

Chapter 3



Pharmacology of the Autonomic Nervous System

Objectives

Upon completion of this chapter, you will be able to

- Describe the divisions of the central and peripheral nervous systems.
- Define key terms relative to pharmacology of the autonomic nervous system.
- Describe the anatomy, neurotransmitters, and receptors of the autonomic nervous system.
- State four classifications of autonomic nervous system drugs on the basis of how and where they work.
- Relate the pharmacology of the autonomic nervous system to the specific chapters and drug classifications that are relevant.

Key Terms

acetylcholine
acetylcholinesterase
adrenergic
adrenergic receptors
afferent nerves
alpha-receptors
antiadrenergic
anticholinergic
autonomic nervous system
beta-receptors

central nervous system
cholinergic
dopamine receptors
efferent nerves
ganglion
muscarinic receptors
nicotinic receptors
norepinephrine
parasympathetic
parasympathetic nervous system

parasympatholytic
parasympathomimetic
peripheral nervous system
reuptake
somatic nervous system
sympathetic
sympathetic nervous system
sympatholytic
sympathomimetic

Abbreviations

ACh	acetylcholine	LABA	long-acting beta ₂ -agonist
AChE	acetylcholinesterase	LAMA	long-acting muscarinic antagonist
ACLS	advanced cardiac life support	MAO	monoamine oxidase
ANS	autonomic nervous system	NE	norepinephrine
CNS	central nervous system	PNS	peripheral nervous system
COMT	catechol-O-methyltransferase	SABA	short-acting beta ₂ -agonist
CPU	central processing unit	SAMA	short-acting muscarinic antagonist
GI	gastrointestinal		

The nervous system and endocrine system represent the control systems of the body. These systems coordinate complex activities to maintain day-to-day functioning and a stable internal homeostatic environment. In times of stress, these systems must quickly integrate complex activities to combat the stress and maintain survival. The endocrine system will be discussed in Chapter 7 under the steroid classification of drugs.

This chapter discusses, in general terms, how the **central nervous system** (CNS) and the **peripheral nervous system** (PNS) receive and process information and how drugs can affect this activity. The nervous system is responsible for day-to-day functioning of both voluntary and involuntary activities throughout the body, and only by understanding how it works will you have the basis for understanding drug effects on various skeletal and smooth muscles, glands, and organs.

The pharmacology of drugs that affect the nervous system is admittedly difficult to understand. The majority of drugs discussed in this chapter work on the PNS. Only the basics of the PNS and CNS will be presented in this chapter, with specifics discussed later in appropriate chapters. For example, drugs that work on the CNS, such as skeletal muscle relaxants and opioid medications for pain, are discussed in Chapter 11. PNS drugs that affect the heart rate and respiratory airway muscle tone are addressed in the relevant chapters on bronchodilators and cardiovascular drugs. This chapter simply lays the foundation for understanding nervous system drug pharmacology; we will build on this foundation in upcoming chapters.

3.1 Nervous System Divisions

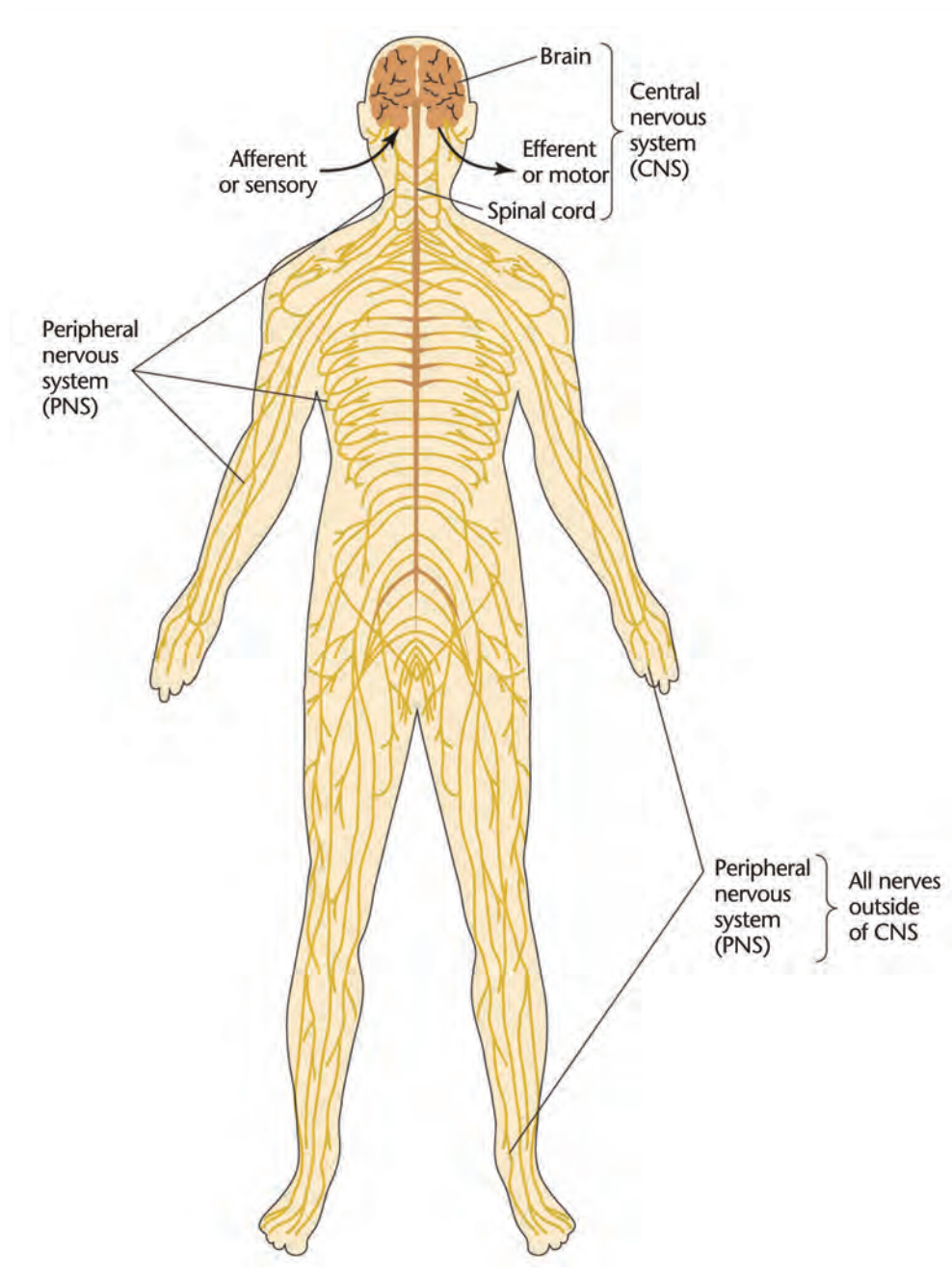
The nervous system consists of the *central nervous system* and the *peripheral nervous system*. The CNS is comprised of the brain and spinal cord. The brain is analogous to the central processing unit (CPU) of a computer, which handles information from a variety of sources. The spinal cord is the main branch that transmits messages to and from the brain.

The PNS is comprised of all the nerves “outside” of the brain and spinal cord. The anatomy and physiology of the PNS are more pertinent to cardiopulmonary pharmacotherapy than are those of the CNS, so this chapter emphasizes the PNS. Basically, the PNS mediates between the CNS and external and internal body environments. Peripheral system nerves carry sensory information along **afferent nerves** from all parts of the body to the CNS. Therefore, *afferent* and *sensory* can be used synonymously in this context. Likewise, the CNS can send information along **efferent nerves** or motor pathways via the PNS and have “effects” on various parts of the body (see Figure 3–1).



Learning Hint

The flow of information into your brain (along afferent nerve fibers), or sensory input, is what helps you understand this book. The output from your brain (along efferent nerve fibers) is what controls your muscles and helps you turn the pages, a motor response.

