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Pharmacology

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Autonomic Pharmacology

Basic principles of neuropharmacology

The nervous system has two main divisions: the central nervous system (CNS) and the peripheral nervous system (PNS).

Divisions of the human nervous system.

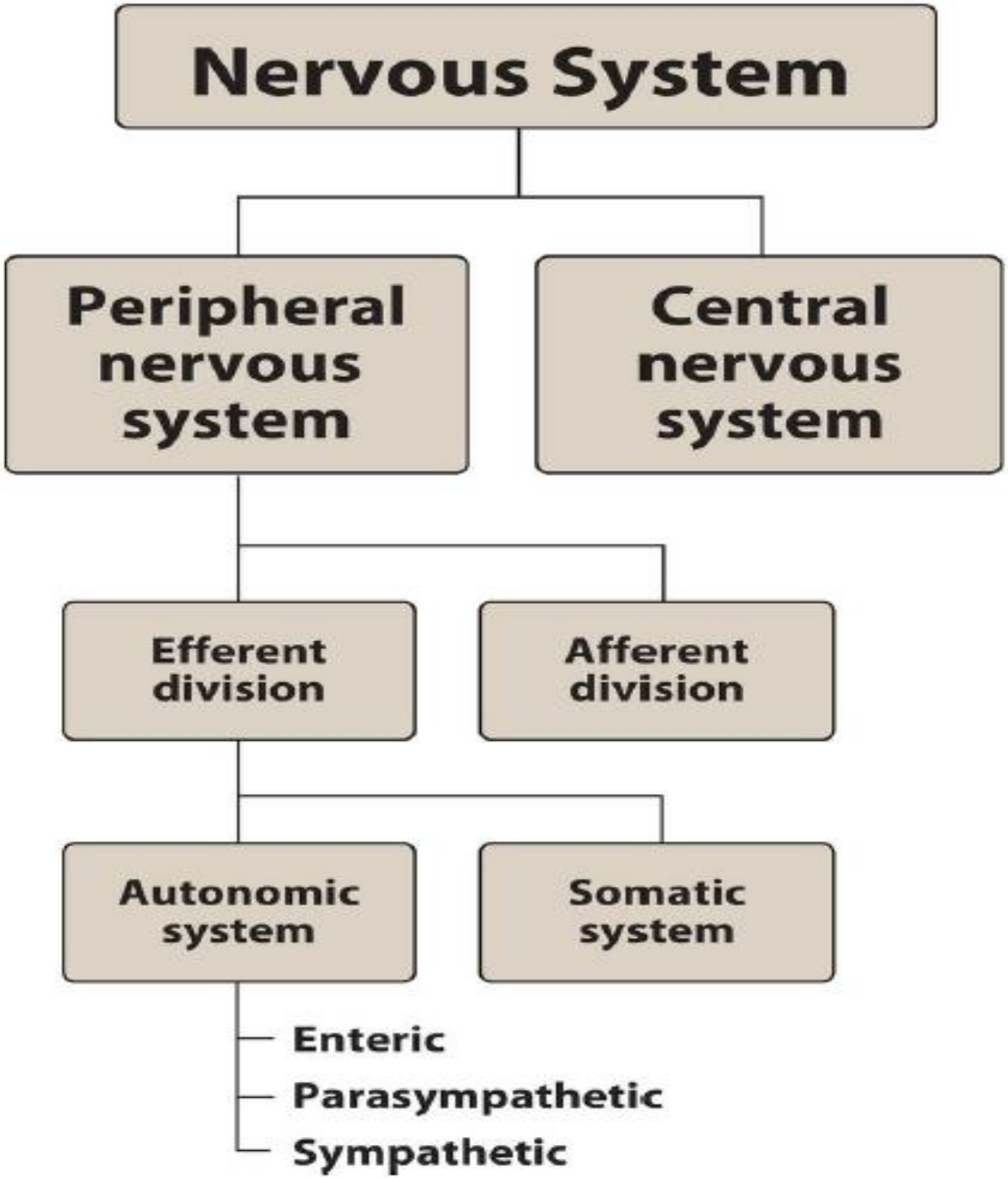
The CNS includes the **brain** and **spinal cord**. It receives and processes incoming sensory information and responds by sending out signals that initiate or modify body processes.

