Faculty of Medicine 2012

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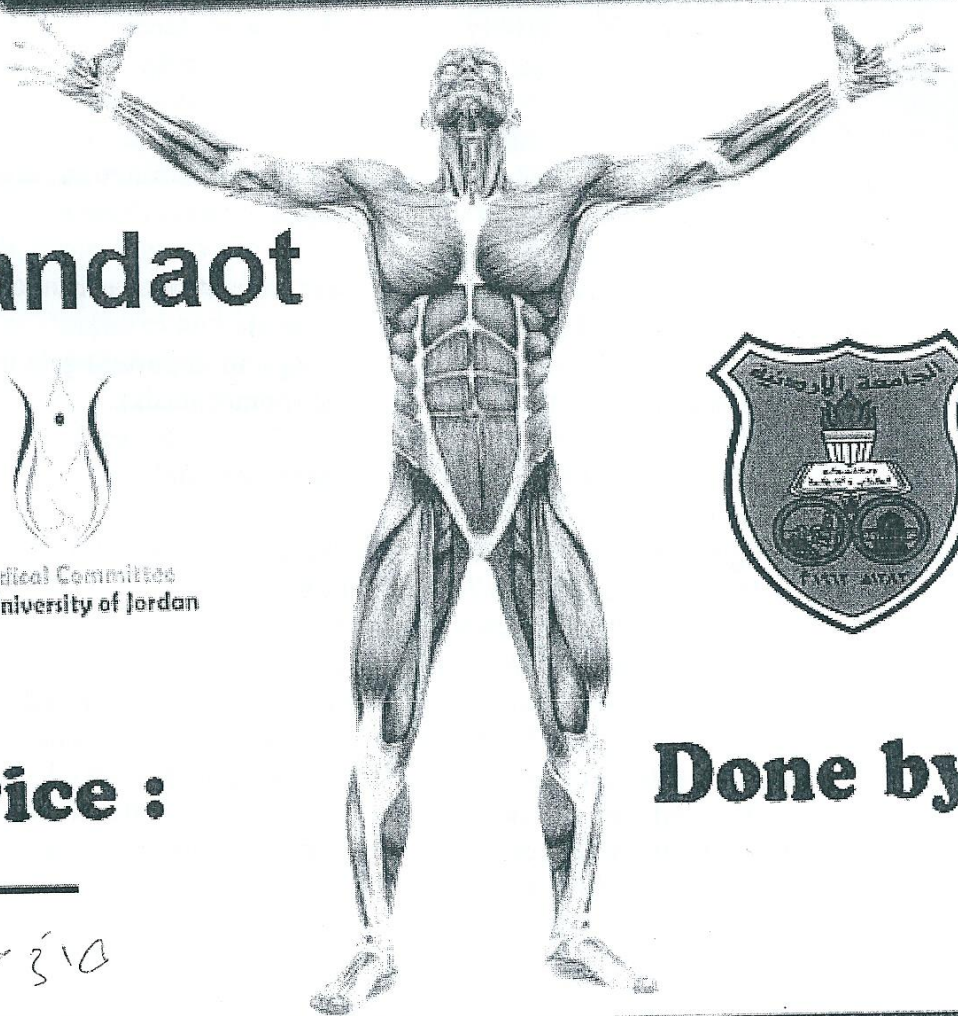
# lecture no. : 2

# PHYSIOLOGY



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Medical Committee
The University of Jordan

**Price :**

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University of Jordan
Faculty of Medicine

Medical students, 2012/2013.

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**Textbook of Medical Physiology,** Guyton, 12th ed: 729-738, 11th ed. P748-760, and 10th ed. p697-708.

# AUTONOMIC NERVOUS SYSTEM (ANS):

This nervous division is anatomically distinct from the motor somatic nervous system, which innervates skeletal muscle. This group of efferent paths originates from the central nervous system and innervates heart, smooth muscle, glandular tissue and enteric nervous system. ANS has two subdivisions, sympathetic and parasympathetic, which together perform the following functions on effector tissues they innervate.

1. Regulation of the activity of visceral organ systems:
   examples of functions under ANS control include:
   - heart rate
   - arterial blood pressure
   - digestion, intestinal motility, secretions (these functions are controlled in conjuction with hormones.
   - emptying of urinary bladder
   - secretory activity of respiratory tract and airways resistance (by regulation of diameter of bronchioles).

