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TEACHERS' TOPICS

Physiology of the Autonomic Nervous System

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This manuscript discusses the physiology of the autonomic nervous system (ANS). The following topics are presented: regulation of activity; efferent pathways; sympathetic and parasympathetic divisions; neurotransmitters, their receptors and the termination of their activity; functions of the ANS; and the adrenal medullae. In addition, the application of this material to the practice of pharmacy is of special interest. Two case studies regarding insecticide poisoning and pheochromocytoma are included. The ANS and the accompanying case studies are discussed over 5 lectures and 2 recitation sections during a 2-semester course in *Human Physiology*. The students are in the first-professional year of the doctor of pharmacy program.

Keywords: autonomic nervous system, sympathetic, parasympathetic, adrenergic, cholinergic, physiology

INTRODUCTION

This manuscript presents a detailed review of the autonomic nervous system (ANS). A thorough knowledge of this system is quite important as it prepares the pharmacy student for further studies in pathophysiology, pharmacology, and therapeutics. The ANS plays a crucial role in the maintenance of homeostasis. Furthermore, this system may play a role in many systemic diseases (eg, heart failure) and drugs that affect this system may improve (eg, β_2-adrenergic agonists and asthma) or exacerbate (eg, α_1-adrenergic agonists and hypertension) various disease symptoms and processes. Although this manuscript focuses primarily on the basic anatomy and physiology of the ANS, references to diseases and medications involving the ANS are included to illustrate the application of this system to the practice of pharmacy.

The ANS and the accompanying case studies are discussed over 5 lectures and 2 recitation sections during a 2-semester course in *Human Physiology*. The lectures typically include 300-325 students, although the recitation sections are much smaller with 20-30 students. The students are in the first professional year of a doctor of pharmacy program.

Also known as the visceral or involuntary nervous system, the ANS functions without conscious, voluntary control. Because it innervates cardiac muscle, smooth muscle, and various endocrine and exocrine glands, this nervous system influences the activity of most tissues and organ systems in the body. Therefore, the ANS makes a significant contribution to homeostasis. The regulation of blood pressure, gastrointestinal responses to food, contraction of the urinary bladder, focusing of the eyes, and thermoregulation are just a few of the many homeostatic functions regulated by the ANS.

At this point in the class discussion, we take a break from our traditional classroom format for a story about my next door neighbor, Joe, and my skeleton, Matilda. Interestingly, the ANS is discussed in this *Human Physiology* course in mid to late October (ie, around Halloween time). Joe leaves for work at 5:00 AM when it is still quite dark outside. On Halloween Eve, we placed Matilda in the driver's seat of Joe's pickup truck. Halloween morning, we arose at 4:45 AM, poured coffee, and waited patiently by the window located nearest to Joe's truck. Completely unsuspecting, Joe came walking down the driveway at his usual time. When he opened the truck door, the sound of "Aghhhh!!!" shattered the quiet of the morning. Poor Joe stood by his truck wide-eyed and clutching his chest. Upon opening our window, we cheerfully wished our friend a "Happy Halloween!" Although Joe's response to our holiday greeting cannot be published in this article, suffice it to say that the students always enjoy it immensely.

I now ask the class "What happened to Joe?" Several events occurred in his body at once. His heart began racing, his blood pressure increased, his pupils dilated, he began sweating, the hair on his arms and the back of his neck stood on end, and he felt a surge of adrenaline. These are some of the effects of sympathetic nervous activity in Joe's body. Meanwhile, as we waited for Joe's early morning arrival, the events occurring in my body were quite different. My heart rate was comparatively slower

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and my digestive system was processing the cream and sugar in my coffee. These are some of the effects of parasympathetic nervous activity. I tell my students that during the next several class periods they will learn in great detail about the many functions of the sympathetic and parasympathetic nervous systems, the neurotransmitters released by their neurons, the receptors to which they bind, and how it is all regulated. At this point, the students often look as afraid as Joe did that Halloween morning. I reassure them (and remind them repeatedly) that it is not necessary to memorize very much at all. I encourage them to let it make sense. The sympathetic system controls "fight-or-flight" responses. In other words, this system prepares the body for strenuous physical activity. The events that we would expect to occur within the body to allow this to happen do, in fact, occur. The parasympathetic system regulates "rest and digest" functions. In other words, this system controls basic bodily functions while one is sitting quietly reading a book.

Specific learning objectives for the discussion of the autonomic nervous system include the following:

- Explain how various regions of the central nervous system regulate autonomic nervous system function;
- Explain how autonomic reflexes contribute to homeostasis;
- Describe how the neuroeffector junction in the autonomic nervous system differs from that of a neuron-to-neuron synapse;
- Compare and contrast the anatomical features of the sympathetic and parasympathetic systems;
- For each neurotransmitter in the autonomic nervous system, list the neurons that release them and the type and location of receptors that bind with them;
- Describe the mechanism by which neurotransmitters are removed;
- Distinguish between cholinergic and adrenergic receptors;
- Describe the overall and specific functions of the sympathetic system;
- Describe the overall and specific functions of the parasympathetic system; and
- Explain how the effects of the catecholamines differ from those of direct sympathetic stimulation.