**Figure 3–1** Major Components of the Nervous System

3.1a PNS Divisions

The peripheral nervous system is what connects the rest of your body, neurologically speaking, to your brain and spinal cord. The PNS has two main divisions, the **somatic nervous system** and the **autonomic nervous system (ANS)**. The somatic nervous system controls skeletal muscles during voluntary movement; therefore, it represents the voluntary portion of the PNS. An example of the somatic nervous system is the control of the muscles in your hand to turn the page of this book. We will focus on the somatic nervous system in Chapter 11, where we discuss skeletal muscle relaxants. The somatic nervous system also conducts sensory information such as pain and touch back to the CNS via afferent nerves.



If you have ever gone to the eye doctor and had to wear dark glasses after the doctor dilated your pupils, it was because a drug had temporarily blocked the autonomic pupil light reflex, which opens and closes the pupil during changing light conditions. This allows the doctor to better examine your dilated eyes so they do not constrict with the examination light. After the examination, the pupils remain dilated for some time and without the dark glasses, you could suffer retinal damage from too much light exposure, especially on a sunny day.

The autonomic nervous system is the involuntary or automatic part of the PNS—we have little or no control over its action. An example of involuntary control is the reaction of the pupil to light on the retina: In bright light conditions, your pupil constricts to protect the retina from too much light exposure, which could be damaging. You do not consciously tell your pupil to constrict; therefore, this is an autonomic response of the PNS.

Other major organ systems in the body that are regulated by the ANS include the cardiopulmonary and digestive systems. Although you may consciously decide to eat a hamburger, using your voluntary or somatic system for this process, the rest of the digestive process is under autonomic control and goes on with little or no thought. In addition to glands and organs, the involuntary muscles controlled by the autonomic nervous system include the specialized cardiac muscles that control the heart and the smooth muscle found in airways, blood vessels, and the reproductive and gastrointestinal (GI) tracts.



● ● ● Time for Review

What branch of the nervous system controls digestive actions?

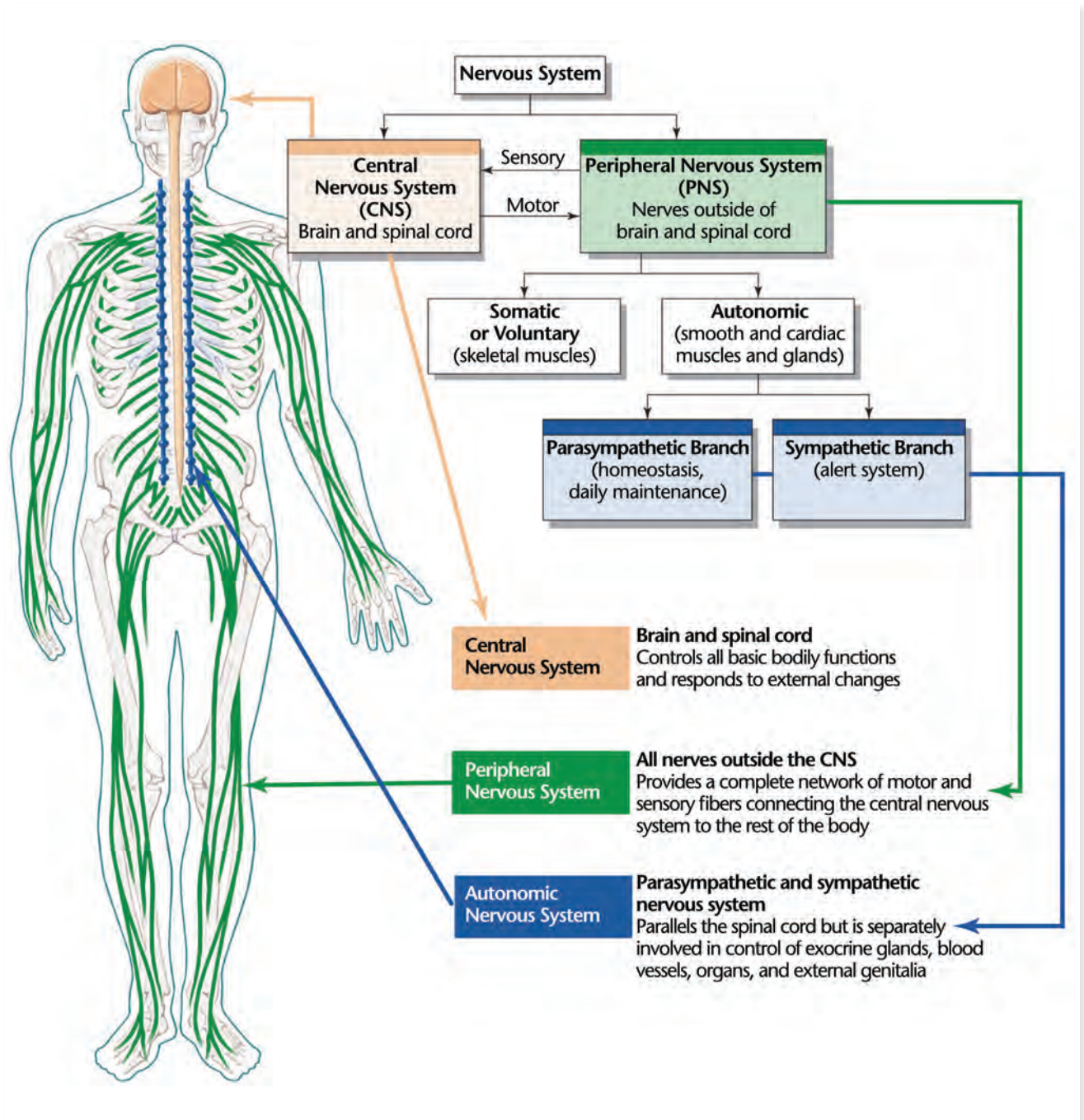


The autonomic system is further divided into the **sympathetic** and **parasympathetic** branches. The **parasympathetic nervous system** is concerned with daily body upkeep and maintaining a homeostatic environment; thus, it is often called the “sleep-and-eat” system. The **sympathetic nervous system** is the alert system for stressful situations and is often referred to as the “fight-or-flight” system. Because the balance between these two systems is what controls our normal heart rate and the smooth muscle tone of our airways, this balance is of major pharmacologic importance. Please see Figure 3–2, which demonstrates the divisions of the nervous system.

