The Autonomic Nervous System

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I. OVERVIEW

The autonomic nervous system (ANS), 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. In contrast, 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 ANS are called autonomic drugs and are discussed in the following four chapters. These autonomic agents act either by stimulating portions of the ANS or by blocking the action of the autonomic nerves. This chapter outlines the fundamental physiology of the ANS and describes the role of neurotransmitters in the communication between extracellular events and chemical changes within the cell.

II. 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 (Figure 3.1). The peripheral nervous system is subdivided into the efferent and afferent divisions. The efferent neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent neurons bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action.
A. 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 ANS (Figure 3.1). The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion. The ANS, conversely, regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. Because of the involuntary nature of the ANS as well as its functions, it is also known as the visceral, vegetative, or involuntary nervous system. 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.

B. Anatomy of the ANS

1. Efferent neurons: The ANS carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons: the preganglionic neurons and the postganglionic neurons (Figure 3.2). The cell body of the first nerve cell, the preganglionic neuron, is located within the CNS. The 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). The ganglia function as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron. The cell body of the postganglionic neuron originates 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.

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

3. Sympathetic neurons: The efferent ANS is divided into the sympathetic and the parasympathetic nervous systems, as well as the enteric nervous system (Figure 3.1). Anatomically, the sympathetic and the parasympathetic neurons originate in the CNS and emerge from two different spinal cord regions. The preganglionic neurons of the sympathetic system come from the thoracic and lumbar regions (T1 to L2) of the spinal cord, and they synapse in two cord-like chains of ganglia that run close to and 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 (see Chapter 6). In most cases, the preganglionic nerve endings of the sympathetic nervous system are highly branched, enabling one preganglionic neuron to interact with many postganglionic neurons. This arrangement enables this division to activate numerous effector organs at the same time. [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, secretes epinephrine (adrenaline), and lesser amounts of norepinephrine, directly into the blood.]

4. **Parasympathetic neurons:** The parasympathetic preganglionic fibers arise from cranial nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus), as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near or on the effector organs. [Note: The vagus nerve accounts for 90% of preganglionic parasympathetic fibers in the body. Postganglionic neurons from this nerve innervate most of the organs in the thoracic and abdominal cavity.] 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 discrete response of this system.

5. **Enteric neurons:** The enteric nervous system is the third division of the ANS. It is a collection of nerve fibers that innervate the gastrointestinal (GI) 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 GI tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

C. **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, and exercise (Figure 3.3).

1. **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 (Figure 3.3). It also affects GI motility and the function of the bladder and sexual organs.

2. **Fight-or-flight response:** The changes experienced by the body during emergencies are referred to as the "fight or flight" response (Figure 3.4). 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. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors (see Chapter 6). The sympathetic nervous system tends to function as a unit and often discharges as a complete system, for example, during severe exercise or in reactions to fear (Figure 3.4). This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities. Although it is not essential for survival, it is nevertheless an important system that prepares the body to handle uncertain situations and unexpected stimuli.
3. The Autonomic Nervous System

D. Functions of the parasympathetic nervous system

The parasympathetic division is involved with maintaining homeostasis within the body. It is required for life, since it maintains essential bodily functions, such as digestion and elimination of wastes. The parasympathetic division usually acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in "rest-and-digest" situations. Unlike the sympathetic system, the parasympathetic system never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation. Instead, parasympathetic fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.

E. Role of the CNS in the control of autonomic functions

Although the ANS is a motor system, it does require sensory input from peripheral structures to provide information on the current state of 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, such as the hypothalamus, medulla oblongata, and spinal cord. These centers respond to the stimuli by sending out efferent reflex impulses via the ANS.

1. Reflex arcs: Most of the afferent impulses are involuntarily translated into reflex responses. 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 (Figure 3.5). [Note: In each case, the reflex arcs of the ANS comprise a sensory (or afferent) arm and a motor (or efferent or effector) arm.]

2. Emotions and the ANS: Stimuli that evoke strong feelings, such as rage, fear, and pleasure, can modify the activities of the ANS.

F. Innervation by the ANS

1. Dual innervation: Most organs in the body are innervated by both divisions of the ANS. 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 continually to control homeostatic organ functions.

2. 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.

G. Somatic nervous system

The efferent somatic nervous system differs from the ANS in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the ANS is involuntary. Responses in the somatic division are generally faster than those in the ANS.