DESIGN AND COURSE CONTENT

Regulation of Autonomic Nervous System Activity

The efferent nervous activity of the ANS is largely regulated by autonomic reflexes. In many of these reflexes, sensory information is transmitted to homeostatic control centers, in particular, those located in the hypothalamus and brainstem. Much of the sensory input from the thoracic and abdominal viscera is transmitted to the brainstem by afferent fibers of cranial nerve X, the vagus nerve. Other cranial nerves also contribute sensory input to the hypothalamus and the brainstem. This input is integrated and a response is carried out by the transmission of nerve signals that modify the activity of preganglionic autonomic neurons. Many important variables in the body are monitored and regulated in the hypothalamus and the brainstem including heart rate, blood pressure, gastrointestinal peristalsis and glandular secretion, body temperature, hunger, thirst, plasma volume, and plasma osmolarity.

An example of this type of autonomic reflex is the baroreceptor reflex. Baroreceptors located in some of the major systemic arteries are sensory receptors that monitor blood pressure. If blood pressure decreases, the number of sensory impulses transmitted from the baroreceptors to the vasomotor center in the brainstem also decreases. As a result of this change in baroreceptor stimulation and sensory input to the brainstem, ANS activity to the heart and blood vessels is adjusted to increase heart rate and vascular resistance so that blood pressure increases to its normal value.

These neural control centers in the hypothalamus and the brainstem may also be influenced by higher brain areas. Specifically, the cerebral cortex and the limbic system influence ANS activities associated with emotional responses by way of hypothalamic-brainstem pathways. For example, blushing during an embarrassing moment, a response most likely originating in the frontal association cortex, involves vasodilation of blood vessels to the face. Other emotional responses influenced by these higher brain areas include fainting, breaking out in a cold sweat, and a racing heart rate.

Some autonomic reflexes may be processed at the level of the spinal cord. These include the micturition reflex (urination) and the defecation reflex. Although these reflexes are subject to influence from higher nervous centers, they may occur without input from the brain.

Efferent Pathways of the Autonomic Nervous System

The efferent pathways of the ANS consist of 2 neurons that transmit impulses from the CNS to the effector tissue. The preganglionic neuron originates in the CNS with its cell body in the lateral horn of the gray matter of the spinal cord or in the brainstem. The axon of this neuron travels to an autonomic ganglion located outside the CNS, where it synapses with a postganglionic neuron. This neuron innervates the effector tissue.

Synapses between the autonomic postganglionic neuron and effector tissue—the neuroeffector junction—differ

greatly from neuron-to-neuron synapses. The postganglionic fibers in the ANS do not terminate in a single swelling like the synaptic knob, nor do they synapse directly with the cells of a tissue. Instead, where the axons of these fibers enter a given tissue, they contain multiple swellings called varicosities. When the neuron is stimulated, these varicosities release neurotransmitters along a significant length of the axon and, therefore, over a large surface area of the effector tissue. The neurotransmitter diffuses through the interstitial fluid to wherever its receptors are located in the tissue. This diffuse release of the neurotransmitter affects many tissue cells simultaneously. Furthermore, cardiac muscle and most smooth muscle have gap junctions between cells. These specialized intercellular communications allow for the spread of electrical activity from one cell to the next. As a result, the discharge of a single autonomic nerve fiber to an effector tissue may alter the activity of the entire tissue.

Divisions of the Autonomic Nervous System

The ANS is composed of 2 anatomically and functionally distinct divisions, the sympathetic system and the parasympathetic system. Both systems are tonically active. In other words, they provide some degree of nervous input to a given tissue at all times. Therefore, the frequency of discharge of neurons in both systems can either increase or decrease. As a result, tissue activity may be either enhanced or inhibited. This characteristic of the ANS improves its ability to more precisely regulate a tissue's function. Without tonic activity, nervous input to a tissue could only increase.

Many tissues are innervated by both systems. Because the sympathetic system and the parasympathetic system typically have opposing effects on a given tissue, increasing the activity of one system while simultaneously decreasing the activity of the other results in very rapid and precise control of a tissue's function. Several distinguishing features of these 2 divisions of the ANS are summarized in Table 1.

Each system is dominant under certain conditions. The sympathetic system predominates during emergency "fight-or-flight" reactions and during exercise. The overall effect of the sympathetic system under these conditions is to prepare the body for strenuous physical activity. More specifically, sympathetic nervous activity will increase the flow of blood that is well-oxygenated and rich in nutrients to the tissues that need it, in particular, the working skeletal muscles. The parasympathetic system predominates during quiet, resting conditions. The overall effect of the parasympathetic system under these conditions is to conserve and store energy and to regulate basic body functions such as digestion and urination.