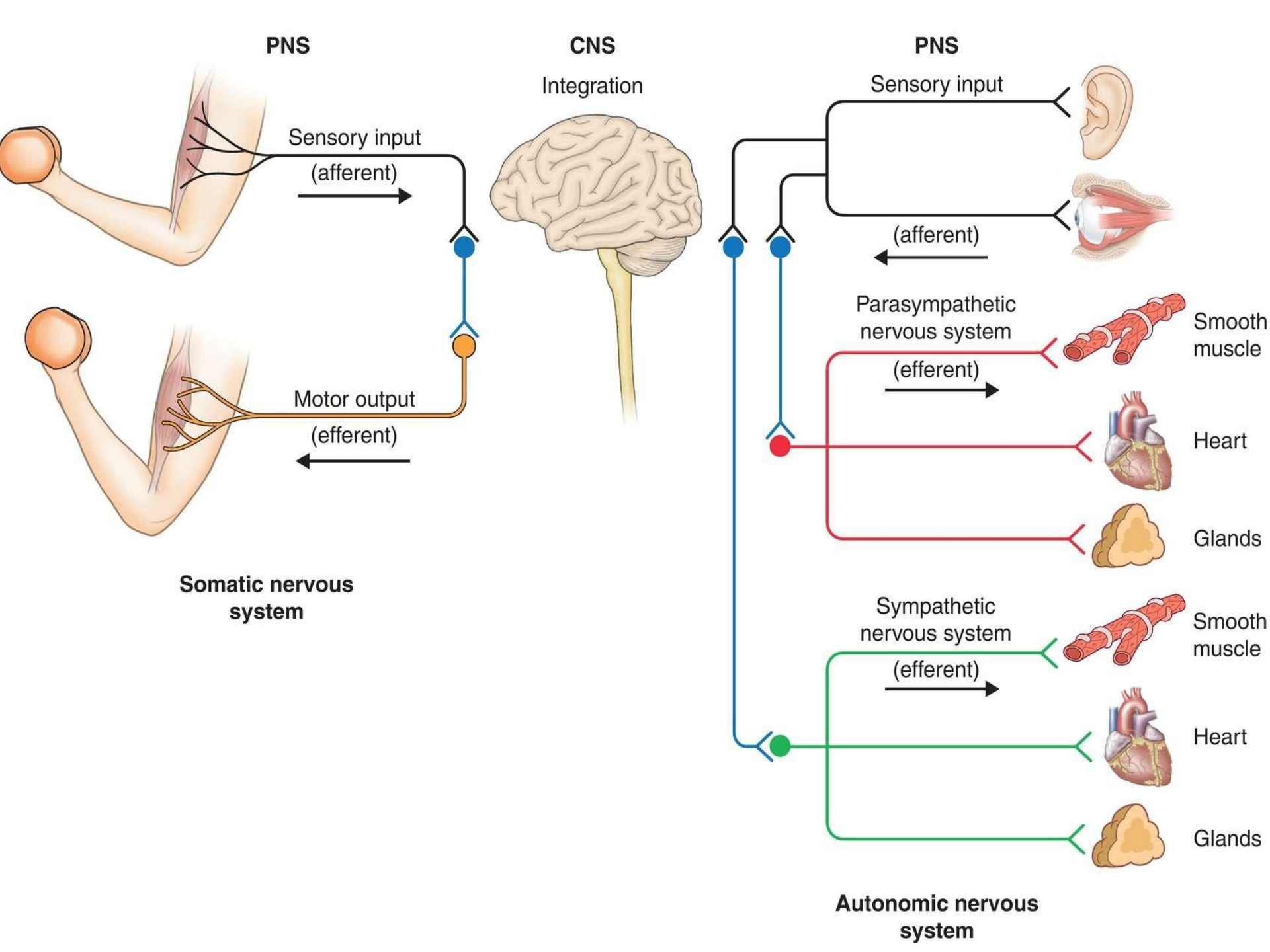
The PNS includes all the neurons and ganglia found outside the CNS.