H. Summary of differences between sympathetic, parasympathetic, and motor nerves

Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division (Figure 3.6). The sympathetic nervous system is widely distributed, innervating practically all effector systems in the body. In contrast, the distribution of the parasympathetic division is more limited. The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic fibers. This type of organization permits a diffuse discharge of the sympathetic nervous system. The parasympathetic division is more circumscribed,
with mostly one-to-one interactions, and the ganglia are also close to, or within, organs they innervate. This limits the amount of branching that can be done by this division. [A notable exception to this arrangement is found in the myenteric plexus, where one preganglionic neuron has been shown to interact with 8000 or more postganglionic fibers.] The anatomical arrangement of the parasympathetic system results in the distinct functions of this division. The somatic nervous system innervates skeletal muscles. One somatic motor neuron axon is highly branched, and each branch innervates a single muscle fiber. Thus, one somatic motor neuron may innervate 100 muscle fibers. This arrangement leads to the formation of a motor unit. The lack of ganglia and the myelination of the motor nerves enable a fast response by the somatic nervous system.

III. CHEMICAL SIGNALING BETWEEN CELLS

Neurotransmission in the ANS is an example of the more general process of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators (Figure 3.7).

A. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body, exerting effects on broadly distributed target cells (see Chapters 24 through 27.)

B. Local mediators

Most cells in the body secrete chemicals that act locally on cells in the immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. Histamine (see Chapter 30) and the prostaglandins are examples of local mediators.

C. Neurotransmitters

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical
signals (neurotransmitters) from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular 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.

1. **Membrane receptors:** All neurotransmitters, and most hormones and local mediators, are too hydrophilic to penetrate the lipid bilayers 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 is coupled to processes that eventually evoke a response. Most receptors are proteins (see Chapter 2).]

2. **Types of neurotransmitters:** Although over 50 signal molecules in the nervous system have been identified, norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-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 ANS, whereas a wide variety of neurotransmitters function in the CNS.

   a. **Acetylcholine:** The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic (Figure 3.8 and Chapters 4 and 5). 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 (the junction of nerve fibers and voluntary muscles) is also cholinergic (Figure 3.8).

   b. **Norepinephrine and epinephrine:** When norepinephrine and epinephrine are the neurotransmitters, the fiber is termed adrenergic (Figure 3.8 and Chapters 6 and 7). In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs. [Note: A few sympathetic fibers, such as those involved in sweating, are cholinergic, and, for simplicity, they are not shown in Figure 3.8.]

### IV. SIGNAL TRANSDUCTION IN THE EFFECTOR CELL

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the phosphorylation of intracellular proteins or
46 3. The Autonomic Nervous System

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 a 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 (see Chapter 2).

A. Membrane receptors affecting ion permeability (ionotropic receptors)

Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules.

Figure 3.8
Summary of the neurotransmitters released, types of receptors, and types of neurons within the autonomic and somatic nervous systems. Cholinergic neurons are shown in red and adrenergic neurons in blue. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit.] *Epinephrine 80% and norepinephrine 20% released from adrenal medulla.
Some receptors, such as the postsynaptic nicotinic receptors in the skeletal muscle cells, are directly linked to membrane ion channels. Therefore, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability (Figure 3.9A). These types of receptors are known as ionotropic receptors.

B. Membrane receptors coupled to second messengers (metabotropic receptors)

Many receptors are not directly coupled to ion channels. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions that ultimately result 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 translate neurotransmitter binding into a cellular response, usually through the intervention of a G protein. The two most widely recognized second messengers are the adenyl cyclase system and the calcium/phosphatidylinositol system (Figure 3.9B, C). The receptors coupled to the second messenger system are known as metabotropic receptors. Muscarinic and adrenergic receptors are examples of metabotropic receptors.

Figure 3.9
Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.
Study Questions

Choose the ONE best answer.

3.1 Which of the following is correct regarding the autonomic nervous system (ANS)?
A. Afferent neurons carry signals from the CNS to the effector organs.
B. The neurotransmitter at the parasympathetic ganglion is norepinephrine (NE).
C. The neurotransmitter at the sympathetic ganglion is acetylcholine (ACh).
D. Sympathetic neurons release ACh in the effector organs.
E. Parasympathetic neurons release NE in the effector organs.

3.2 Which of the following is correct regarding somatic motor neurons?
A. The neurotransmitter at the somatic motor neuron ganglion is acetylcholine.
B. The neurotransmitter at the somatic motor neuron ganglion is norepinephrine.
C. Somatic motor neurons innervate smooth muscles.
D. Somatic motor neurons do not have ganglia.
E. Responses in the somatic motor nervous system are generally slower than in the autonomic nervous system.

3.3 Which of the following physiological changes could happen when a person is attacked by a grizzly bear?
A. Increase in heart rate.
B. Increase in lacrimation (tears).
C. Constriction of the pupil (miosis).
D. Increase in gastric motility.

3.4 Which of the following changes could theoretically happen in a person when the parasympathetic system is inhibited using a pharmacological agent?
A. Reduction in heart rate.
B. Constriction of the pupil (miosis).
C. Increase in gastric motility.
D. Dry mouth (xerostomia).
E. Contraction of detrusor muscle in the bladder.