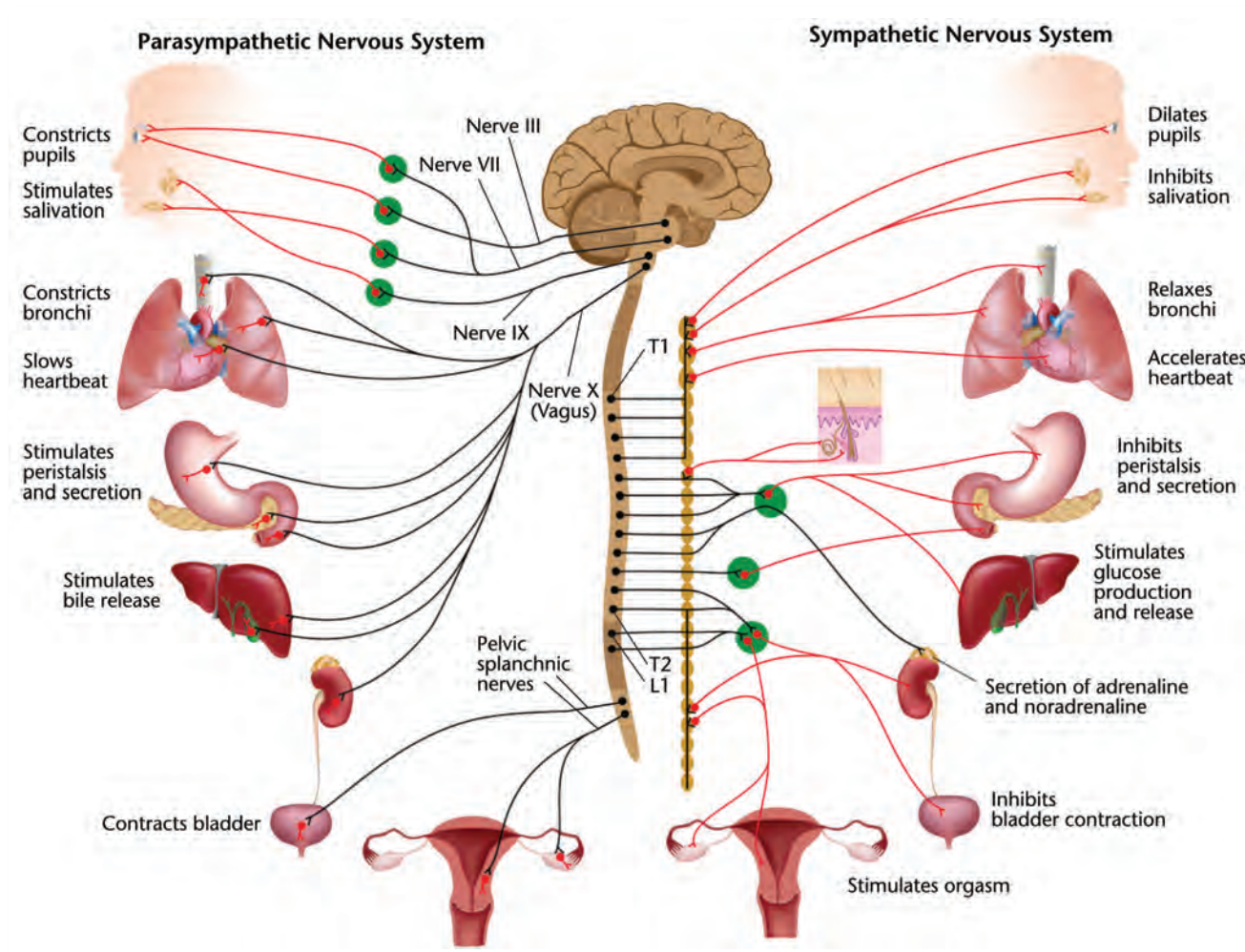
It is important to note that the parasympathetic and sympathetic systems usually work in a coordinated but opposing fashion to regulate autonomic control. For example, if you were confronted by a stranger with a knife in a dark alley, several physiological changes would occur because the sympathetic system would be alerted. Your pupils would dilate to bring in more light for the situation at hand. Your heart rate and force of contraction would increase to get much-needed oxygen to muscles for the impending “fight or flight.” Your respiratory system would be stimulated to increase ventilation to bring in more oxygen. Certain vascular changes would occur to provide more blood flow to essential areas and constrict blood flow to nonessential areas, such as the GI tract.



Figure 3–2 Organization of the Nervous System



However, you cannot maintain this hypermetabolic state for long periods of time; once the danger is removed (hopefully, by peaceful police intervention), you will eventually return to a homeostatic state. Then, we presume, you will wonder why you were ever in that dark alley in the first place. The parasympathetic system would then become dominant and bring your heart rate and respirations back toward normal resting levels. See Figure 3–3, which shows the effects of the parasympathetic and sympathetic nervous systems and their origins on the spinal column. Note how they work in opposition to each other.

Figure 3–3 Effects of the Parasympathetic and Sympathetic Nervous Systems

Source: Adapted Shutterstock

What was just described is a physiologic response to stress and a return to homeostasis via the two branches of the autonomic nervous system. The activity of each of these branches can also be altered by pharmacologic means. This is good because some pathologic conditions of the organs can be treated pharmacologically by capitalizing on the knowledge of these interactions. Please see Table 3–1 for actions of the parasympathetic and sympathetic nervous systems.

Table 3–1 Effects of the Parasympathetic and Sympathetic Nervous Systems

Organ or System	Parasympathetic Effect	Sympathetic Effect
Heart	Decreases rate and contractile force	Increases rate and contractile force
Lungs	Bronchoconstricts	Bronchodilates
Eyes	Pupil constriction	Pupil dilation
Hair muscles	Relaxes	Contracts and causes hair to stand on end (piloerection)
Gastrointestinal system	Increases digestion	Decreases digestion
Urinary system	Constricts bladder	Relaxes bladder



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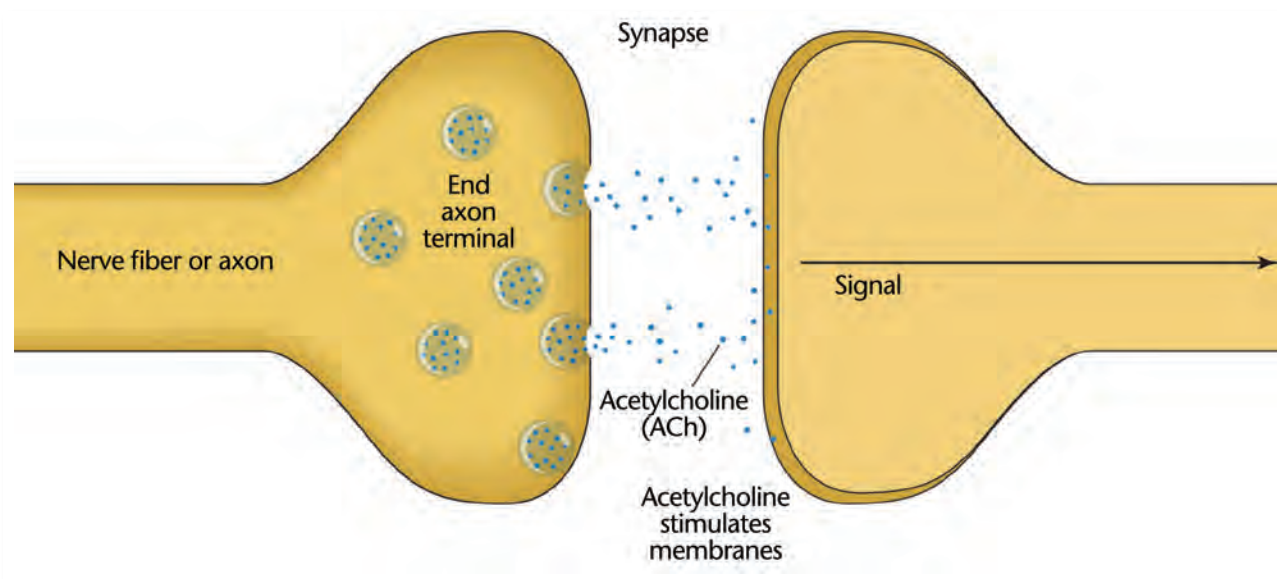
Have you ever heard the saying, “That made the hairs on the back of my neck stand up”? Would you consider this a sympathetic or parasympathetic response, and why?



3.2 Nervous System Conduction

To understand how drugs affect neurotransmission, you must know how messages are transmitted or conducted from one nerve (neuron) to another. When a resting nerve receives stimulation, an electrical impulse carries the signal along the nerve fiber or axon. At the terminal end of each axon is a small junction or synapse that may connect either to another nerve or to a muscle or gland. Regardless of where the connection leads, for the impulse to be carried on, a chemical substance called a *neurotransmitter* must now travel across the synapse. These chemicals are manufactured and stored at the terminal end of the axon and released upon stimulation by the electrical impulse. The two main neurochemical substances stored or manufactured at the ends of the nerve fibers are **acetylcholine (ACh)** and **norepinephrine (NE)**. See Figure 3–4, which demonstrates the transmission of a nerve impulse with ACh as the neurotransmitter.