Sympathetic Division

The preganglionic neurons of the sympathetic system arise from the thoracic and lumbar regions of the spinal cord (segments T_1 through L_2). Most of these preganglionic axons are short and synapse with postganglionic neurons within ganglia found in the sympathetic ganglion chains. These ganglion chains, which run parallel immediately along either side of the spinal cord, each consist of 22 ganglia. The preganglionic neuron may exit the spinal cord and synapse with a postganglionic neuron in a ganglion at the same spinal cord level from which it arises. The preganglionic neuron may also travel more rostrally or caudally (upward or downward) in the ganglion chain to synapse with postganglionic neurons in ganglia at other levels. In fact, a single preganglionic neuron may synapse

Table 1. Distinguishing Features of the Sympathetic and Parasympathetic Systems

Sympathetic System	Parasympathetic Systems
Originates in thoracic and lumbar regions of the spinal cord (T_1-L_2)	Originates in brainstem (cranial nerves III, VII, IX, and X) and sacral region of spinal cord (S2-S4)
Ganglia located in paravertebral sympathetic ganglion chain or collateral ganglia	Terminal ganglia located near or embedded within target tissue
Short cholinergic preganglionic fibers; long adrenergic postganglionic fibers	Long cholinergic preganglionic fibers; short cholinergic postganglionic fibers
Ratio of preganglionic fibers to postganglionic fibers is 1:20	Ratio of preganglionic fibers to postganglionic fibers is 1:3
Divergence coordinates activity of neurons at multiple levels of spinal cord	Limited divergence
Activity often involves mass discharge of the entire system	Activity normally to discrete organs
Primary neurotransmitter of postganglionic neurons is norepinephrine	Primary neurotransmitter of postganglionic neurons is acetylcholine
Predominates during emergency "fight-or-flight" reactions and exercise	Predominates during quiet resting conditions

with several postganglionic neurons in many different ganglia. Overall, the ratio of preganglionic fibers to postganglionic fibers is about 1:20. The long postganglionic neurons originating in the ganglion chain then travel outward and terminate on the effector tissues. This divergence of the preganglionic neuron results in coordinated sympathetic stimulation to tissues throughout the body. The concurrent stimulation of many organs and tissues in the body is referred to as a mass sympathetic discharge.

Other preganglionic neurons exit the spinal cord and pass through the ganglion chain without synapsing with a postganglionic neuron. Instead, the axons of these neurons travel more peripherally and synapse with postganglionic neurons in one of the sympathetic collateral ganglia. These ganglia are located about halfway between the CNS and the effector tissue.

Finally, the preganglionic neuron may travel to the adrenal medulla and synapse directly with this glandular tissue. The cells of the adrenal medulla have the same embryonic origin as neural tissue and, in fact, function as modified postganglionic neurons. Instead of the release of neurotransmitter directly at the synapse with an effector tissue, the secretory products of the adrenal medulla are picked up by the blood and travel throughout the body to all of the effector tissues of the sympathetic system.

An important feature of this system, which is quite distinct from the parasympathetic system, is that the postganglionic neurons of the sympathetic system travel within each of the 31 pairs of spinal nerves. Interestingly, 8% of the fibers that constitute a spinal nerve are sympathetic fibers. This allows for the distribution of sympathetic nerve fibers to the effectors of the skin including blood vessels and sweat glands. In fact, most innervated blood vessels in the entire body, primarily arterioles and veins, receive only sympathetic nerve fibers. Therefore, vascular smooth muscle tone and sweating are regulated by the sympathetic system only. In addition, the sympathetic system innervates structures of the head (eye, salivary glands, mucus membranes of the nasal cavity), thoracic viscera (heart, lungs) and viscera of the abdominal and pelvic cavities (eg, stomach, intestines, pancreas, spleen, adrenal medulla, urinary bladder).

Parasympathetic Division

The preganglionic neurons of the parasympathetic system arise from several nuclei of the brainstem and from the sacral region of the spinal cord (segments S_2-S_4). The axons of the preganglionic neurons are quite long compared to those of the sympathetic system and synapse with postganglionic neurons within terminal ganglia which are close to or embedded within the effector tissues. The axons of the postganglionic neurons, which are very short, then provide input to the cells of that effector tissue.

The preganglionic neurons that arise from the brainstem exit the CNS through the cranial nerves. The occulomotor nerve (III) innervates the eyes; the facial nerve (VII) innervates the lacrimal gland, the salivary glands and the mucus membranes of the nasal cavity; the glossopharyngeal nerve (IX) innervates the parotid (salivary) gland; and the vagus nerve (X) innervates the viscera of the thorax and the abdomen (eg, heart, lungs, stomach, pancreas, small intestine, upper half of the large intestine, and liver). The physiological significance of this nerve in terms of the influence of the parasympathetic system is clearly illustrated by its widespread distribution and the fact that 75% of all parasympathetic fibers are in the vagus nerve. The preganglionic neurons that arise from the sacral region of the spinal cord exit the CNS and join together to form the pelvic nerves. These nerves innervate the viscera of the pelvic cavity (eg, lower half of the large intestine and organs of the renal and reproductive systems).