By regulation of these functions, ANS plays an important role in maintaining constancy of internal environment (homeostasis).

2. Rapid responses to specific environmental stimuli,
   these include:
   - Light: constriction of the pupil to bright light (miosis), and dilation of pupil to low light (midriasis).
   - Temperature: cutaneous vasodilation and sweating in a warm environment, and vasoconstriction in cold.
   - Stress: The ANS (mainly the sympathetic and the adrenal medulla) mediates the immediate response (fight or flight response) to threatening stimuli. This involves a series of well coordinated responses to meet the metabolic demands for severe physical exertion. The features of this response include:

- increase heart rate and force of contraction.
- Widely dilated pupils.
- Pallor (pale of fear) as blood is directed to the skeletal muscle.
- Goose pimpling.
- Cold sweat.
- Dry mouth.

**Characteristics of autonomic responses:**

1. Speed of onset: ANS can produce dramatic changes in the level of activity of organs they innervate within seconds. Changes in heart rate, sweating, goose pimpling, and rise or fall in blood pressure can take place within few seconds (3-5 sec).

2. Automatic nature: regulation of visceral functions occurs **without conscious control**. Some functions are brought under voluntary control such as urination and defecation through the participation of voluntary muscles. The impulses in ANS to target organs are set up **reflexively** in response to specific type of sensory information. The reflex responses are sensitive to emotional states of the body. Stress, excitements, euphoria, fear, anxiety or anger can influence reflexes and induce a variety of symptoms, such as sweating, palpitation, or digestive disturbances.

3. Tonic activity: The ANS fires continuous impulses to target organs at very low rate. The basal rate of firing is called "sympathetic tone" and "parasympathetic tone". These tones establish basal rate of contractile activity in smooth muscle cells, and secretory activity of glandular tissues. The activity of these effector cells can be changed as a result of an increase or a decrease in the activity of any divisions of the ANS.

**Physiological anatomy:**

Two neurons carry impulses of the ANS from the CNS to the effector organs. The first is known as **preganglionic neuron**, the cell

body is located in the CNS (in appropriate nucleus in the brain or in the lateral gray of the spinal cord). The fibers of preganglionic are small and myelinated, and usually end within a ganglion where they synapse with the second neuron called **postsynaptic neuron**. The second neuron (postsynaptic) carries impulses to target organ.

## DIVISIONS OF ANS:

There are two divisions of the ANS sympathetic and parasympathetic autonomic nervous systems.

## Sympathetic nervous system:

The cell bodies of preganglionic neurons lie in lateral gray of spinal cord at segmental levels of T1 through L3. Axons leaves spinal cord via ventral roots, then leave ventral root via white rami communicans to enter a vertebral ganglion of the sympathetic chain at the same segmental level. The preganglionic axon then can:

* Synapse with postganglionic cells at the **same segmental level**.

* Turn cranial or caudal and synapse with sympathetic postganglionic neuron at **higher or lower segmental level.**

Synapse may occur at more than one postganglionic neuron.

After synapse with neurons at paravertebral ganglia, axons of second neurons leave ganglia via gray rami communicans to return to the corresponding spinal nerve.

* Some preganglionic fibers that enter ganglia **pass without any synapse** at the paravertebral ganglia and continue to some ganglia located in the abdomen known as **prevertebral ganglia**, where they have the synapse with the second neuron. There are three unpaired prevertebral ganglia: celiac, superior mesenteric and inferior mesenteric ganglia.

* Some preganglionic fibers pass without synapse in paravertebral ganglia and celiac ganglion. These fibers continue to adrenal gland where they synapse onto chromaffin cells. These cells liberate epinephrine into blood stream.

### Synaptic organization of sympathetic ganglia:

Individual postsynaptic neuron in vertebral ganglia can receive signals from many preganglionic fibers (**convergence**) and one preganglionic neuron can relay impulse to many postganglionic neurons at different segmental levels (**divergence**). This organization of the sympathetic system induces widespread effects on target cells innervated by sympathetic postganglionic fibers.