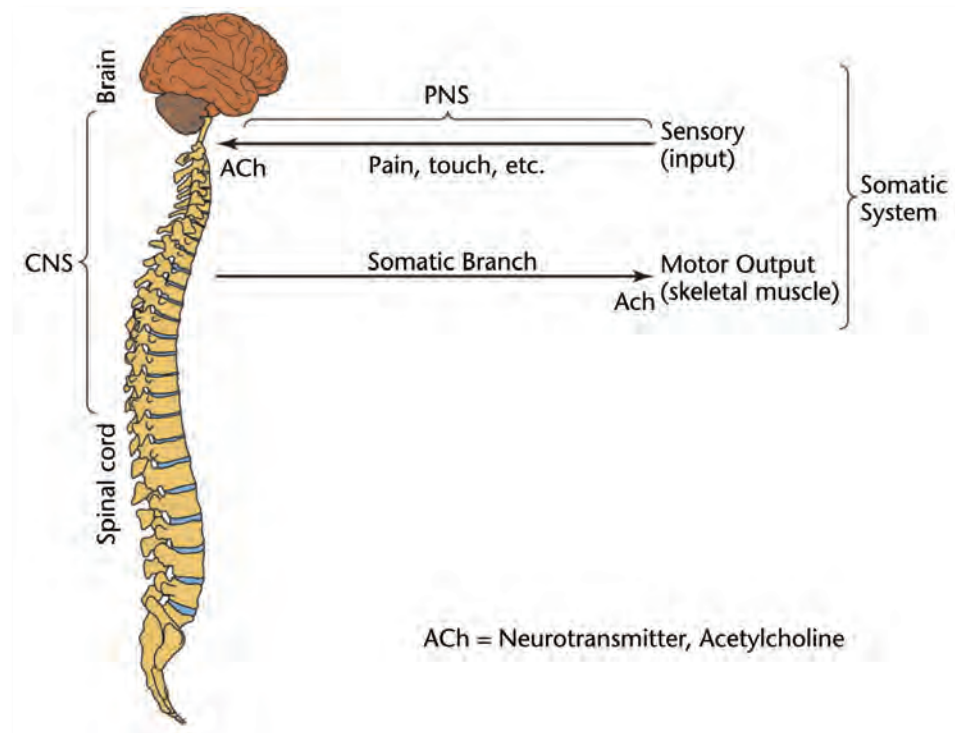
Figure 3–4 Transmission of a Nerve Impulse



3.2a Types and Location of Neurotransmitters

The somatic nervous system, which controls the skeletal muscles, is a one-connection system in which the stimulus travels via a single nerve axon and then travels to one gap or synapse. The neurotransmitter must then pass the signal on to the CNS to convey sensory input such as pain, or on to the affected skeletal muscle for motor output to control the muscle (see Figure 3–5). Notice that ACh is the neurotransmitter substance found within the somatic system. The synapse in the somatic system is the neuromuscular junction that connects the nerve to the skeletal muscle or the synapse to the CNS to bring in sensory information.

Figure 3–5 Somatic Nervous System Transmission

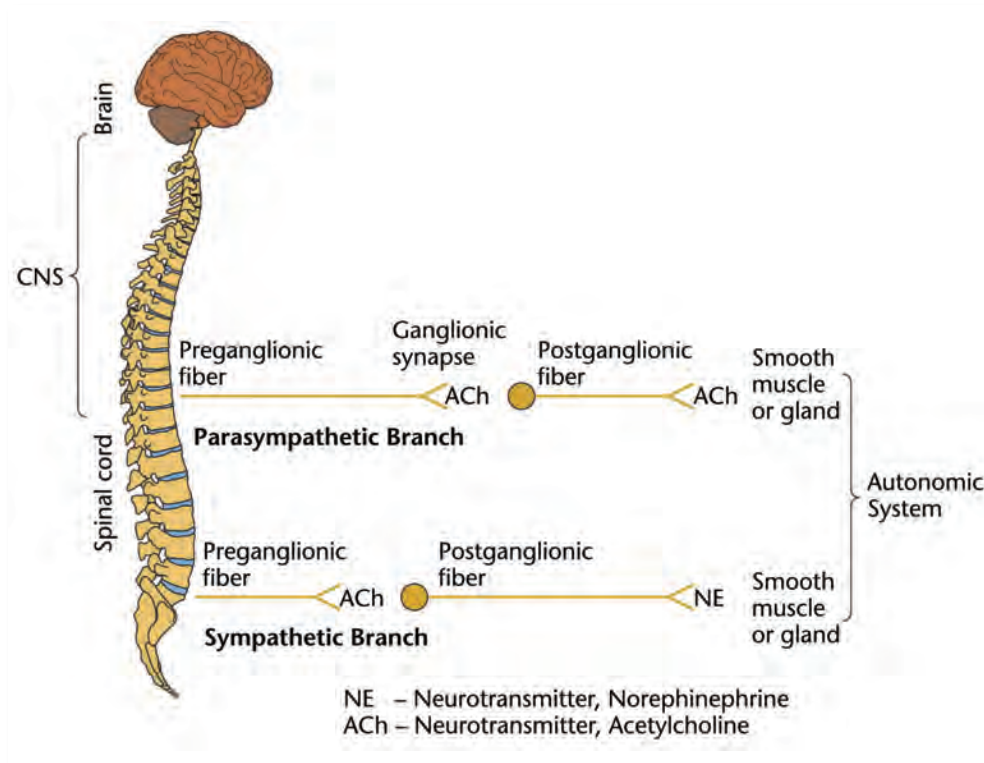


The autonomic branch of the PNS has two junctions to traverse in order for the signal to reach the intended site of an involuntary muscle or gland. The first neuron is a presynaptic or preganglionic neuron. A **ganglion** (plural, *ganglia*) can be thought of as simply a cluster of nerves that lie outside the CNS. Therefore, the first part of the journey from the brain is to the first junction (synapse) and ganglia beyond. The second neuron is a postsynaptic or postganglionic neuron, and it travels from the ganglia to the target site of either an involuntary muscle (cardiac or smooth) or a gland.

Both the parasympathetic and the sympathetic systems have preganglionic and postganglionic neurons. The neurotransmitter ACh is present at both preganglionic sites. ACh is also found at the postganglionic site of the parasympathetic system. However, the neurotransmitter norepinephrine carries the impulse to the involuntary muscle or gland at the postganglionic junction of the sympathetic system. See Figure 3–6, which now adds the autonomic branches of the peripheral nervous system.



Figure 3–6 Synapses and Neurotransmitter Substances of the Autonomic Nervous System

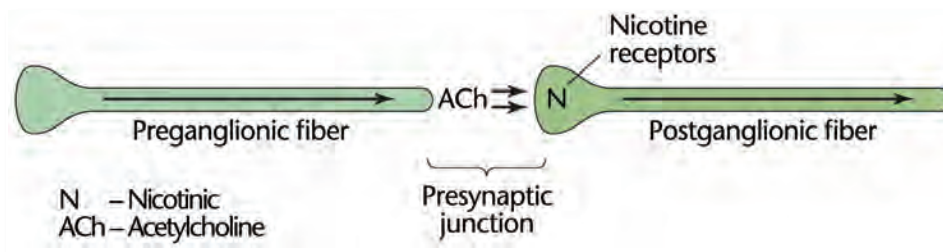


3.2b Receptors

In Chapter 1, we learned that receptor sites are where the action is. Once the neurotransmitter is released, it binds to a receptor to elicit a response. If the stimulus begins in the ANS, it must first release ACh across the presynaptic junction and then diffuse and bind to postsynaptic receptors found on the postsynaptic nerve to pass the signal on. When ACh diffuses across the presynaptic junction in either the parasympathetic or the sympathetic system, it binds to **nicotinic receptors**. These receptors simply pass the signal on to the postsynaptic neuron and it is then carried to the target gland, organ, smooth muscle, or cardiac muscle (see Figure 3–7).

Figure 3–7 Preganglionic Transmission in the ANS

This occurs in both parasympathetic and sympathetic systems, with only the length and location of the nerve fibers being different.