Because the terminal ganglia are located within the innervated tissue, there is typically little divergence in the parasympathetic system compared to the sympathetic system. In many organs, there is a 1:1 ratio of preganglionic fibers to postganglionic fibers. Therefore, the effects of the parasympathetic system tend to be more discrete and localized, with only specific tissues being stimulated at any given moment, compared to the sympathetic system where a more diffuse discharge is possible.

Neurotransmitters of the Autonomic Nervous System

The 2 most common neurotransmitters released by neurons of the ANS are acetylcholine and norepinephrine. Neurotransmitters are synthesized in the axon varicosities and stored in vesicles for subsequent release. Several distinguishing features of these neurotransmitters are summarized in Table 2. Nerve fibers that release acetylcholine are referred to as cholinergic fibers. These include all preganglionic fibers of the ANS, both sympathetic and parasympathetic systems; all postganglionic fibers of the parasympathetic system; and sympathetic postganglionic fibers innervating sweat glands. Nerve fibers that release norepinephrine are referred to as adrenergic fibers. Most sympathetic postganglionic fibers release norepinephrine.

As previously mentioned, the cells of the adrenal medulla are considered modified sympathetic postganglionic neurons. Instead of a neurotransmitter, these cells release hormones into the blood. Approximately 20% of the hormonal output of the adrenal medulla is norepinephrine. The remaining 80% is epinephrine. Unlike true

Table 2. Distinguishing Features of Neurotransmitters of the Autonomic Nervous System

Feature	Acetylcholine	Norepinephrine	Epinephrine
Site of release	All preganglionic neurons of ANS; all postganglionic neurons of parasympathetic system; some sympathetic postganglionic neurons to sweat glands	Most sympathetic postganglionic neurons; adrenal medulla (20% of secretion)	Adrenal medulla (80% of secretion)
Receptor	Nicotinic, muscarinic (cholinergic)	α_1, α_2, β_1 (adrenergic)	α_1, α_2, β_1, β_2 (adrenergic)
Termination of activity	Enzymatic degradation by cholinesterase	Reuptake into nerve terminals; diffusion out of synaptic cleft, metabolic transformation by monoamine oxidase (within nerve terminal) or catechol-O-methyl-transferase within liver	Metabolic transformation by catechol-O-methyl-transferase within liver

postganglionic neurons in the sympathetic system, the adrenal medulla contains an enzyme that methylates norepinephrine to form epinephrine. The synthesis of epinephrine, also known as adrenaline, is enhanced under conditions of stress. These 2 hormones released by the adrenal medulla are collectively referred to as the catecholamines.

Termination of Neurotransmitter Activity

For any substance to serve effectively as a neurotransmitter, it must be rapidly inactivated or removed from the synapse or, in this case, the neuroeffector junction. This is necessary in order to allow new signals to get through and influence effector tissue function.

The primary mechanism used by cholinergic synapses is enzymatic degradation. Acetylcholinesterase hydrolyzes acetylcholine to its component choline and acetate. It is one of the fastest acting enzymes in the body and acetylcholine removal occurs in less than 1 msec. The most important mechanism for the removal of norepinephrine from the neuroeffector junction is the reuptake of this neurotransmitter into the sympathetic nerve that released it. Norepinephrine may then be metabolized intraneuronally by monoamine oxidase (MAO). The circulating catecholamines, epinephrine and norepinephrine, are inactivated by catechol-O-methyltransferase (COMT) in the liver.

Receptors for Autonomic Neurotransmitters

As discussed in the previous section, all of the effects of the ANS in tissues and organs throughout the body, including smooth muscle contraction or relaxation, alteration of myocardial activity, and increased or decreased glandular secretion, are carried out by only 3 substances, acetylcholine, norepinephrine, and epinephrine. Furthermore, each of these substances may stimulate activity in some tissues and inhibit activity in others. How can this wide variety of effects on many different tissues be carried out by so few neurotransmitters or hormones? The effect caused by any of these substances is determined by the receptor distribution in a particular tissue and the biochemical properties of the cells in that tissue, specifically, the second messenger and enzyme systems present within the cell.

The neurotransmitters of the ANS and the circulating catecholamines bind to specific receptors on the cell membranes of the effector tissue. All adrenergic receptors and muscarinic receptors are coupled to G proteins which are also embedded within the plasma membrane. Receptor stimulation causes activation of the G protein and the formation of an intracellular chemical, the second messenger. (The neurotransmitter molecule, which cannot enter the cell itself, is the first messenger.) The function of the intracellular second messenger molecules is to elicit tissue-specific biochemical events within the cell which alter the cell's activity. In this way, a given neurotransmitter may stimulate the same type of receptor on 2 different types of tissue and cause 2 different responses due to the presence of different biochemical pathways within each tissue.

