



Drugs Affecting the Autonomic Nervous System-1

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The autonomic nervous system, 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
- The nervous system exerts its influence 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 :are drugs that produce their primary therapeutic effect by mimicking or altering the functions of the autonomic nervous system

These autonomic agents act either by:

➤ Stimulating portions of the autonomic nervous system

or

➤ Blocking the action of the autonomic nerves

Divisions of the Nervous System

➤ Central Nervous System

- Brain
- Spinal cord

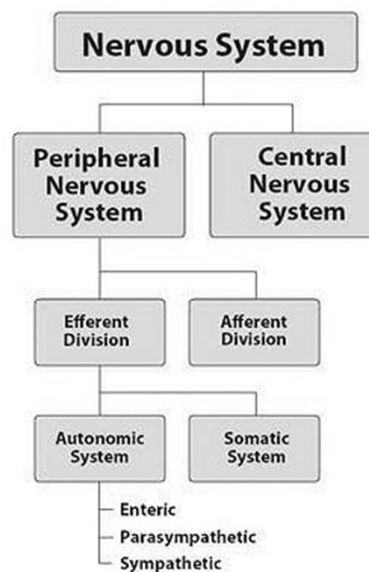
➤ Peripheral Nervous System

- Nerves
- Sense organs

The peripheral nervous system is subdivided into :

- Efferent division
- Afferent division
- **Efferent division:** the neurons of which carry signals away from the brain and spinal cord to the peripheral tissues
- **Afferent division:** the neurons of which bring information from the periphery to the CNS.
- Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs, that is, neural pathways that mediate a reflex action.

Organization of the nervous system



Peripheral Nervous System

➤ **Somatic Nervous System**

Voluntary action: skeletal muscle contraction and movement

➤ **Autonomic Nervous System**

Involuntary activities: respiration, circulation, digestion, sweating

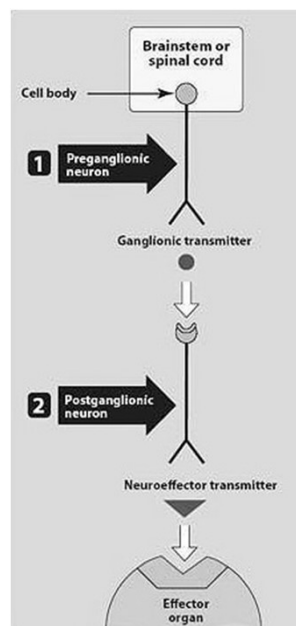
The efferent autonomic nervous system is divided into:

- The sympathetic nervous systems
- The parasympathetic nervous systems
- The enteric nervous system.

Efferent neurons of the autonomic nervous system :
The autonomic nervous system carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons

- **Preganglionic neuron** its cell body is located within the CNS, emerge from the brainstem or spinal cord and make a synaptic connection in ganglia
- **Postganglionic neuron** has a cell body originating in the ganglion. It is generally nonmyelinated and terminates on effector organs, such as smooth muscles of the viscera, cardiac muscle, and the exocrine glands.

Efferent neurons of the autonomic nervous system



Sympathatic neurons:

- They originate in the CNS and emerge from two different spinal cord regions.
- The preganglionic neurons of the sympathetic system come from thoracic and lumbar regions of the spinal cord, and they synapse in two cord-like chains of ganglia that run in parallel on each side of the spinal cord.

Length of pre & post ganglionic fibers:

- The preganglionic neurons are short in comparison to the postganglionic ones. Axons of the postganglionic neuron extend from these ganglia to the tissues that they innervate and regulate

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, influences other organs by secreting the hormone epinephrine, also known as adrenaline, and lesser amounts of norepinephrine into the blood.

Parasympathetic neurons:

- The parasympathetic preganglionic fibers arise from the cranium (from cranial nerves III, VII, IX, and X) and from the sacral region(S2-S4) of the spinal cord (craniosacral) and synapse in ganglia near or on the effector organs.

Length of pre & post ganglionic fibers:

Because of the location of the ganglia, The preganglionic fibers of PSNS are long &the post ganglionic fibers are short

Enteric neurons:

- It is a collection of nerve fibers that innervate the gastrointestinal tract, pancreas, and gallbladder,
- Controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract.
- It is modulated by both the sympathetic and parasympathetic nervous systems.