Learning Hint

Remember that the neurotransmitter ACh is found everywhere (skeletal neuromuscular junction, sensory synapses, both preganglionic junctions, and the postganglionic junction of the parasympathetic nervous system), but NE is found only at the postganglionic junction of the sympathetic system.

Learning Hint

Remember that the nicotinic receptors are found at presynaptic sites and help to pass the impulse along to the postganglionic neuron. The muscarinic receptors at the postsynaptic sites are the actual effector site of the parasympathetic nervous system. In Chapter 5 you will learn about bronchodilator agents that work by blocking the muscarinic receptors and thus blocking the parasympathetic response of bronchoconstriction. Some are short acting and some are long acting and they are given the names SAMAs and LAMAs (for short-acting muscarinic antagonists and long-acting muscarinic antagonists, respectively).

Receptors are also found on the postsynaptic junction located on involuntary muscles or glands. This is where the “main” action is, so to speak, and it is referred to as the neuroeffector site. Once the neurochemical transmitter binds to receptor sites there, it initiates biochemical triggers that result in physiological responses, depending on what the nerve innervates (connects to). After the chemical transmitter has interacted with the receptor and initiated a response, its job is done and action is terminated. The neurotransmitter must be destroyed or removed after receptor activation. The neurotransmitters that do not bind are destroyed by enzymes or taken back into the synapse, or they diffuse away.

The neurotransmitter ACh is present in the postsynaptic junction of the parasympathetic nervous system. ACh binds with **muscarinic receptors** found on involuntary muscles or glands. For example, if the parasympathetic system is stimulated and muscarinic receptors innervating the heart bind with ACh, the physiological reaction is the parasympathetic response of slowing heart rate.

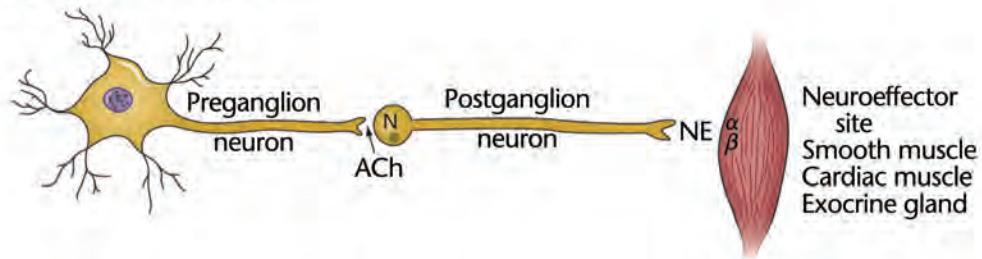
However, if the sympathetic nervous system is stimulated and the impulse reaches the postsynaptic site, norepinephrine is released and binds with the **adrenergic receptors** found on the glands or smooth or cardiac muscle.

For example, if the sympathetic system is stimulated and adrenergic receptors found in the heart bind with NE, the physiological reaction is the sympathetic response of increasing heart rate. The adrenergic receptors are further classified as alpha- or beta-receptors, which will be discussed further in Chapter 5. See Figure 3–8, which shows the synapses, ganglia, neurotransmitters, and receptors of the ANS.

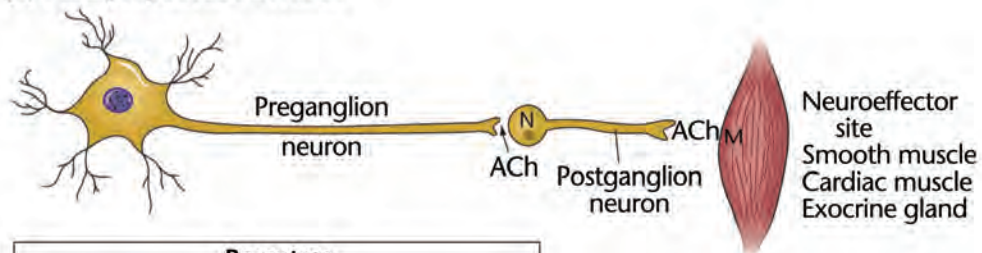
Figure 3–8 Synapses, Ganglia, Neurotransmitters, and Receptors of the ANS

Note: Adrenergic receptors are classified as alpha (α) or beta (β).

(1) Sympathetic Division



(2) Parasympathetic Division



Receptors	
M = muscarinic receptor	N = nicotinic receptor
α = alpha-receptor	β = beta-receptor
NE = norepinephrine	— = nerve terminal
ACh = acetylcholine	



● ● ● Time for Review

Identify where nicotinic and muscarinic receptors can be found in the parasympathetic and sympathetic nervous systems.



3.2c Receptor Classification

Receptors are classified by the type of neurotransmitter to which they respond at the various nerve endings. The receptors that bind with *acetylcholine* are termed *cholinergic receptors*. Cholinergic receptors are of two types, termed *muscarinic* or *nicotinic*, depending on their location.

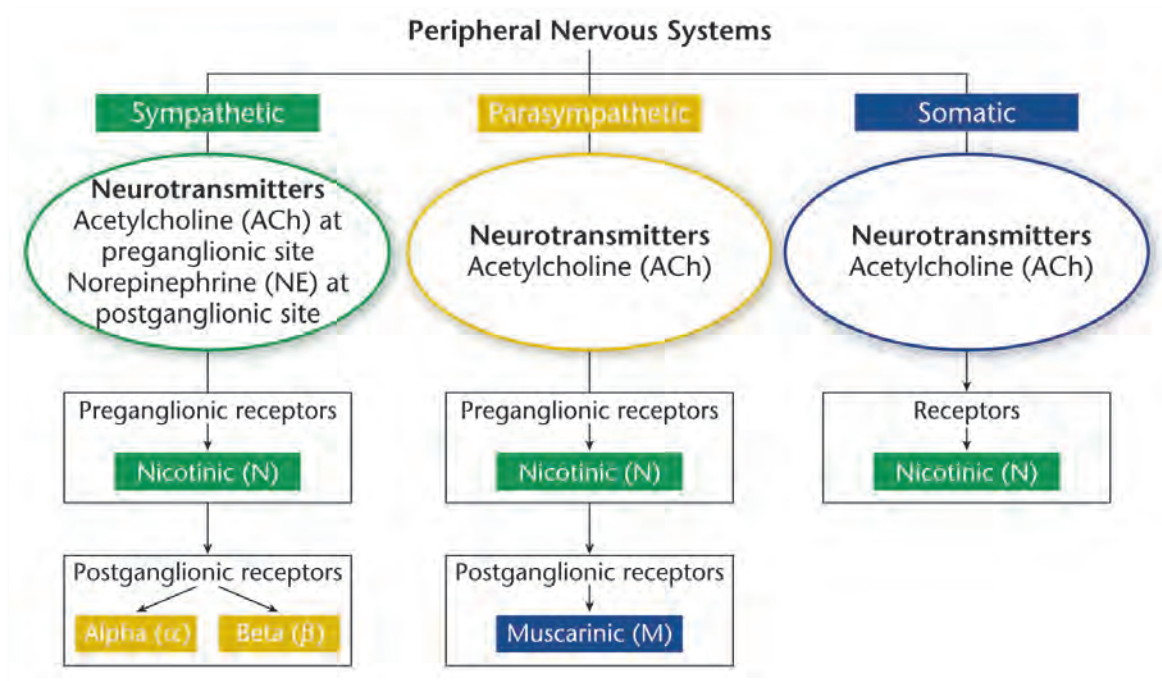
The receptors that bind with NE are called *adrenergic receptors*. Sympathetic agonists stimulate adrenergic receptors of either the **alpha-receptor** or **beta-receptor** type, depending on where they are found in the body. Alpha-receptors, found primarily in smooth muscle of blood vessels, can be of two types, either α_1 or α_2 . Generally, alpha stimulation causes vasoconstriction. Beta-receptors are termed either β_1 or β_2 . β_1 -receptors are found primarily in the cardiac muscle, where stimulation results in positive chronotropic (increase in rate), dromotropic (increase in conduction), and inotropic (increase in contraction) effects on the cardiac system. They are further discussed in Chapters 9 and 10. β_2 -receptors are found abundantly within the smooth muscle of the airways and in certain blood vessels. β_2 -receptor stimulation results in vasodilation and bronchodilation. β_2 -agonists are the foundation for treatment of bronchospasm and are discussed further in Chapter 5, where you will learn about short-acting β_2 -agonists (SABAs) and long-acting β_2 -agonists (LABAs) and their role in bronchodilator therapy. See Figure 3–9 for the receptors found at nerve endings.