Afferent neurons carry sensory input **from the periphery** to the CNS and modify motor output through the action of reflex arcs.

Efferent neurons carry motor signals **from the CNS** to the peripheral areas of the body.

Ganglia are nerve cell clusters that house the cell bodies of the afferent nerves .The efferent portion of the PNS has two subdivisions: the **somatic nervous** system and the **autonomic nervous** system (ANS).


Nervous System
Peripheral nervous system
Central nervous system
Efferent division
Afferent division
Autonomic system
Somatic system
Enteric
Parasympathetic
Sympathetic

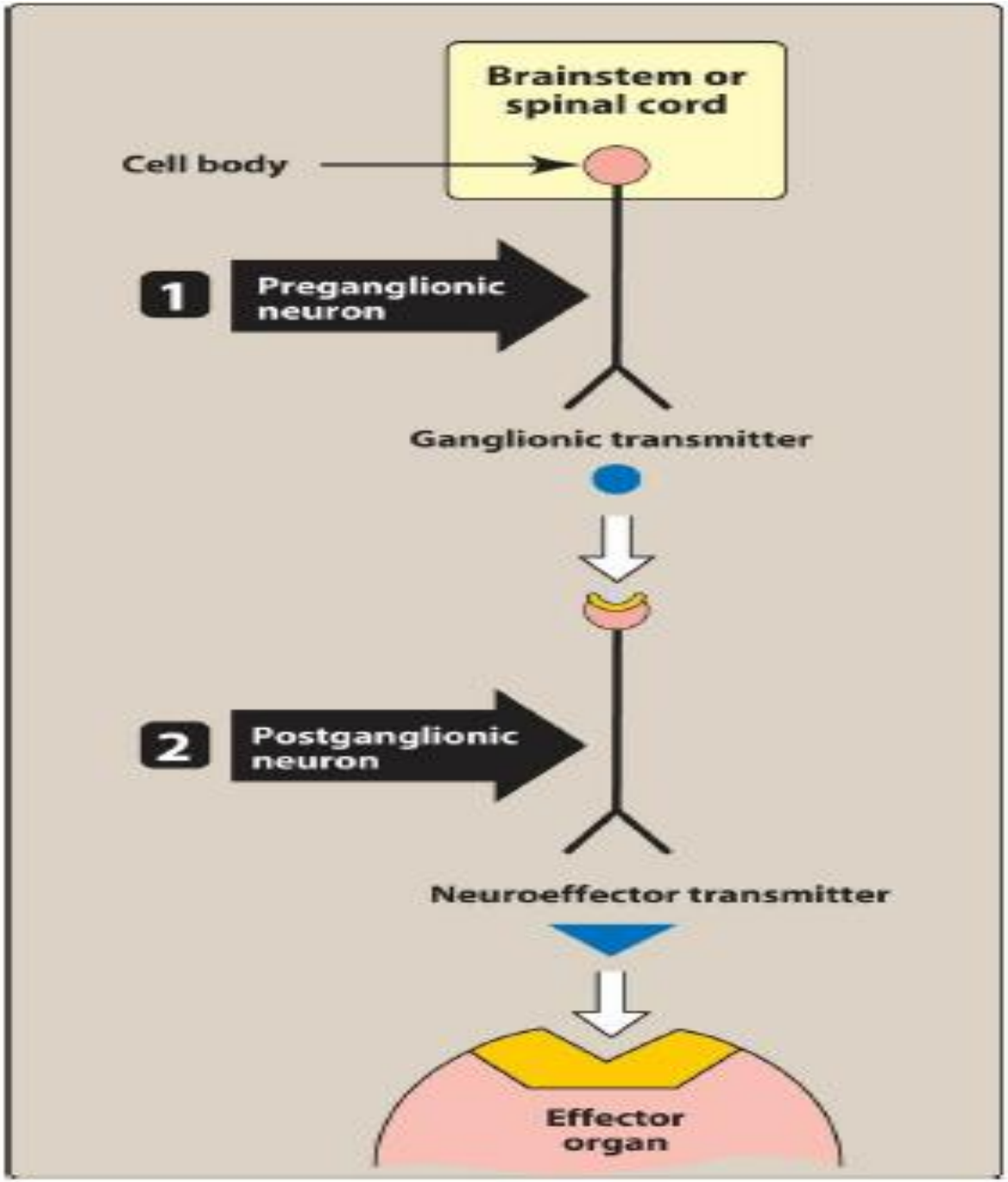

PNS
CNS
PNS
Integration
Sensory input
(afferent)
Motor output
(efferent)
Somatic nervous system
Sensory input
(afferent)
Parasympathetic nervous system
(efferent)
Smooth muscle
Heart
Glands
Sympathetic nervous system
(efferent)
Smooth muscle
Heart
Glands
Autonomic nervous system

The somatic nervous system innervates **skeletal muscles** and **controls voluntary movement**.

The ANS, **without conscious thought** or effort, controls **involuntary activities** in smooth muscle, in secretory glands, and in the visceral organs of the body such as the heart

Structure and Function of the Autonomic Nervous System

Structural centers in the CNS, including the **hypothalamus**, **brainstem**, and **spinal cord**, regulate the ANS. There are two parts of the ANS: the **sympathetic nervous system** (SNS) and the **parasympathetic nervous system**. The functions of the ANS can be broadly described as activities designed to maintain a constant internal environment (homeostasis), to respond to stress or emergencies, and to repair body tissues.


Brainstem or spinal cord
Cell body
1
Preganglionic neuron
Ganglionic transmitter
2
Postganglionic neuron
Neuroeffector transmitter
Effector organ

Sympathetic Nervous System

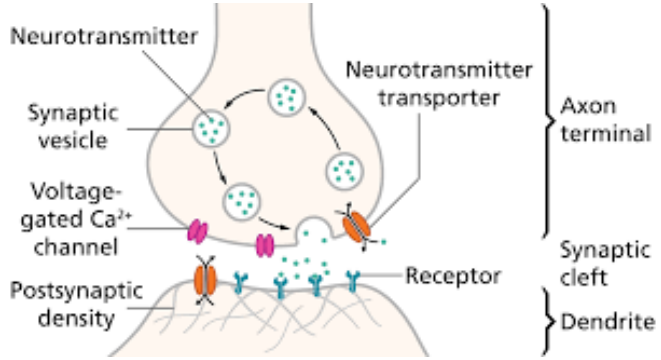
The SNS is stimulated by **physical** or **emotional stress**, such as active exercise or work, pain, hemorrhage, intense emotions, and temperature extremes. The reaction produced by the SNS is essentially a whole-body response and includes:

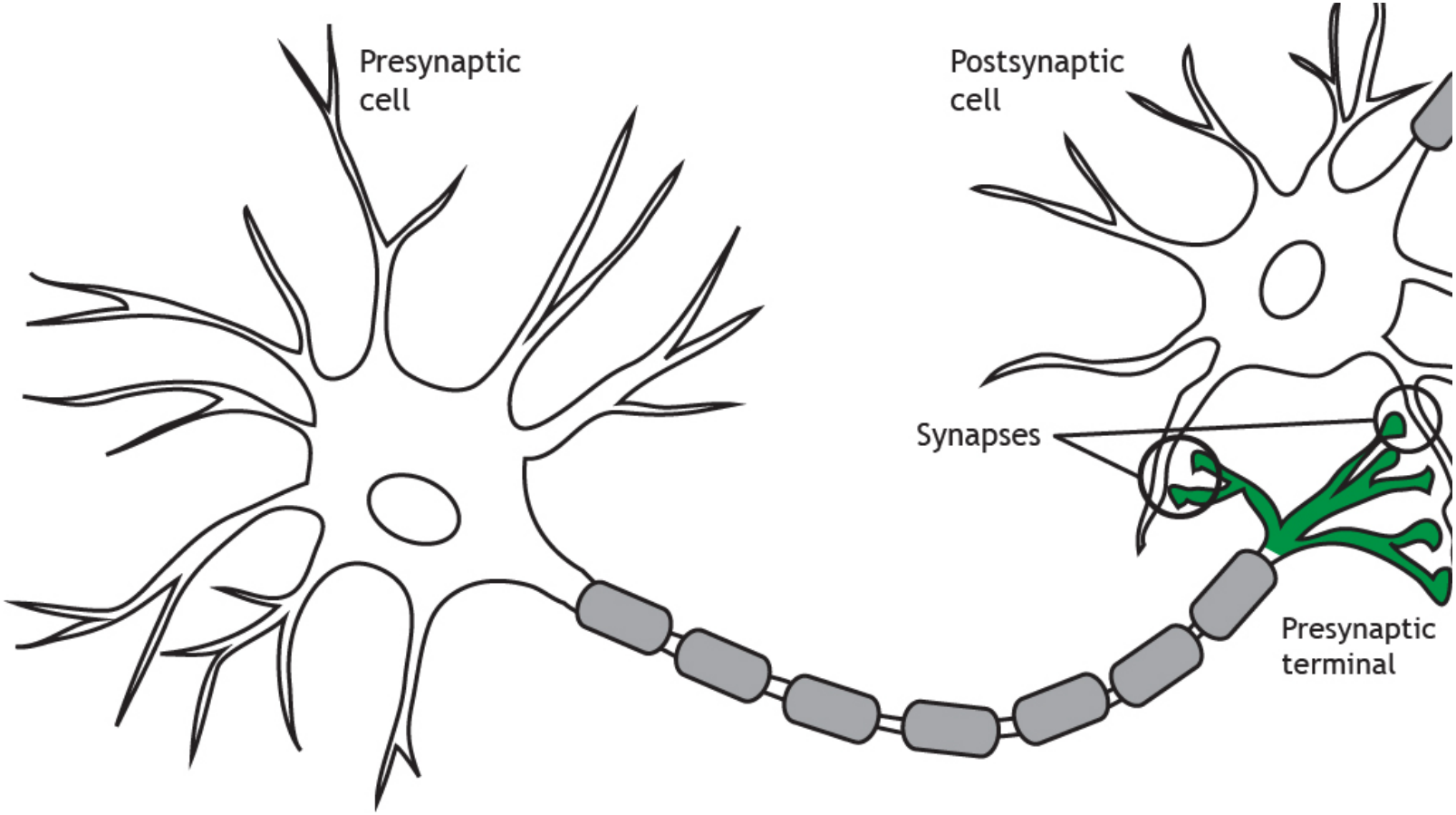
- Increased arterial blood pressure and cardiac output
- Increased blood flow to the brain, heart, and skeletal muscles; decreased blood flow to the viscera, skin, and other organs not needed for “fight or flight” (whether real or imaginary)
- Increased rate of cellular metabolism, with increased oxygen consumption and carbon dioxide production

- Increased breakdown of muscle glycogen for energy
- Increased blood glucose
- Increased mental activity and ability to think clearly
- Increased muscle strength
- Increased rate of blood coagulation
- Increased rate and depth of respiration
- Pupil dilation to aid vision
- Increased sweating
- The intensity and duration of the sympathetic response depend on the existing amounts of the **neurotransmitters** norepinephrine and epinephrine.

Neurotransmitters

Norepinephrine (NE) is synthesized in adrenergic nerve endings and released into the synapse when adrenergic nerve endings are stimulated. The effects of **(NE)** are terminated by reuptake of most of the neurotransmitter back into the nerve endings, where it is packaged into **vesicles** for reuse as a neurotransmitter. This reuptake and termination process can be inhibited by **cocaine** and **tricyclic antidepressant medications** and is responsible for the activation of the SNS seen with these drugs. The remainder of the **(NE)** , which was not taken back into the nerve endings, diffuses into surrounding tissue fluids and blood or is metabolized by **monoamine oxidase (MAO**) **or catechol-*O* methyltransferase (COMT)**




Presynaptic cell
Postsynaptic cell
Synapses
Presynaptic terminal

Norepinephrine also functions as a circulating **neurohormone**, along with **epinephrine**. In response to adrenergic nerve stimulation, **(NE)** and **(E)** are secreted into the bloodstream by the **adrenal medullae** and transported to all body tissues. They are continually present in arterial blood in amounts that vary according to the degree of stress present and the ability of the adrenal medullae to respond to stimuli. The larger proportion of the circulating hormones (~80%) is **(E).**
(NE) and **(E)** exert the same effects on target tissues, but the effects last longer because the hormones are removed from the blood more **slowly**.

Response to Activation of Alpha- and Beta- Receptors

Activation of alpha1 and beta1 receptors causes stimulatory responses:

- When activating **alpha1** receptors, **(NE)** causes a greater response than does **(E)**
- When activating **beta1** receptors, **(E)** and **(NE)** cause equal responses.
- Activation of **alpha2**, **beta2**, and **beta3** receptors causes **inhibitory responses:**
- When activating **alpha2** receptors, **(E)** causes a greater or equal response than does **(NE)** .
- When activating **beta2** receptors, **(E)** causes a significantly greater response than does **(NE)**

Dopamine is also an adrenergic neurotransmitter and a catecholamine. **In the brain**, dopamine is essential for normal function. **In peripheral tissues**, its main effects are on the heart and blood vessels of the renal system and viscera, where it produces vasodilation

Adrenergic Receptors

When **(NE)** and **(E)** act on body cells that respond to sympathetic nerve or catecholamine stimulation, they interact with two distinct adrenergic receptors, **alpha** and **beta**. **(NE)** acts mainly on **alpha** receptors, and **(E)** acts on both **alpha**- and **beta**-receptors. These receptors have been further subdivided into **alpha1**, **alpha2**, **beta1**, **beta2**, and **beta3** receptors.

When **dopamine** acts on body cells that respond to adrenergic stimulation, it can activate **alpha1** and **beta1** receptors as well as dopaminergic receptors

Dopamine receptors are located in the brain, in blood vessels of the kidneys and other viscera. Like alpha- and beta receptors, dopamine receptors are divided into several subtypes (D1–D5), and specific effects depend on which subtype of receptor is activated.

