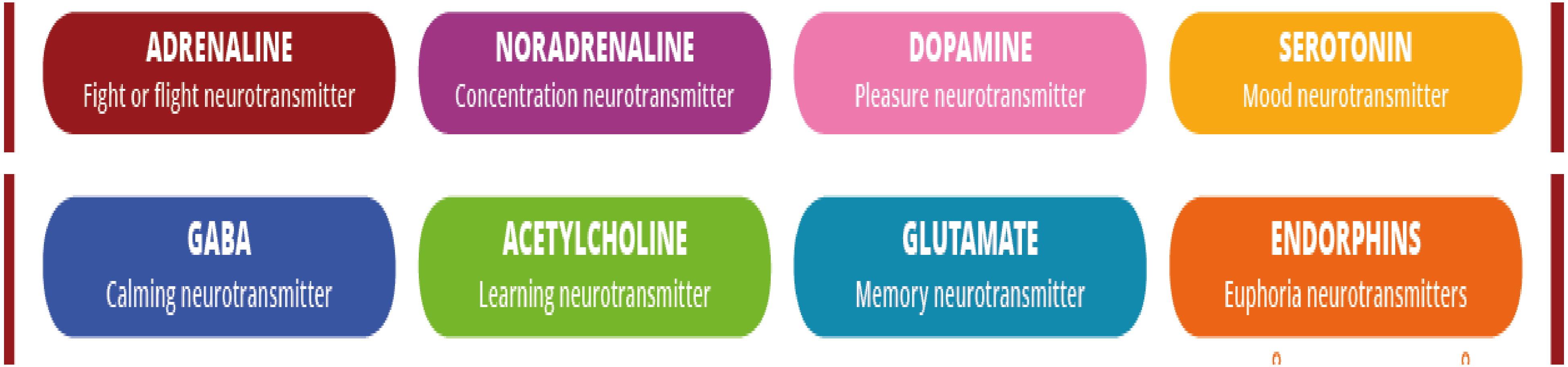
- **Communication** between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (**neurotransmitters**) from the nerve terminals.
- The release is triggered by arrival of the action potential at the nerve ending, leading to depolarization.
- An **increase in intracellular 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.

1. 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.

2. 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.