Learning Hint

We did not forget about the somatic branch of the PNS. Remember that this is a one-branch system innervating skeletal muscles, and nicotinic receptors are found at the receptor sites as shown in Figure 3–9. Again, we will have more to say about this in Chapter 11.

Figure 3–9 Receptors Found at Nerve Endings



One other type of adrenergic receptor we have not yet mentioned are the **dopamine receptors** found in renal tissues. Their stimulation causes relaxation of the renal arteries and increases perfusion to the kidneys. See Table 3–2, which shows the various adrenergic receptor types, their locations, and their actions when stimulated.

Table 3–2 Types of Adrenergic Receptors (Adrenoreceptors)

Type	Tissue	Action
Alpha ₁	Vascular smooth muscle Pupil Pilomotor smooth muscle	Contracts Dilates (mydriasis) “Goose bumps”
Beta ₁	Heart	Stimulates rate and force
Beta ₂	Respiratory Somatic motor (voluntary muscle)	Bronchodilates Tremors
Dopamine	Renal	Relaxes arteries

Note: Beta₃-receptors have also been identified that enhance the breakdown of fat (*lipolysis*) in *adipose tissue* and help to generate heat (*thermogenesis*) in *skeletal muscle*.



● ● ● Time for Review

State the effects on the heart, blood vessels, or lungs from stimulating the following receptors: alpha, beta₁, beta₂, and muscarinic.



3.3 ANS Drug Terminology

To recap, the ANS has two major divisions: the parasympathetic and sympathetic nervous systems. One can think of the sympathetic system as a response system and the parasympathetic as a homeostatic or maintenance system. They work together to balance each other out. The parasympathetic nervous system controls essential activities and conserves energy for daily body maintenance and metabolic functioning. The sympathetic system allows for adjustments to activity and stresses that occur in life. Each division of the ANS has a direct effect on organ systems such as the heart and lungs, and we will use these two organs as examples in the following classification system. Drugs that affect the function of the ANS are classified into four categories.

Learning Hint

Think of the medical terms *-lytic*, which means “to block or work against,” and *-mimetic*, “to mimic or imitate.”



- (1) Drugs that mimic parasympathetic neurotransmitters or stimulate the parasympathetic receptors are called **cholinergics** or **parasympathomimetics**. Responses to these drugs include slowing of the heart rate and bronchoconstriction. Remember from Chapter 1 that these drugs can also be called *cholinergic agonists* because agonists stimulate a receptor. In addition, they can be called *muscarinic drugs* because they stimulate the muscarinic receptors found in the parasympathetic system.
- (2) Drugs that block parasympathetic receptors are called **anticholinergics** or **parasympatholytics**. Responses to these drugs include speeding up of the heart and bronchodilation—as opposed to what the parasympathetic system will do if stimulated. Remember that these drugs can also be called *cholinergic antagonists* or *antimuscarinic agents*. How do we use this information clinically? Airway obstruction in asthma and chronic obstructive pulmonary disease (COPD) is partly related to abnormally elevated parasympathetic tone (wanting to constrict more). Anticholinergic medications, such as ipratropium bromide, reduce airway obstruction in these disease states by lowering parasympathetic tone.
- (3) Drugs that mimic sympathetic neurotransmitters or stimulate sympathetic receptors are termed **adrenergics** or **sympathomimetics**. They include alpha- and beta-adrenergic drugs, depending on the receptor they stimulate. More specifically, beta₁-adrenergics speed up the heart rate and beta₂-adrenergics cause bronchodilation. An alpha-adrenergic causes vasoconstriction of blood vessels.
- (4) Drugs that antagonize the sympathetic response are called **antiadrenergics** or **sympatholytics**. They are also referred to as blockers; therefore, a beta-blocker blocks the expected effects of bronchodilation and increase in heart rate and thus causes bronchoconstriction and a decrease in heart rate. An alpha-blocker (blocks the normal constricted response) causes vasodilation of blood vessels and therefore could be used to lower blood pressure.



Learning Hint

To connect *adrenergic* to *sympathetic*, when you think of the sympathetic nervous system being stimulated, think of the adrenaline rush.

Controversy

It certainly does get confusing when several terms can mean the same thing. For example, a *parasympatholytic* can be called an *anticholinergic*, or a *parasympathetic antagonist*, or a *vagolytic* (after the major nerve, *vagus*, of the parasympathetic system). We can even throw in the term *antimuscarinic*.

Lung sounds also have several different terms that can mean the same thing because of carryover—such as a *rale* (an older term), which is the same thing as a *crackle*. Attempts have been made to standardize lung sound terminology to be less confusing. Wouldn't it be nice if the same were done for nervous system terminology?



As you can again see, functionally the sympathetic and parasympathetic divisions are opposing. Stimulating one autonomic division may increase the activity

of an organ and stimulating the other division may inhibit the activity. One easy way of remembering what each nervous system does to a particular organ is to recall the common names for each: the fight-or-flight (sympathetic) and the sleep-and-eat (parasympathetic) nervous systems. Stimulation of the sympathetic system causes an increase in heart rate and blood pressure (fight or flight), for example. Stimulation of the parasympathetic system would increase gastrointestinal motility (eat) and lower heart rate (sleep). Drug therapy can disrupt the balance of sympathetic and parasympathetic activity. For example, sympathetic influences on the heart cause increased force of contraction and heart rate, and parasympathetic influences result in bradycardia and decrease in contractile force. Smooth muscles in the vessels are relaxed with a decrease in sympathetic activity and vasoconstricted with an increase in sympathetic activity.



● ● ● Time for Review

Which of the four autonomic categories can cause bronchodilation? Which can cause a decrease in heart rate?



Learning Hint

AChE can also be called **acetylcholinesterase**. Remember that AChE is the **Enzyme** that breaks down ACh.

3.3a Direct- and Indirect-Acting Agents

Drugs can affect different steps in the neurotransmission process. Thus far we have talked about stimulating the receptors (agonists), which is a direct-acting agent. Indirect-acting agents that block the receptor site (antagonists) have also been mentioned. However, other indirect methods, such as increasing or decreasing transmitter substances by enhancing or inhibiting the enzymes that break them down, still need to be discussed. We will take one final look at the four classifications of autonomic drugs and further develop the concept of indirect-acting drugs.

3.3b Parasympathomimetics

Acetylcholine is the main neurotransmitter in all autonomic preganglionic sites and at parasympathetic postganglionic synapses. Acetylcholine is synthesized from acetyl-coenzyme A (acetyl-CoA) and choline by the enzyme choline acetyltransferase. ACh is a simple molecule, yet it has activity at several different receptors. ACh is not a useful drug therapeutically because it is not specific enough at receptors and it is rapidly broken down in the body. As we discussed earlier, drugs that act on acetylcholine receptors are called cholinergic or parasympathomimetics.

Acetylcholine action is terminated when it is metabolized by **acetylcholinesterase** (AChE). Cholinergic drugs are subdivided according to whether they act directly at the receptor by increasing production of ACh or indirectly through inhibition of AChE, the enzyme that breaks down ACh. In either scenario, the



A potential antidote that soldiers carry with them when they might be exposed to nerve gas is, of course, a parasympatholytic agent, such as the drug atropine, which can block the overstimulation of the parasympathetic system by nerve gas.



action of ACh is enhanced either directly by increasing production or indirectly by preventing its rapid breakdown, thus allowing ACh to remain active longer.