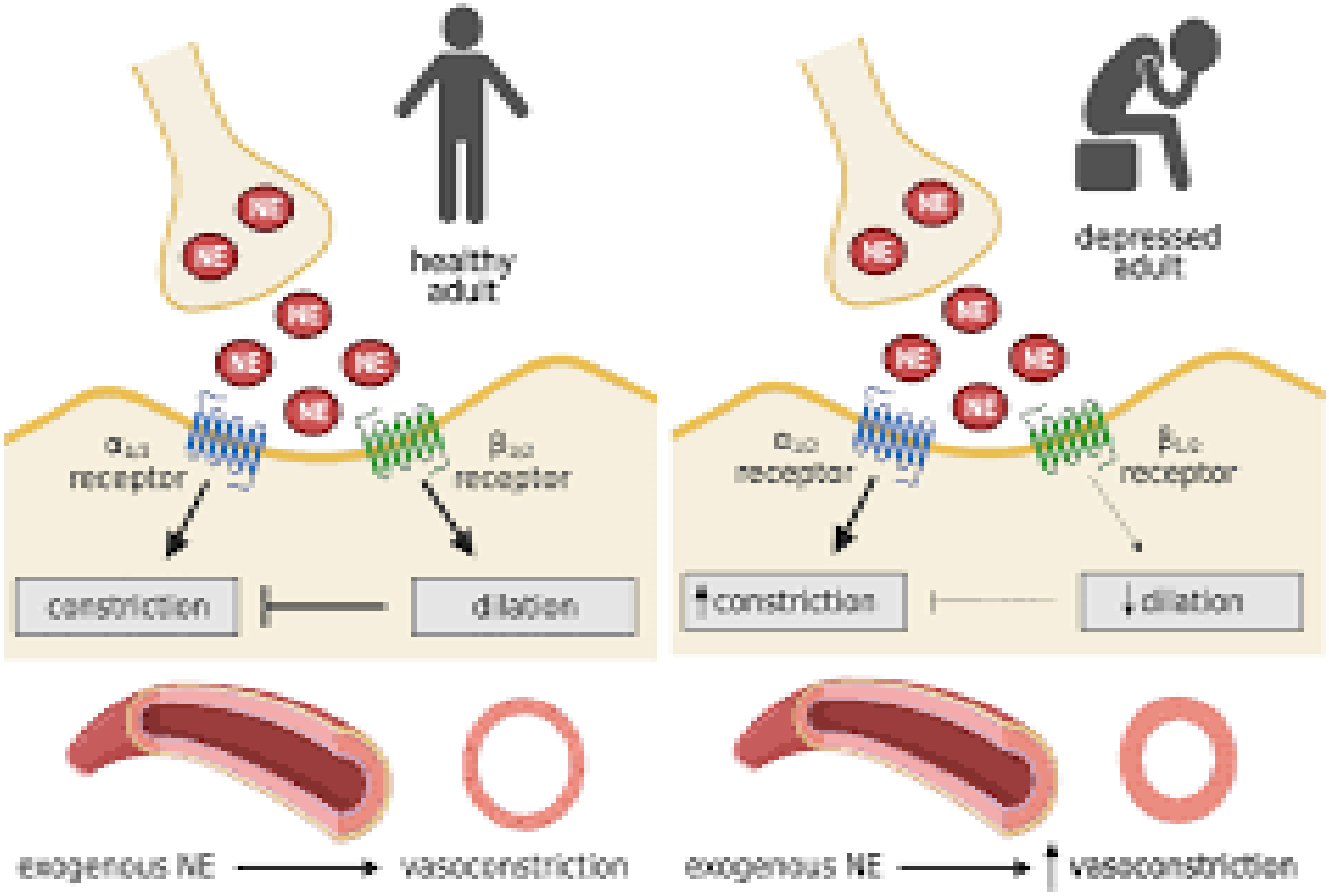
- ***Alpha* 1 *receptors***: Activation of alpha1 receptors in smooth muscle cells is thought to open ion channels, allow calcium ions to move into the cell, and produce muscle contraction (e.g., vasoconstriction, gastrointestinal and bladder sphincter contraction).

Alpha* 2 *receptors: In the brain, some of the **(NE)** released into the synaptic cleft between neurons returns to the nerve endings from which it was released and stimulates presynaptic alpha2 receptors. This negative feedback prevents calcium-mediated release of **(NE)** from storage vesicles into the synapse, resulting in decreased sympathetic outflow and an antiadrenergic effect.

- **Beta 1, beta 2, and beta 3 receptors**: Activation of these receptors stimulates activity of **adenyl cyclase** (which increases intracellular cAMP activity).Drugs such as theophylline inhibit phosphodiesterase and increase cAMP concentrations, resulting in bronchodilation
- **Dopaminergic receptors D 1 and D 5**: Activation of these receptors is thought to stimulate the production of cAMP, as does activation of **beta1** and **beta2** receptors

Dopaminergic receptors D 2, D 3, and D 4: Activation of this receptor is thought to inhibit formation of cAMP and to alter calcium and potassium ion currents. **D3** and **D4** receptors are grouped with **D2** receptors, but the effects of their activation have not been clearly delineated

The resulting **decrease** in beta-adrenergic responsiveness is called desensitization or **downregulation** of receptors.
The resulting increase in beta-adrenergic responsiveness, called hypersensitization or **upregulation**




Thanks