Acetylcholine binds to 2 types of cholinergic receptors. Nicotinic receptors are found on the cell bodies of all postganglionic neurons, both sympathetic and parasympathetic, in the ganglia of the ANS. Acetylcholine released from the preganglionic neurons binds to these nicotinic receptors and causes a rapid increase in the cellular-permeability to Na^+ ions and Ca^{++} ions. The resulting influx of these 2 cations causes depolarization and excitation of the postganglionic neurons the ANS pathways.

Muscarinic receptors are found on the cell membranes of the effector tissues and are linked to G proteins

and second messenger systems which carry out the intracellular effects. Acetylcholine released from all parasympathetic postganglionic neurons and some sympathetic postganglionic neurons traveling to sweat glands binds to these receptors. Muscarinic receptors may be either inhibitory or excitatory, depending on the tissue upon which they are found. For example, muscarinic receptor stimulation in the myocardium is inhibitory and decreases heart rate while stimulation of these receptors in the lungs is excitatory, causing contraction of airway smooth muscle and bronchoconstriction.

There are 2 classes of adrenergic receptors for norepinephrine and epinephrine, alpha (α) and beta (β). Furthermore, there are at least 2 subtypes of receptors in each class: α_1, α_2, β_1 and β_2. All of these receptors are linked to G proteins and second messenger systems which carry out the intracellular effects.

Alpha receptors are the more abundant of the adrenergic receptors. Of the 2 subtypes, α_1 receptors are more widely distributed on the effector tissues. Alpha one receptor stimulation leads to an increase in intracellular calcium. As a result, these receptors tend to be excitatory. For example, stimulation of α_1 receptors causes contraction of vascular smooth muscle resulting in vasoconstriction and increased glandular secretion by way of exocytosis.

Pharmacy Application: Alpha One Adrenergic Receptor Antagonists. Hypertension, or a chronic elevation in blood pressure, is a major risk factor for coronary artery disease, congestive heart failure, stroke, kidney failure, and retinopathy. An important cause of hypertension is excessive vascular smooth muscle tone or vasoconstriction. Prazosin, an α_1-adrenergic receptor antagonist, is very effective in the management of hypertension. Because α_1-receptor stimulation causes vasoconstriction, drugs that block these receptors result in vasodilation and a decrease in blood pressure.

Compared to α_1 receptors, α_2 receptors have only moderate distribution on the effector tissues. Alpha 2 receptor stimulation causes a decrease in cAMP and, therefore, inhibitory effects such as smooth muscle relaxation and decreased glandular secretion. However, α_2 receptors have important presynaptic effects. Where α_1 receptors are found on the effector tissue cells at the neuroeffector junction, the α_2 receptors are found on the varicosities of the postganglionic neuron. Norepinephrine released from this neuron binds to not only the α_1 receptors on the effector tissue to cause some physiological effect; it also binds to the α_2 receptors on the neuron itself. Alpha 2 receptor stimulation results in "presynaptic inhibition" or in a decrease in the release of norepinephrine. In this way, norepinephrine inhibits its own release from the sympathetic postganglionic neuron and controls its own activity. Both α_1 and α_2 receptors have equal affinity for norepinephrine released directly from sympathetic neurons as well as circulating epinephrine released from the adrenal medulla.

Stimulation of each type of β receptor leads to an increase in intracellular cAMP. Whether this results in an excitatory or an inhibitory response depends upon the specific cell type. As with α receptors, β receptors are also unevenly distributed with β_2 receptors, the more common subtype on the effector tissues. Beta 2 receptors tend to be inhibitory. For example, β_2 receptor stimulation causes relaxation of vascular smooth muscle and airway smooth muscle resulting in vasodilation and bronchodilation, respectively. Beta 2 receptors have a significantly greater affinity for epinephrine than for norepinephrine. Furthermore, terminations of sympathetic pathways are not found near these receptors. Therefore, β_2 receptors are stimulated only indirectly by circulating epinephrine instead of by direct sympathetic nervous activity.

Beta 1 receptors are the primary adrenergic receptor on the heart (a small percentage of the adrenergic receptors on the myocardium are β_2). Both subtypes of β receptors on the heart are excitatory and stimulation leads to an increase in cardiac activity. Beta 1 receptors are also found on certain cells in the kidney. Epinephrine and norepinephrine have equal affinity for β_1 receptors.

Beta three (β_3) receptors are found primarily in adipose tissue. Stimulation of these receptors, which have a stronger affinity for norepinephrine, causes lipolysis.