AChE inhibitors are also widely used in agriculture as insecticides (malathion, parathion). In addition, they have unfortunately been used as nerve gas in chemical warfare; overstimulation of the parasympathetic nervous system results in severe bradycardia, hypotension, and death.

Muscarinic agonists are direct-acting parasympathomimetic agents; they stimulate the parasympathetic nervous system by increasing ACh production at the effector site. Methacholine is a drug with muscarinic activity. Chemically, it is close to acetylcholine, and it is used clinically as part of a bronchial challenge test to cause bronchoconstriction (parasympathetic response) and thereby diagnose asthma. Asthma, of course, is normally a contraindication for a parasympathomimetic drug, but here the drug is used in small doses for diagnostic purposes.

Drugs can also act specifically at nicotinic receptor sites where ACh is the neurotransmitter substance. Remember, ACh transmits both sympathetic and parasympathetic impulses from preganglionic neurons to nicotinic ganglionic receptors on postganglionic neurons. Nicotinic receptors are also found at the skeletal muscles in the somatic nervous system. Nicotinic agonists are classified by whether they stimulate predominantly at the ganglionic level in the autonomic branch of the PNS or at the skeletal muscles of the somatic branch at the neuromuscular level. See Table 3–3 for sample cholinergic agonists and their indications.



The drug edrophonium (Enlon®) is used to test patients for the neuromuscular disease myasthenia gravis, which is a descending paralysis beginning with the facial muscles. It is caused by insufficient or ineffective ACh at the neuromuscular junction. Edrophonium works by inhibiting AChE from metabolizing ACh, so ACh accumulates and becomes more effective at the neuromuscular junction. A positive edrophonium test results in the return of facial tone after the medication has been administered.

Table 3–3 Sample Cholinergic Agonists and Indications

Drug Action	Drug	Indication
Direct-acting: directly stimulates cholinergic receptors	bethanechol succinylcholine pilocarpine	Urinary retention Neuromuscular blockade—intubation Glaucoma
Indirect-acting: decreased AChE activity	neostigmine pyridostigmine malathion	Myasthenia gravis Reversal of neuromuscular blockade Insecticide

● ● ● Time for Review



Differentiate ACh and AChE. Now relate these terms to direct- and indirect-acting agents.



Learning Hint

A mnemonic used for atropine toxicity is “dry as a bone, red as a beet, mad as a hatter, and blind as a bat.” “Dry as a bone” refers to decreased sweating, salivation, and lacrimation. “Red as a beet” refers to the vasodilation of arms, head, neck, and trunk that occurs with atropine overdoses. “Mad as a hatter” refers to CNS toxicity effects such as delirium. “Blind as a bat” refers to the pupil changes. You can see that excessive blockage of the parasympathetic system may not be tolerated well by patients.

3.3c

Parasympatholytics

Parasympatholytic drugs or anticholinergic drugs are pharmacologic antagonists of the parasympathetic nervous system. Cardiovascular effects from anticholinergics, such as atropine, include tachycardia, bronchodilation, and drying of secretions, which are all opposite to parasympathetic stimulant responses. Atropine derivatives such as ipratropium bromide, mentioned in Chapter 5, are used for their bronchodilation effects. In addition, atropine is part of the advanced cardiac life support (ACLS) course for treatment of bradycardia.

Anticholinergic drug subgroups are also named antimuscarinic agents because the drugs block the effect at the postganglionic site where muscarinic receptors are found. They can also block the nicotinic receptors. Nicotinic blockers are further divided according to the two sites where nicotinic receptors are found: the ganglia and the skeletal muscles. Ganglionic blockers are not used clinically because they block both sympathetic and parasympathetic nerves. Neuromuscular blockers produce skeletal muscle paralysis and can be used for surgery or in critical care when patients need to be totally motionless or to facilitate mechanical ventilation. The significance of this will be discussed in Chapter 11. See Table 3–4 for some examples of anticholinergic drugs.

Table 3–4 Anticholinergic Drug Class

Drug Type	Category and function	Drug
Antimuscarinics	Increase heart rate Bronchodilation	atropine ipratropium bromide
Nicotinic blockers	At preganglionic sites—prevent nervous transmission	hexamethonium

Patient & Family Education

Common Side Effects



Certain common adverse effects of anticholinergic medications should be stressed when educating patients and/or their families. These include confusion, urinary retention, constipation, dry mouth, and blurry vision. These problems are more likely to occur in the elderly.



Life Span Considerations

Anticholinergics and the Elderly

Elderly patients are particularly susceptible to the adverse effects of anticholinergic medications. In general, these drugs should not be prescribed if alternative therapies are available. Aerosol use via the inhalation route is generally an exception due to its minimal systemic effects.

3.3d Sympathomimetics

To review, adrenergic drugs stimulate and therefore act like the sympathetic nervous system, which dominates in times of stress. It is a survival response that enables the body to prepare to face or flee from a perceived danger. The autonomic sympathetic nerves kick into high gear automatically, so you don't have to think before you act and precious life-or-death time isn't wasted. In danger, the heart rate increases, pupils dilate, blood flow increases in the vital organs where it is needed, and the lungs bronchodilate to take in more oxygen. At the same time, some nonessential areas are shut down so energy can concentrate where it is needed the most.

Drugs that act on norepinephrine (NE) receptors are called sympathomimetic or adrenergic agonists and mimic sympathetic responses. In the sympathetic or adrenergic system, NE transmits most of the impulses in the sympathetic postganglionic synapse. NE synthesis is more complex than ACh synthesis. NE is released from the sympathetic nerve endings by the same mechanism as ACh, but the termination is different. Once it is released, NE crosses the synaptic cleft and binds to postsynaptic adrenergic receptors. There is not an enzyme that immediately breaks down NE to interfere or inactivate its action at the synaptic cleft. Instead of being metabolized immediately, NE is recycled back into the synaptic knob to be stored for future use. This process is called **reuptake**. Excess norepinephrine that does not participate in the reuptake process can eventually be metabolized by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (see Figure 3–10). The reuptake and metabolism of NE by COMT and MAO will be important concepts in Chapter 5.