3.5 Which of the following statements is correct regarding the sympathetic and parasympathetic systems?
A. Acetylcholine activates muscarinic receptors.
B. Acetylcholine activates adrenergic receptors.
C. Norepinephrine activates muscarinic receptors.
D. Activation of the sympathetic system causes a drop in blood pressure.
Study Questions 49

3.6 Which of the following statements concerning the parasympathetic nervous system is correct?
A. The parasympathetic system uses norepinephrine as a neurotransmitter.
B. The parasympathetic system often discharges as a single, functional system.
C. The parasympathetic division is involved in accommodation of near vision, movement of food, and urination.
D. The postganglionic fibers of the parasympathetic division are long compared to those of the sympathetic nervous system.
E. The parasympathetic system controls the secretion of the adrenal medulla.

Correct answer = C. The parasympathetic nervous system maintains essential bodily functions, such as vision, movement of food, and urination. It uses acetylcholine, not norepinephrine, as a neurotransmitter, and it discharges as discrete fibers that are activated separately. The postganglionic fibers of the parasympathetic system are short compared to those of the sympathetic division. The adrenal medulla is under the control of the sympathetic system.

3.7 Which of the following is correct regarding neurotransmitters and neurotransmission?
A. Neurotransmitters are released from the presynaptic nerve terminals.
B. Neurotransmitter release is triggered by the arrival of action potentials in the postsynaptic cell.
C. Intracellular calcium levels drop in the neuron before the neurotransmitter is released.
D. Serotonin and dopamine are the primary neurotransmitters in the ANS.

Correct answer = A. Neurotransmitters are released from presynaptic neurons, triggered by the arrival of an action potential in the presynaptic neuron (not in the postsynaptic cell). When an action potential arrives in the presynaptic neuron, calcium enters the presynaptic neuron and the calcium levels increase in the neuron before the neurotransmitter is released. The main neurotransmitters in the ANS are norepinephrine and acetylcholine.

3.8 An elderly man was brought to the emergency room after he ingested a large quantity of carvedilol tablets, a drug that blocks $\alpha_1$, $\beta_1$, and $\beta_2$ adrenergic receptors, which mainly mediate the cardiovascular effects of epinephrine and norepinephrine in the body. Which of the following symptoms would you expect in this patient?
A. Increased heart rate (tachycardia).
B. Reduced heart rate (bradycardia).
C. Dilation of the pupil (mydriasis).
D. Increased blood pressure.

Correct answer = B. Activation of $\alpha_1$ receptors causes mydriasis, vasoconstriction, and an increase in blood pressure. Activation of $\beta_1$ receptors increases heart rate, contractility of the heart, and blood pressure. Activation of $\beta_2$ receptors causes dilation of bronchioles and relaxation of skeletal muscle vessels. Thus, inhibition of these receptors will cause vasorelaxation ($\alpha_1$ blockade), reduction in heart rate ($\beta_1$ blockade), reduction in contractility of the heart ($\beta_1$ blockade), reduction in blood pressure, bronchoconstriction ($\beta_2$ blockade), and constriction of blood vessels supplying skeletal muscles ($\beta_2$ blockade).

3.9 All of the following statements regarding central control of autonomic functions are correct except:
A. Baroreceptors are pressure sensors located at various cardiovascular sites.
B. The parasympathetic system is activated by the CNS in response to a sudden drop in blood pressure.
C. The parasympathetic system is activated by the CNS in response to a sudden increase in blood pressure.
D. The sympathetic system is activated by the CNS in response to a sudden drop in blood pressure.

Correct answer = B. When there is a sudden drop in blood pressure, the baroreceptors send signals to the brain, and the brain activates the sympathetic system (not the parasympathetic system) to restore blood pressure to normal values.
3.10 Which of the following is correct regarding membrane receptors and signal transduction?

A. ANS neurotransmitters bind to membrane receptors on the effector cells, which leads to intracellular events.

B. Cholinergic muscarinic receptors are examples of ionotropic receptors.

C. Cholinergic nicotinic receptors are examples of metabotropic receptors.

D. Metabotropic receptors activate ion channels directly.

Correct answer = A. Neurotransmitters generally bind to the membrane receptors on the postsynaptic effector cells and cause cellular effects. Acetylcholine (ACh) binds to cholinergic muscarinic receptors in the effector cells and activates the second messenger pathway in the effector cells, which in turn causes cellular events. These types of receptors that are coupled to second messenger systems are known as metabotropic receptors. Thus, metabotropic receptors do not directly activate ion channels. ACh also binds to cholinergic nicotinic receptors and activates ion channels on the effector cells directly. These types of receptors that activate ion channels directly are known as ionotropic receptors.