Functions of the sympathetic nervous system

- It is active to some degree (for example, in maintaining the tone of vascular beds)
- Adjusting the response to stressful situations (trauma, fear, hypoglycemia, cold, or exercise)

Effects of stimulation of the sympathetic division:

- Increase heart rate and blood pressure
- To mobilize energy stores of the body
- Increase blood flow to skeletal muscles and the heart
- Sympathetic stimulation results in dilation of the pupils and the bronchioles
- It also affects gastrointestinal motility and the function of the bladder and sexual organs.

The sympathetic nervous system tends to function as a unit (complete system)

Example:

during severe exercise or in reactions to fear. This system, with its diffuse distribution of postganglionic fibers, is involved in a wide of physiologic activities.

Sympathetic and parasympathetic actions are elicited by different stimuli

"Fight or flight"
stimuli



Sympathetic output
(diffuse because postganglionic neurons may innervate more than one organ)

"Rest and digest"
stimuli



Parasympathetic output
(discrete because postganglionic neurons are not branched, but are directed to a specific organ)

Sympathetic and parasympathetic actions often oppose each other



Fight or flight or fright response: The changes by the body during emergencies

- Pupil dilatation
- Bronchiole dilatation
- Tachycardia(Increase heart rate)
- Hypertension(increase blood pressure)&supply redistribution
- Vasodilation of skeletal muscle &heart muscle
- Vasoconstriction of skin,&vescera)
- Increase energy supply (blood glucose)
- Increase glycogenolysisin liver
- Decrease insulin secretion from b-cell of pancrease

- These reactions are triggered both by direct sympathetic activation of the effector organs & by stimulation of the adrenal medulla to release epinephrine and lesser amounts of norepinephrine.
- These hormones enter the bloodstream and promote responses in effector organs that contain adrenergic receptors.

Functions of the parasympathetic nervous system

- Maintains essential bodily functions, such as digestive processes and elimination of wastes, and is required for life.
- Acts to oppose or balance the actions of the sympathetic division.
- Generally dominant over the sympathetic system in rest and digest situations.
- The parasympathetic system is not a complete system(Parasympathetic fibers are activated separately, and the system functions to affect specific organs, such as the stomach or eye).

Role of the CNS in autonomic control functions

- Although the autonomic nervous system is a motor system, it does require sensory input from peripheral structures
- Afferent impulses travel to the CNS (hypothalamus, medulla oblongata, and spinal cord)
- These centers respond to the stimuli by sending out efferent reflex impulses via the autonomic nervous system.

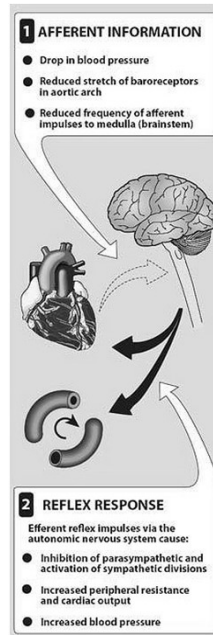
Reflex arcs:

- In each case, the reflex arcs of the autonomic nervous system comprise a sensory (or afferent) arm, and a motor (or efferent, or effector) arm

Example of Reflex arcs:

- 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 tachycardia

Baroreceptor reflex arc responds to a decrease in blood pressure



Innervation by the autonomic nervous system

1. Dual innervation: Most organs in the body are innervated by both divisions of the autonomic nervous system.

- Thus, vagal parasympathetic innervation slows the heart rate, and sympathetic innervation increases the heart rate.

Despite this dual innervation, one system usually predominates in controlling the activity of a given organ. For example, in the heart, the vagus nerve is the predominant factor for controlling rate..