2. Types of neurotransmitters

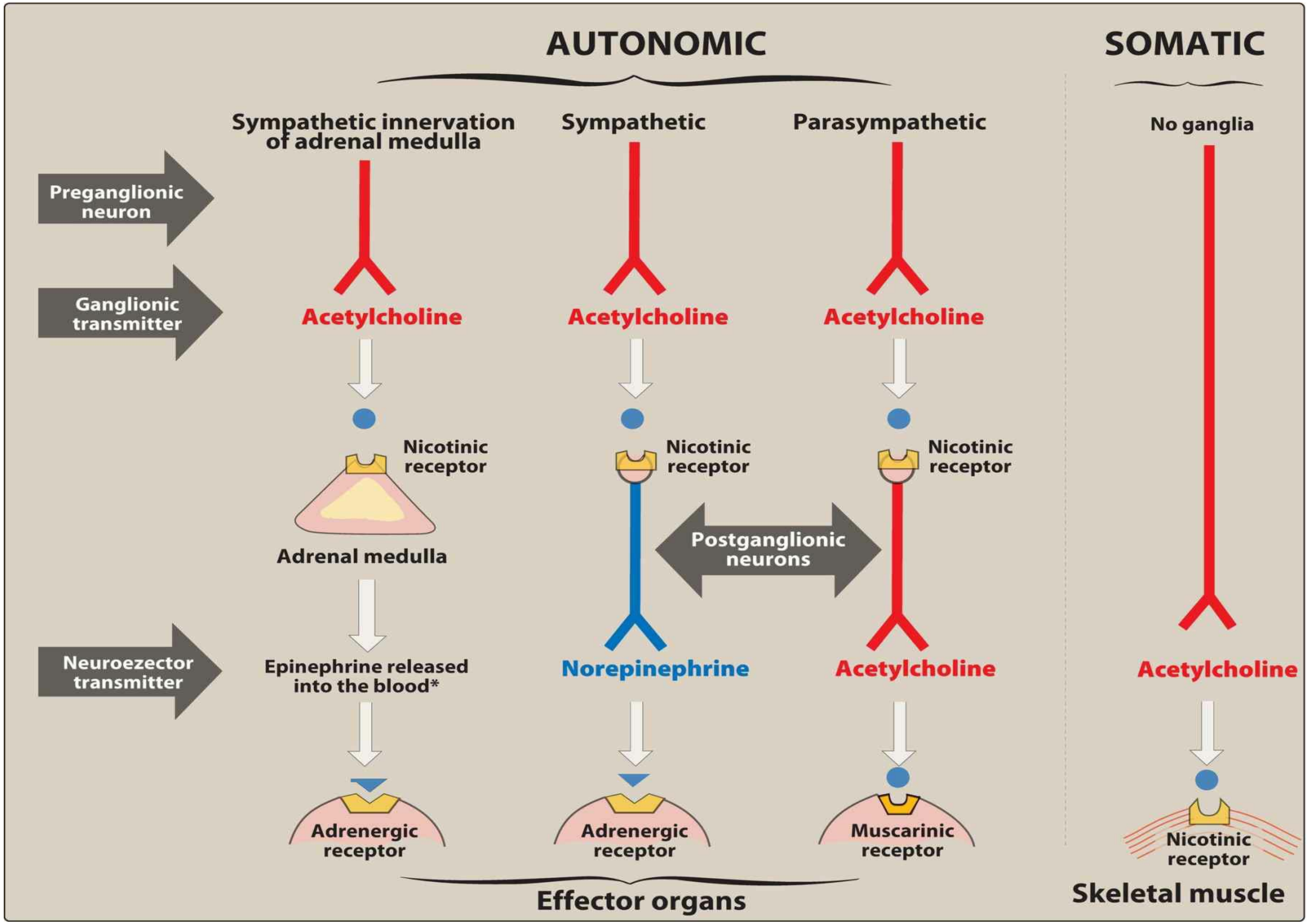
- Each of these chemical signals binds to a specific family of receptors. **Acetylcholine and norepinephrine** are the primary chemical signals in the **ANS**, whereas a wide variety of neurotransmitters function in the CNS.

3. 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**.

1. Acetylcholine mediates the transmission of nerve impulses across **autonomic ganglia in both the sympathetic and parasympathetic nervous systems**.
2. It is the neurotransmitter at **the adrenal medulla**.
3. 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.
4. In the somatic nervous system, **transmission at the neuromuscular junction** (the junction of nerve fibers and voluntary muscles) is also cholinergic.

Summary of the neurotransmitters released, types of receptors, and types of neurons within the autonomic and somatic nervous systems. Cholinergic neurons are shown in *red* and adrenergic neurons in *blue*. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit.] *Epinephrine 80% and norepinephrine 20% released from adrenal medulla.



4. 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**, and, for simplicity, they are not shown in Figure]

IV. 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.
- Second messenger molecules produced in response to a neurotransmitter binding to a receptor translate the extracellular signal into a response that may be further propagated or amplified within the cell.
- Each component serves as a link in the communication between extracellular events and chemical changes within the cell.

A. Membrane receptors affecting ion permeability (ionotropic receptors)

- Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules.
- 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**.
- Therefore, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability.
- These types of receptors are known as **ionotropic receptors**.

B. Membrane receptors coupled to second messengers (metabotropic receptors)

- All **adrenergic** receptors and **cholinergic muscarinic** receptors are **G protein**–coupled receptors (**metabotropic receptors**).
- Many receptors are not directly coupled to ion channels.
- Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions that ultimately result in a specific intracellular response.
- **Second messenger molecules**, so named because they intervene between the original message (the neurotransmitter or hormone) and the ultimate effect on the cell, are part of the cascade of events that translate neurotransmitter binding into a cellular response, usually through the intervention of a G protein.

B. Membrane receptors coupled to second messengers (metabotropic receptors)

- The two most widely recognized second messengers are the **adenylyl cyclase system** and the **calcium/phosphatidylinositol** system .
- The receptors coupled to the second messenger system are known as **metabotropic receptors**.
- **Muscarinic and adrenergic receptors** are examples of metabotropic receptors.

Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.