## Parasympathetic nervous system:

The preganglionic fibers arise in appropriate cranial nuclei and in segments S3 and S4 (sometimes S2, S5 also). These fibers leave the CNS in the III, VII, IX, and X (vagus) nerves for fibers of cranial origin and in pelvic nerve for fibers of sacral origin. The preganglionic fibers are long and go all the way to the effector organ where they synapse with the second postganglionic neuron located within the tissue of the effector organ or to a ganglion located very close to the effector organ. The axons of postsynaptic neurons are short.

### Synaptic organization of parasympathetic nervous system:

In parasympathetic there is no or little branching of preganglionic fibers (divergence). The ratio of pre to post ganglionic neurons is 1:1 or 1:2. As a result of this arrangement, the parasympathetic actions tend to be more discrete and confined to the innervated organ.

### Organization of the autonomic neuroeffector junction:

The terminals of autonomic nerve fibers are unlike terminals of the somatic motor fibers (skeletal neuromuscular junction). The autonomic terminals are highly branched forming extensive network of fibers beaded with small swellings or varicosities. These varicosities are sites from where transmitter is released.

The receptors on effector cells are scattered widely over the innervated organ. Unlike skeletal muscle, there is no specialized receptive region at the effector cell. The effect of ANS on these cells can be stimulatory or inhibitory. This effect depends on transmitter type,

receptor subtype and changes in functional proteins induced in cell by binding of transmitter to its receptor.

**Effects of sympathetic stimulation:**

Sympathetic system innervates widely distributed tissues. These include, *sweat glands, smooth muscle cells of blood vessels* supplying skeletal muscle, skin, etc, *smooth muscle cells of hair follicles*. This innervation is consistent with diffuse projections of the sympathetic postganglionic fibers that originate in vertebral ganglia and distribute with the spinal nerves.

In human, **the previously mentioned target tissues do not have any parasympathetic innervation**. Thus, the sympathetic which has excitatory effects on these tissues regulates:

- Blood pressure (blood vessels supplying skeletal muscle are major players). In addition to that the effect on heart also contributes in regulation of blood pressure.
- Body temperature by the sympathetic effects on cutaneous blood vessels and sweat glands.

In addition to its effect on widely distributed tissues, sympathetic system is involved in handling **stress responses** (fight or flight reaction). Together with adrenal gland, the sympathetic system is designed to promote the production of energy for muscular work and to shut down organs which have nonessential functions in reaction to stressful situations. These effects on the following systems include:

- Cardiovascular system: effects on vessels will result in redistribution of blood by enhancing blood flow to skeletal muscle and reducing blood flow to skin and mesentery.

  Effects on heart: increasing cardiac output (volume of blood pumped per minute).
- Respiratory system: causes relaxation of bronchila muscle which result in bronchdilation.
- Digestive system: inhibition of motility and secretion.
- Metabolic effects:
  - Mobilization of glucose.

- Increased lipolysis.
- Increased metabolic rate.

**Effects of parasympathetic stimulation:**

Overall, the parasympathetic, in contrast to sympathetic system is viewed as regulator of activities involved in replenishment of energy supply and general maintenance of the organism.

The control provided by parasympathetic system is discrete and selectively directed to individual organs.

The types of actions produced by parasympathetic stimulation include:

- Gastrointestinal system: increases motility and secretory activity.
- Glands: increases secretory activity (but remember sweat glands are under sympathetic control).
- Heart: decrease rate of contraction (bradycardia).
- Pupil: control pupil diameter by papillary light reflex (myosis) (regulates the amount of light falling on retina).
- Accommodation of the lens for near vision.
- Voiding the urinary bladder (micturation).

## MOLECULAR BASIS OF PHYSIOLOGICAL ACTIONS OF THE ANS:

**Transmitters:**

At ganglion: preganglionic neurons of both sympathetic and parasympathetic release **acetylcholine** (Ach).

At effector organs:

- Post ganglionic terminals of parasympathetic fibers release **acetylcholine**.

- Post ganglionic terminals of sympathetic fibers release **norepinephrine**. An

exception for sympathetic nerves to sweat glands, which release **acetylcholine** (Ach).

The released Ach by parasympathetic system is inactivated by breakdown by *acetylcholinesterase*. Epinephrine is inactivated by recapture by postganglionic nerve varicosities.

## Receptors and signal transduction mechanisms:

Receptors are found at postsynaptic or post junctional membranes and interact with transmitters released from the nerve terminals.

These receptors function as coding system and they have high degree of specificity. The nature of response elicited in a particular tissue to a given transmitter is very precise and depends on the properties of receptor and the signaling mechanisms employed in that tissue.

### Receptors at ganglion:

On post synaptic membrane of sympathetic and parasympathetic there are **nicotinic receptors**. These receptors are excited by acetylcholine. The drug nicotine can also stimulate these receptors. This receptor is similar but not identical (they have different subunit structures) to nicotinic receptor of the neuromuscular junction. This receptor gates ligand gated Na+ channel. Activation of this receptor will cause depolarization on postsynaptic membrane.

### Receptors on effector cells:

### - Muscarinic receptors:

These cholinergic receptors lie on effector cells of parasympathetic neuro-effector junctions. They differ from nicotinic receptors found on ganglia and neuromuscular junction.

Many muscarinic receptors have been known (M1-M5) at these junctions. All these receptors are coupled to G protein.

- The inhibitory receptor that is found in the heart (M2) is coupled via G protein to K+ channels. Activation of this receptor will slow the rate of depolarization.

- Other inhibitory muscarinic receptors

are negatively coupled via Gi protein to adenylyl cyclase and decrease production of c-AMP.

- The excitatory receptors (M1, M3, M5) found on smooth muscle and glands are coupled via Gq protein to phospholipase C. This enzyme increases production of inositol-1,4,5-trisphosphate (IP3). IP3 causes release of Ca++ from internal stores in muscle or glands, causing contraction or secretion.

These receptors are activated by muscarine and inhibited by atropin.

The targets of muscarine receptors' stimulation are illustrated by muscarine poisoning. These effects include:

- stimulation of secretory activity: salivation, tearing, sweating, nasal and bronchial secretion.
- Increase gastrointestinal tract motility→ vomiting and diarrhea.
- Contraction of urinary bladder →urination.
- Slowing of the heart →Bradycardia.

These receptors are blocked by **atropine** from a plant *atropa belladona* which induces reversal effects of muscarine poisoning. Effects of atropine include:

- Inhibition of glandular secretions→ dry mouth, dry eyes, and dry nasal passages.
- Tachycardia. (increase heart rate).
- Loss of pupillary light reflex.
- Loss of ability to focus the lens for near vision.

## - Adrenergic receptors:

These receptors respond to **catecholamines** (epinephrine (EP) and norepinephrine (NE)).

Two types of receptors are known alpha ($\alpha$) and beta ($\beta$) receptors.

**Alpha receptors:**

The alpha receptors are subdivided into $\alpha_1$ and $\alpha_2$ receptors.

The **alpha 1 ($\alpha_1$)** receptor is widely distributed on smooth muscles with the exception of bronchial muscle. NE and EPI are about equally effective on these receptors.

Stimulation of this receptor produces excitation. This effect involves IP3 production and release of Ca++ from intracellular stores. Some ($\alpha_1$ are coupled to Ca++ gated channels).

Alpha2 receptors: are found on sympathetic postganglionic nerve terminals. These receptors are important for self inhibition of NE release.

Similar receptors are found on nonadrenergic terminals are called Alpha2 heteroreceptors.

These receptors are negatively coupled to adenylyl cyclase via Gi protein and decrease c-AMP production.

## Beta receptors:

These receptors are subdivided into beta1 ($\beta_1$) and beta 2 ($\beta_2$) receptors. Both of them are more sensitive to catecholamines than alpha receptors (catecholamines stimulate these receptors at much lower concentration than stimulation of alpha receptors).

**Beta 1 ($\beta_1$) receptors**: found on heart and produces **excitation** in the heart.

**Beta 2 ($\beta_2$) receptors**: found on tracheal and bronchial smooth muscle, in the gastrointestinal tract, and on smooth muscles of blood vessels supplying skeletal muscles (occurs along with alpha 1 receptors). The $\beta_2$ receptors are preferentially activated by EPI rather than NE.

Both receptors are positively coupled to adenylyl cyclase via Gs protein, and increase c-AMP. This will result in subsequent activation of protein kinase and phosphorylation of one or more proteins. The response elicited depends on the role of phosphorylated proteins.

All subclasses of adrenergic receptors can be blocked by specific blocking agents (antagonists). $\beta_1$ blockers are useful as antiarythmic drugs. $\beta_2$ selective agonist (produce activation of $\beta_2$ receptor) will dilate bronchi. This agonist is useful in asthma.