2. Organs receiving only sympathetic innervation:

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

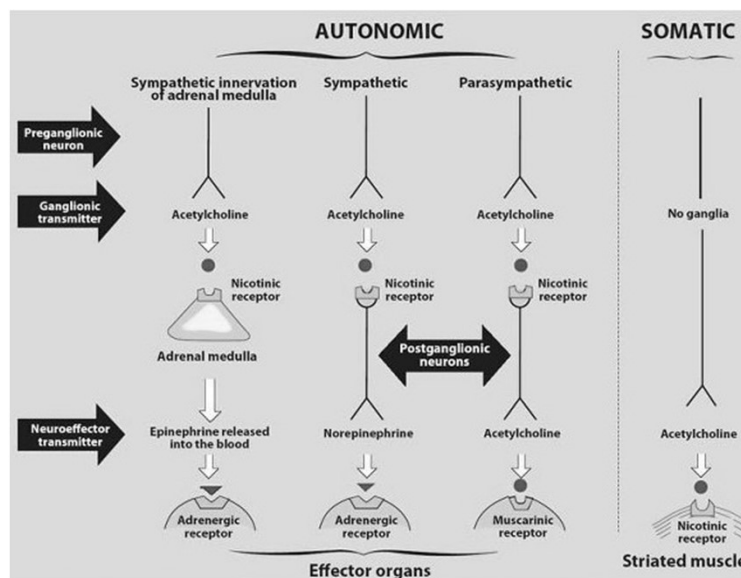
Somatic nervous system:

- The efferent somatic nervous system differs from the autonomic system in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia
- The somatic nervous system is under voluntary control, whereas the autonomic is an involuntary system.

Chemical Signaling Between Cells:

- Neurotransmission in the autonomic nervous system is an example of the more general process of chemical signaling between cells.
- Local mediators
- Secretion of hormones.

Summary of the neurotransmitters released and the types of receptors found within the autonomic and somatic nervous systems.



Local Mediators:

- Most cells in the body secrete chemicals that act locally, which are rapidly destroyed or removed(not enter the blood and are not distributed throughout the body.

Examples of local mediators:

- Histamine &the prostaglandins

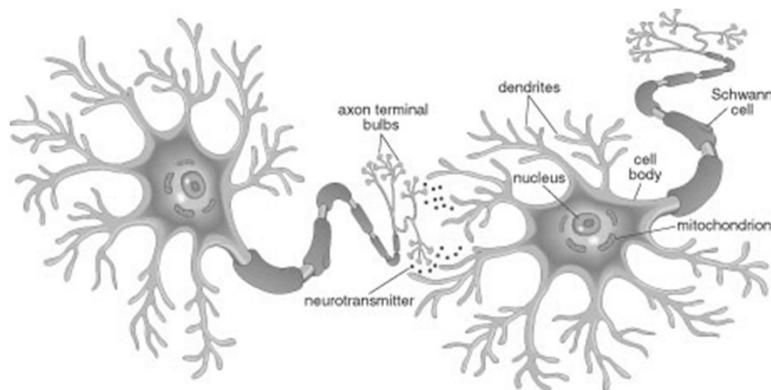
Hormones

Specialized endocrine cells secrete hormones into the bloodstream, they travel throughout the body exerting effects on distributed cells in the body.

Neurotransmitters

- All neurons are distinct anatomic units, and no structural continuity exists between most neurons.
- Communication between nerve cells and between nerve cells and effector organs occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals.
- The neurotransmitters rapidly diffuse across the synapse between neurons and combine with specific receptors on the postsynaptic (target) cell

Communication by Neurotransmitters



Neurotransmitters are released from one axon and received by another neuron's dendrites.

Types of neurotransmitters:

- Norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and 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 autonomic nervous system, whereas a wide variety of neurotransmitters function in the CNS.

Acetylcholine:

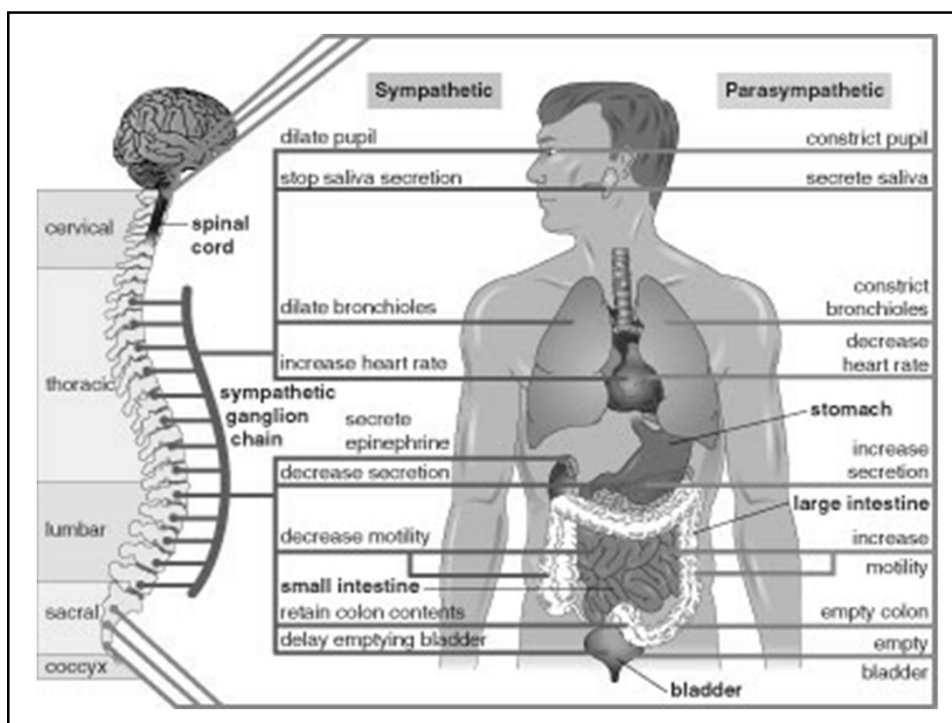
The autonomic nerve fibers can be divided into two groups based on the chemical nature of the neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic

- Acetylcholine is ganglionic transmitter in both the sympathetic and parasympathetic nervous systems.
- It is the neurotransmitter at the adrenal medulla.
- It is neuroeffector transmitter in the parasympathetic system & in the somatic nervous system (between nerve fibers and voluntary muscles)

Norepinephrine and epinephrine:

When norepinephrine or epinephrine (adrenaline) is the transmitter, the fiber is termed adrenergic

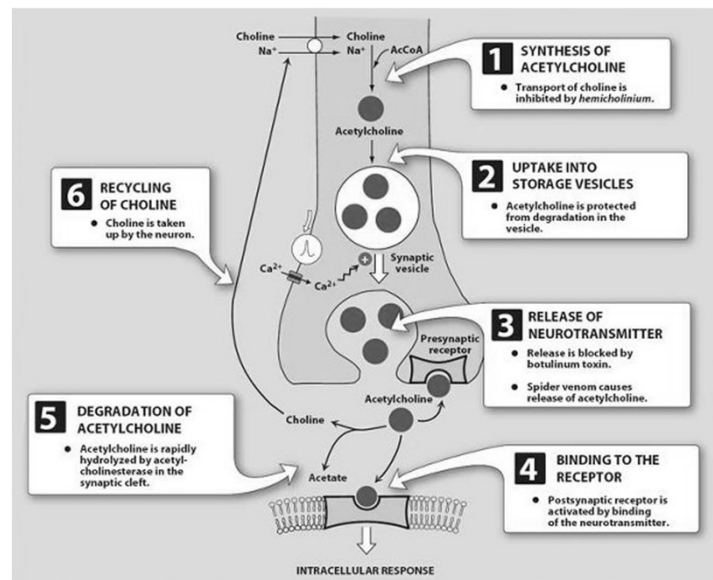
- It is neuroeffector transmitter, it mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs.
- It act on receptors called Norepinephrine and adrenergic receptors



Drugs affecting the autonomic nervous system are divided into two groups

- The cholinergic drugs, which act on receptors that are activated by acetylcholine.
- Adrenergic drugs which act on receptors that are stimulated by norepinephrine or epinephrine.
- Cholinergic and adrenergic drugs both act by either stimulating or blocking receptors of the autonomic nervous system

Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A



(Synthesis & release of Ach)

Neurotransmission in cholinergic neurons involves six steps.:

1. Synthesis of acetylcholine:

- choline is transported from the extra-cellular fluid into cholinergic neuron by an energy-dependent carrier system that cotransports sodium and that can be inhibited by the drug hemicholinium
- Choline acetyltransferase enzyme catalyzes the reaction between choline and acetyl Co A to form acetylcholine.