Pharmacy Application: Sympathomimetic Drugs. Sympathomimetic drugs are those that produce effects in a tissue resembling those caused from stimulation by the sympathetic nervous system. An important use for these drugs is in the treatment of bronchial asthma which is characterized by bronchospasm. As discussed, bronchodilation occurs following β_2-adrenergic receptor stimulation. Non-selective β receptor agonists, such as epinephrine and isoproterenol, are capable of causing bronchodilation. However, a potential problem with these drugs is that they stimulate *all* β-receptors including β_1 receptors on the heart. Therefore, in patients with bronchospasm, an undesirable side effect of treatment with these non-selective agents is an increase in heart rate. Instead, β_2-selective drugs, such as albuterol, are chosen for this therapy. They are equally effective in causing bronchodilation with a much lower risk of adverse cardiovascular effects.

Functions of the Autonomic Nervous System

The 2 divisions of the ANS are dominant under different conditions. As stated previously, the sympathetic

system is activated during emergency ''fight-or-flight'' reactions and during exercise. The parasympathetic system is predominant during quiet conditions (''rest and digest''). As such, the physiological effects caused by each system are quite predictable. In other words, all of the changes in organ and tissue function induced by the sympathetic system work together to support strenuous physical activity and the changes induced by the parasympathetic system are appropriate for when the body is resting. Several of the specific effects elicited by sympathetic and parasympathetic stimulation of various organs and tissues are summarized in Table 3.

The ''fight-or-flight'' reaction elicited by the sympathetic system is essentially a whole body response. Changes in organ and tissue function throughout the body are coordinated so that there is an increase in the delivery of well-oxygenated, nutrient-rich blood to the working skeletal muscles. Both heart rate and myocardial contractility are increased so that the heart pumps more blood per minute. Sympathetic stimulation of vascular smooth muscle causes widespread vasoconstriction, particularly in the organs of the gastrointestinal system and in the kidneys. This vasoconstriction serves to ''redirect'' or redistribute the blood away from these metabolically inactive tissues and toward the contracting muscles. Bronchodilation in the lungs facilitates the movement of air in and out of the lungs so that the uptake of oxygen from the atmosphere and the elimination of carbon dioxide from the body are maximized. An enhanced rate of glycogenolysis (breakdown of glycogen into its component glucose molecules) and gluconeogenesis (formation of new glucose from noncarbohydrate sources) in the liver increases the concentration of glucose molecules in the blood. This is necessary for the brain as glucose is the only nutrient molecule that it can utilize to form metabolic energy. An enhanced rate of lipolysis in adipose tissue increases the concentration of fatty acid molecules in the blood. Skeletal muscles then utilize these fatty acids to form metabolic energy for contraction. Generalized sweating elicited by the sympathetic system enables the individual to thermoregulate during these conditions of increased physical activity and heat production. Finally, the eye is adjusted such that the pupil dilates letting more light in toward the retina (mydriasis) and the lens adapts for distance vision.

The parasympathetic system decreases heart rate which helps to conserve energy under resting conditions. Salivary secretion is enhanced to facilitate the swallowing of food. Gastric motility and secretion are stimulated to begin the processing of ingested food. Intestinal motility and secretion are also stimulated to continue the processing and to facilitate the absorption of these nutrients. Both exocrine and endocrine secretion from the pancreas is promoted. Enzymes released from the exocrine glands of the pancreas contribute to the chemical breakdown of the food in the intestine and insulin released from the pancreatic islets promotes the storage of nutrient molecules within the tissues once they are absorbed into the body. Another bodily maintenance type of function caused by the parasympathetic system is contraction of the urinary bladder which results in urination. Finally, the eye is adjusted such that the pupil contracts (miosis) and the lens adapts for near vision.

Pharmacy application: cholinomimetic drugs. Cholinomimetic drugs are those that produce effects in a tissue resembling those caused from stimulation by the parasympathetic nervous system. These drugs have many important uses including the treatment of gastrointestinal and urinary tract disorders that involve depressed smooth muscle activity without obstruction. For example, postoperative ileus is characterized by a loss of tone or paralysis of the stomach or bowel following surgical manipulation. Urinary retention may also occur postoperatively or it may be secondary to spinal cord injury or disease (neurogenic bladder). Normally, parasympathetic stimulation of the smooth muscle in each of these organ systems causes contraction to maintain gastrointestinal motility as well as urination. There are 2 different approaches in the pharmacotherapy of these disorders. One type of agent would be a muscarinic receptor agonist which would mimic the effect of the parasympathetic neurotransmitter, acetylcholine, and stimulate smooth muscle contraction. One of the more commonly used agents in this category is bethanechol which can be given subcutaneously. Another approach is to increase the concentration and, therefore, activity of endogenously produced acetylcholine in the neuroeffector junction. Administration of an acetylcholinesterase inhibitor prevents the degradation and removal of neuronally-released acetylcholine. In this case, neostigmine is the most widely used agent. Neostigmine may be given intramuscularly, subcutaneously, or orally.

Pharmacy application: muscarinic receptor antagonists. Inspection of the retina during an ophthalmoscopic examination is greatly facilitated by mydriasis, or the dilation of the pupil. Parasympathetic stimulation of the circular muscle layer in the iris causes contraction and a decrease in the diameter of the pupil. Administration of a muscarinic receptor antagonist, such as atropine or scopolamine, prevents this smooth muscle contraction. As a result, sympathetic stimulation of the radial muscle layer is unopposed. This causes an increase in the diameter of the pupil. These agents are given in the form of eye

Table 3. Effects of Autonomic Nerve Activity on Some Effector Tissue

Tissue	Sympathetic Receptor	Sympathetic Stimulation	Parasympathetic Stimulation
Eye			
Radial muscle of iris	α_1	Contraction (dilation of pupil; mydriasis)	–
Sphincter muscle of iris		–	Contraction (constriction of pupil; miosis)
Ciliary muscle	β_2	Relaxation for far vision	Contraction for near vision
Heart	β_1, β_2	↑ Heart rate	↓ Heart rate
		↑ Force of contraction	↓ Rate of conduction
		↑ Rate of conduction	
Arterioles			
Skin	α_1	Strong constriction	–
Abdominal viscera	α_1	Strong constriction	–
Kidney	α_1	Strong constriction	–
Skeletal muscle	α_1, β_2	Weak constriction	–
Spleen	α_1	Contraction	
Lungs			
Airways	β_2	Bronchodilation	Bronchoconstriction
Glands	α_1, β_2	↓ Secretion	↑ Secretion
Liver	α_1, β_2	Glycogenolysis	–
		Gluconeogenesis	–
Adipose tissue	β_3	Lipolysis	–
Sweat glands	Muscarinic;	Generalized sweating	–
	α_1	Localized sweating	–
Piloerector muscles	α_1	Contraction (erection of hair, goose bumps)	–
Adrenal medullae	Nicotinic	↑ Secretion of epinephrine, norepinephrine	–
Salivary glands	α_1, β_2	Small volume K^+ and water secretion	Large volume K^+ and water secretion; amylase secretion
Stomach			
Motility	α_1, β_2	Decreased	Increased
Sphincters	α_1	Contraction	Relaxation
Secretion			Stimulation
Intestine			
Motility	α_1, β_2	Decreased	Increased
Sphincters	α_1	Contraction	Relaxation
Secretion			Stimulation
Gallbladder	β_2	Relaxation	Contraction
Pancreas			
Exocrine	α	↓ Enzyme secretion	↑ Enzyme secretion
Endocrine (Islets β cells)	α	↓ Insulin secretion	↑ Insulin secretion
Urinary bladder			
Detrusor muscle (bladder wall)	β_2	Relaxation	Contraction
Urethra sphincter		Contraction	Relaxation
Kidney	β_1	↑ Renin secretion	–

drops which act locally and limit the possibility of systemic side effects.

Adrenal Medulla

A mass sympathetic discharge, which typically occurs during the "fight-or-flight" response and during exercise, involves the simultaneous stimulation of organs and tissues throughout the body. Included among these tissues are the adrenal medullae which release epinephrine and norepinephrine into the blood. In large part, the indirect effects of these catecholamines are similar to and, therefore, reinforce those of direct sympathetic stimulation. However, there are some important differences in the effects of the circulating catecholamines and those of norepinephrine released from sympathetic nerves.

The duration of activity of the catecholamines is significantly longer than that of neuronally released norepinephrine. Therefore, the effects on the tissues are more prolonged. This difference has to do with the mechanism of inactivation of these substances. Norepinephrine is immediately removed from the neuroeffector synapse by way of reuptake into the postganglionic neuron. This rapid removal limits the duration of the effect of this neurotransmitter. In contrast, there are no enzymes in the blood to degrade the catecholamines. Instead, the catecholamines are inactivated by COMT in the liver. As one might expect, the hepatic clearance of these hormones from the blood would require several passes through the circulation. Therefore, the catecholamines are available to cause their effects for a comparatively longer period of time (up to 1-2 minutes as opposed to milliseconds).

Because they travel in the blood, organs and tissues throughout the body are exposed to the catecholamines. Therefore, they are capable of stimulating tissues that are not directly innervated by sympathetic nerve fibers: airway smooth muscle, hepatocytes, and adipose tissue, in particular. As a result, the catecholamines have a much wider breadth of activity compared to norepinephrine released from sympathetic nerves.

The third important feature that distinguishes the catecholamines from neuronally released norepinephrine involves epinephrine's affinity for β_2 receptors. Norepinephrine has a very limited affinity for these receptors. Therefore, circulating epinephrine causes effects that differ from those of direct sympathetic innervation including a greater stimulatory effect on the heart and relaxation of smooth muscle (vascular, bronchial, gastrointestinal, and genitourinary).

Epinephrine and norepinephrine have equal affinity for β_1 receptors, the predominant adrenergic receptor on the heart. However, the human heart also contains a small percentage of β_2 receptors which, like β_1 receptors are excitatory. Therefore, epinephrine is capable of stimulating a greater number of receptors and of causing a greater stimulatory effect on the myocardium.

Beta two adrenergic receptors are also found on smooth muscle in several organ systems. These receptors tend to be inhibitory and cause relaxation of the smooth muscle. Vascular smooth muscle in skeletal muscle contains both α_1 and β_2 receptors. Norepinephrine, which stimulates only the excitatory α_1 receptors, causes strong vasoconstriction. However, epinephrine, which stimulates both types of receptors, causes only weak vasoconstriction. The vasodilation resulting from β_2 receptor stimulation opposes and, therefore, weakens the vasoconstriction resulting from α_1 receptor stimulation. Given that skeletal muscle may account for 40% of an adult's body weight, the potential difference in vasoconstriction, blood pressure, and the distribution of blood flow could be quite significant.

Another noteworthy example of the relaxation of smooth muscle by way of β_2 receptor stimulation involves the airways. Bronchodilation, or the opening of the airways, facilitates airflow in the lungs. Any direct sympathetic innervation to the lungs is irrelevant in this respect, as only circulating epinephrine is capable of stimulating these receptors on airway smooth muscle.

Application of the ANS to Pharmacy

In addition to the "Pharmacy Application" sections found throughout the discussion, further application of the lecture material to the practice of pharmacy is provided by required case studies. The case studies are then discussed in recitation sections. These exercises serve to separate students who have simply memorized aspects of the ANS from students who have a more thorough understanding of this system. Successful completion of the case studies requires higher level critical-thinking and problem-solving skills.

Case #1: Insecticide Poisoning

CD is a 44-year-old woman who had spent much of the day working in her garden. A blustery wind caused her to unintentionally inhale the insecticide that she was spraying throughout the garden. When she began wheezing severely, she was taken to the emergency room. The attending physician observed other symptoms including constricted pupils and a slowed heart rate. CD was treated with the intravenous administration of atropine sulfate.

1. Insecticides contain organophosphates which inhibit acetylcholinesterase. What is the function of acetylcholinesterase?
2. Which types of autonomic receptors are excessively stimulated as a result of this inhibition?

3. Which division of the ANS has been primarily affected, the sympathetic or the parasympathetic?
4. Under what conditions does this division of the ANS normally predominate?
5. Explain how the insecticide resulted in her presenting symptoms.
6. What effects may the insecticide have on the gastrointestinal system? Explain.
7. What effect may the insecticide have on generalized sweating in this patient? Localized sweating? Explain.
8. If exposed to high enough doses, what effect might the insecticide have on the patient's skeletal muscles?
9. Would the administration of a β-adrenergic receptor antagonist be useful in the treatment of this patient? Why or why not?
10. Would the administration of a β-adrenergic receptor agonist be useful in the treatment of this patient? Why or why not?
11. Why is atropine an appropriate treatment?
12. The "nerve gas," sarin, is a potent, irreversible organophosphate. What is the likely cause of death resulting from exposure to this extremely toxic agent?

Case Study #2: Pheochromocytoma

AF is a 55-year-old woman who had been experiencing heart palpitations, a throbbing headache, sweating, pain in the abdomen, nausea and vomiting. Because these symptoms had failed to subside, she went to see her primary care physician. A urinalysis revealed the presence of catecholamines and their metabolites, including vanillylmandelic acid (VMA). A subsequent CT scan confirmed the presence of a tumor in the adrenal medulla. Surgery to remove the tumor was scheduled.

1. What is pheochromocytoma?
2. What are the catecholamines? Which is the predominant compound?
3. Describe the relationship of the adrenal medulla to the autonomic nervous system. Under what conditions are the catecholamines typically released?
4. How are catecholamines normally eliminated from the blood?
5. Is heart rate slower or faster than average in this patient? Why? What autonomic receptors are involved with this change in heart rate?
6. Is blood pressure likely to be lower or higher than average in this patient? Why? What autonomic receptors are involved with this change in blood pressure?
7. Describe the mechanism of excessive sweating in the patient. What autonomic receptors are involved with this sweating?
8. Would you expect the patient's pupils to be constricted or dilated when her other symptoms are at a peak? What is the clinical term used to describe this condition?
9. How does the duration of activity of the circulating catecholamines compare to that of neuronally released norepinephrine? Explain.
10. How does the breadth of activity of the circulating catecholamines compare to that of neuronally released norepinephrine? Explain.
11. In order to prepare the patient for surgery, what types of autonomic nervous system medications may be used to stabilize her blood pressure within the normal range?

SUMMARY

An in depth understanding of the autonomic nervous system is critical for pharmacy students as they progress through the curriculum to advanced courses such as pathophysiology, pharmacology, and therapeutics. Frequent reference to disease processes and pharmacology (as basic as it is at this level) is appreciated by the students as they begin to understand how physiological concepts may be applied to the practice of pharmacy. The inclusion of case studies in the *Human Physiology* courses has been particularly beneficial in this respect. Students find the opportunity to apply their knowledge and problem solve both enjoyable and academically rewarding.

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