

## **College of pharmacy**

### **3<sup>rd</sup> year stage, pharmacology lecture.**

#### **The Autonomic Nervous System**

The autonomic nervous system, along with the endocrine system, coordinates the regulation and integration of bodily functions. 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.

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

#### **Introduction to the 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 is subdivided into the efferent division, the neurons of which carry signals away from the brain and spinal cord to the peripheral tissues, and the 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.

#### **Functional divisions within the nervous system**

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions, the somatic and the autonomic systems . The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion. On the other hand, the autonomic system regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. It is composed of efferent neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

### **Anatomy of the autonomic nervous system**

**Efferent neurons:** The autonomic nervous system carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons . The first nerve cell is called a preganglionic neuron, and its cell body is located within the CNS. 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). These ganglia function as relay stations between a preganglionic neuron and a second nerve cell, the postganglionic neuron. The latter 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.

**Afferent neurons:** The afferent neurons (fibers) of the autonomic nervous system are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and signaling the CNS to influence the efferent branch of the system to respond .

**Sympathetic neurons:** The efferent autonomic nervous system is divided into the sympathetic and the parasympathetic nervous systems, as well as the enteric nervous system. Anatomically, 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. 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. Lacking axons, 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 of the spinal cord and synapse in ganglia near or on the effector organs. 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 the discrete response of this division.

**Enteric neurons:** The enteric nervous system is the third division of the autonomic nervous system. It is a collection of nerve fibers that innervate the gastrointestinal tract, pancreas, and gallbladder, and it constitutes the -brain of the gut.- This system functions independently of the CNS and 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**

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

**Effects of stimulation of the sympathetic division:** The effect of sympathetic output is to increase heart rate and blood pressure, to mobilize energy stores of the body, and to increase blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs. 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.

**Fight or flight response:** The changes experienced by the body during emergencies have been referred to as the -fight or flight- response . These reactions are triggered both by direct sympathetic activation of the effector organs and 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 . The sympathetic nervous system tends to function as a unit, and it 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, but it is not essential for life.

## **Functions of the parasympathetic nervous system**

The parasympathetic division maintains essential bodily functions, such as digestive processes and elimination of wastes, and is required for life. It usually acts to oppose or balance the actions of the sympathetic division and is generally dominant over the sympathetic system in -rest and digest- situations. The parasympathetic system is not a functional entity as such, and it never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms. Instead, discrete 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 to provide information on the state of affairs in 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-that is, the 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:** Most of the afferent impulses are translated into reflex responses without involving consciousness. 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 tachycardia . [Note: 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.]

**Emotions and the autonomic nervous system:** Stimuli that evoke feelings of strong emotion, such as rage, fear, or pleasure, can modify the activity of the autonomic nervous system.

### **Innervation by the autonomic nervous system**

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. This type of antagonism is considered to be dynamic and is fine-tuned at any given time to control homeostatic organ functions.

**Organs receiving only 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. The control of blood pressure is also mainly a sympathetic activity, with essentially no participation by the parasympathetic 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. In addition to neurotransmission, other types of chemical signaling are the release of local mediators and the secretion of hormones.

### **Local mediators**

Most cells in the body secrete chemicals that act locally-that is, on cells in their immediate environment. These chemical signals are rapidly destroyed or removed; therefore, they do not enter the blood and are not distributed throughout the body. Histamine and the prostaglandins are examples of local mediators.

### **Hormones**

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body exerting effects on broadly distributed target 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. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. Uptake of  $\text{Ca}^{2+}$  initiates fusion of the 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 bilayer of target-cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs. [Note: A receptor is defined as a recognition site for a substance. It has a binding specificity, and it is coupled to processes that eventually evoke a response. Most receptors are proteins. They need not be located in the membrane.

**Types of neurotransmitters:** Although over fifty signal molecules in the nervous system have tentatively been identified, six signal compounds-norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and  $\gamma$ -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 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 (that is, between nerve fibers and voluntary muscles) is also cholinergic .



**Norepinephrine and epinephrine:** When norepinephrine or epinephrine is the transmitter, the fiber is termed adrenergic (adrenaline being another name for epinephrine). In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs

### **Second-Messenger Systems in Intracellular Response**

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately result 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 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**

Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules. Some receptors, such as the postsynaptic receptors of nerve or muscle, are directly linked to membrane ion channels; thus, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability .

#### **B. Regulation involving second-messenger molecules**

Many receptors are not directly coupled to ion gates. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions, which ultimately results 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 translates neurotransmitter binding into a cellular response, usually through the intervention of a G protein. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system . [Note:  $G_s$  is the protein involved in the activation of adenylyl cyclase, and  $G_q$  is the subunit that activates phospholipase C to release diacylglycerol and inositol trisphosphate .