2.Storage of acetylcholine in vesicles:

- Acetylcholine is packaged into vesicles by active process. The mature vesicle contains not only acetylcholine but also adenosine triphosphate (ATP) and proteoglycan

3.Release of acetylcholine:

- When an action potential propagated by the action of voltage-sensitive sodium channels arrives at a nerve ending, the sensitive calcium channel in the presynaptic membrane open & cause increase in the concentration of intracellular calcium, this promote the fusion of the vesicle with the cell membrane and release of Ach into the synapse .

4. Binding to receptor :

- Acetylcholine that released from the synaptic vesicle diffuse across synaptic space and binds to either of two postsynaptic receptors on the target cell or to presynaptic receptors in the membrane of the neuron that released the acetylcholine.
- Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells as mediated by second-messenger molecules.

5. Degradation of Ach:

acetylcholinesterase cleaves acetylcholine to choline and acetate in the synaptic

Note: Pseudocholinesterase is found in the plasma, but it does not play a significant role in termination of acetylcholine's effect in the synapse.

6. Recycling of choline :

Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron, where it is acetylated into acetylcholine that is stored until released by a subsequent action potential into the neuron where it is acetylated and stored.

Cholinergic Receptors (Cholinoceptors)

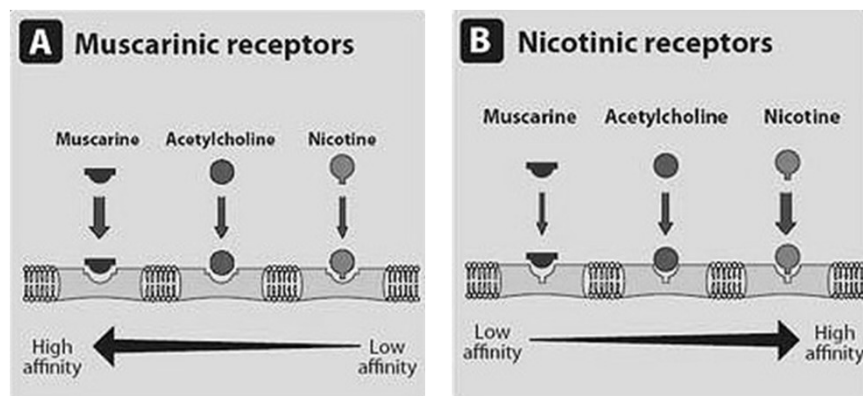
- These receptors respond to Ach & its analogues.
- These receptors are subdivided as follows:

- 1. Muscarinic receptors:**

- 2. Nicotinic receptors:**

Can be distinguished from each other on the basis of their different affinities for agents that mimic the action of acetylcholine (cholinomimetic agents or parasympathomimetics).

Types of cholinergic receptors



Muscarinic Receptors: MR

- These receptors respond to acetylcholine as well as muscarins (alkaloid that is present in certain poisonous mushrooms)

Subclasses of muscarinic receptors

- M₁
- M₂
- M₃
- M₄
- M₅.

- M₁ (Neuronal): Nerve endings (peripheral nerve) mainly & CNS.
- M₂ receptors on cardiac cells and smooth muscle
- M₃ receptors on the bladder, exocrine glands, and smooth muscle

Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration they may show some activity at nicotinic receptors.

Locations of Muscarinic Receptors

1. Postganglionic neurons of PSNS (N ending, heart, glands, sm.m).
2. Postganglionic cholinergic neurons of sympathetic nervous system (sweat glands).
3. Non innervated receptors on blood vessels.
4. In CNS.

Nicotinic Receptors:

- These receptors respond to nicotine but show only a weak affinity for muscarine
- 2 major subtypes:
 - N_N : in autonomic ganglia.
 - N_M : endplate (N-M junction).

Locations of Nicotinic Receptors:

1. Autonomic ganglia: Synapse between preganglion and postganglionic neuron of SNS & PSNS.
2. Motor endplates at skeletal (striated) muscle at the neuromuscular junction (somatic nerve i.e. to voluntary muscle).
3. Secretion of adrenaline from adrenal medulla.
4. In CNS.

- The nicotinic receptors of autonomic ganglia differ from those of the neuromuscular junction. For example, ganglionic receptors are selectively blocked by hexamethonium, whereas neuromuscular junction receptors are specifically blocked by tubocurarine.

Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems