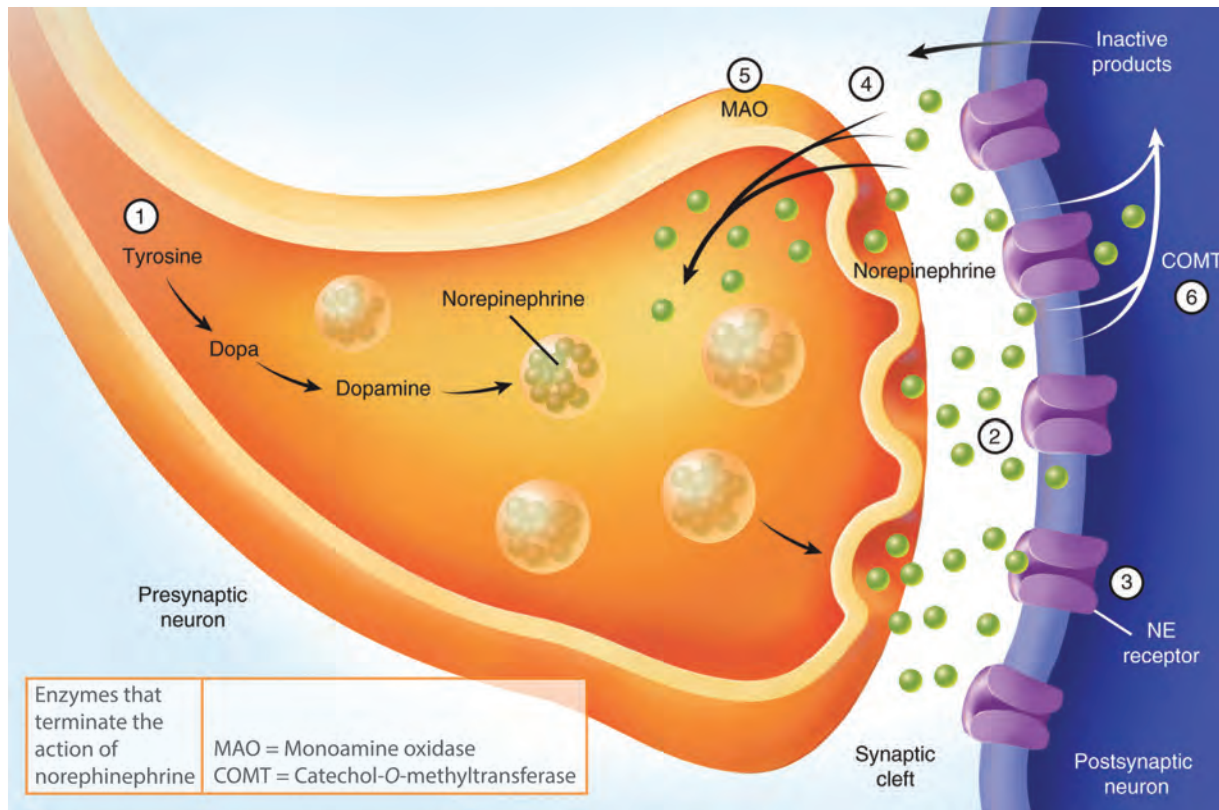
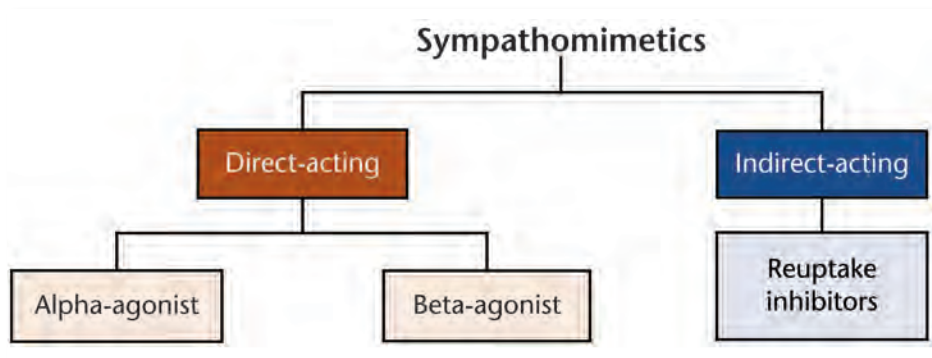
Sympathomimetics can also be either direct- or indirect-acting. Direct-acting sympathomimetics increase NE production and bind with the adrenergic receptors found on the postsynaptic junction of the sympathetic nervous systems. These receptors can be either alpha- or beta-receptors, depending on location and action. Indirect sympathomimetics inhibit the reuptake and enzyme deactivation of NE, thereby preventing its breakdown. See Figure 3–11 for sympathomimetic drug subgroups.



What, no cheese, wine, or chocolate? There is a group of drugs called MAO inhibitors (sometimes used to treat depression) that interact with sympathomimetic amines and lead to hypertension. MAO is a digestive enzyme that normally breaks down catecholamines. Any food or cold medication that contains sympathomimetics, such as pseudoephedrine, should not be used with an MAO inhibitor. Wine, cheese, and chocolate have sympathomimetic components. This is one of the first drug–diet interactions that was ever recognized.

Figure 3–10 Life Cycle of Norepinephrine (NE)

(1) NE is synthesized from the amino acid tyrosine; (2) NE is released into the synaptic cleft; (3) NE binds to receptors on the postsynaptic membrane; (4) NE is taken back into the presynaptic neuron (reuptake); (5) NE is degraded by MAO; (6) Small amounts of NE enter the postsynaptic cell and are degraded by COMT.

**Figure 3–11** Sympathomimetic Drug Subgroups

• • • **Time for Review**

Contrast the mechanisms of neurotransmitter inactivation in the parasympathetic and sympathetic nervous systems.





Adrenergic agents may be catecholamines or noncatecholamines. Catecholamines include dobutamine, dopamine, epinephrine, and norepinephrine. They all have a common basic chemical structure, and they are all destroyed by digestive enzymes if they are ingested orally. Noncatecholamine adrenergic drugs include phenylephrine and albuterol. They are used for local or systemic vasoconstriction and bronchodilation, respectively, and will be discussed in upcoming chapters.

Epinephrine is considered the prototype sympathomimetic, with effects on α_1 -, α_2 -, β_1 -, and β_2 -receptors, and it is used to treat anaphylactic shock. Norepinephrine, an α - and β -agonist, causes vasoconstriction and therefore can be used to treat low blood pressure. Alpha-adrenergic agents applied locally or taken orally can relieve symptoms of nasal congestion by constricting swollen vessels in the nasal passageways. Phenylephrine topically does the same thing by acting directly on α -receptors. Alpha, beta, and dopamine drugs are used for applications in cardiovascular and respiratory medicine and will be discussed further in later chapters. See Table 3–5 for representative sympathomimetic drugs.

Table 3–5 Sympathomimetic Drugs

Drug Category	Drug	Indications
Catecholamines	epinephrine norepinephrine dopamine dobutamine	Anaphylaxis Hypotension Shock Shock, heart failure
Other sympathomimetics	phenylephrine albuterol	Nasal congestion, hypotension Asthma

3.3e Sympatholytics

Just like adrenergic agonists, sympatholytics or adrenergic blockers have many cardiovascular indications. However, their general effect is to block or slow the effects of the sympathetic system. These drugs consist of α - and β -blockers used to treat tachyarrhythmias and hypertension. In addition to their cardiovascular indications, α -blockers have direct action on the urethral sphincter, reducing urinary hesitancy in prostate hyperplasia. Adverse effects of β -blockers can include bradycardia, atrioventricular blockade, and exacerbation of asthma. However, there are more selective β_1 -blockers, which affect only the heart with minimal effects on the β_2 -receptors found in the lungs. This will be covered in more depth in Chapters 9 and 10. Subgroups of adrenergic-blocking drugs or sympatholytics are described in Table 3–6 along with sample drugs and indications.

Table 3–6 Sympatholytic Drug Subgroups

Sympatholytic subgroup	Drug	Indication
Alpha-blocker	doxazosin	Hypertension Benign prostatic hyperplasia
Beta-blocker	propranolol	Hypertension

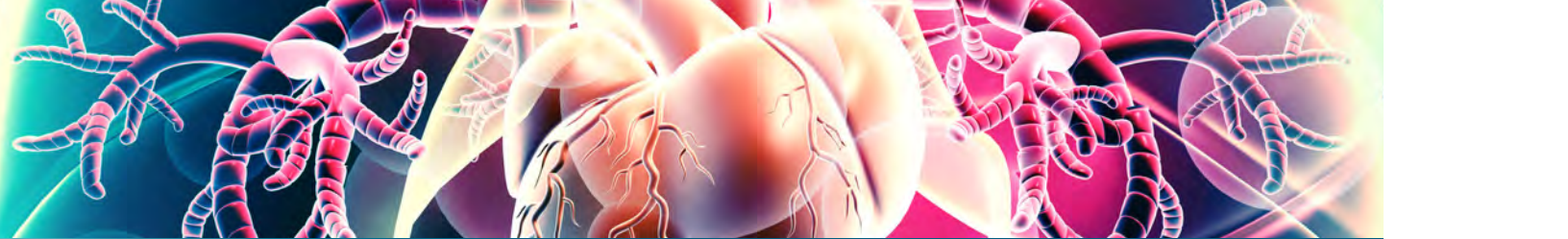


Beta-blockers can mask the signs and symptoms of hypoglycemia, such as tremor and tachycardia, so they are used cautiously in patients with diabetes.



Learning Hint

Have you ever experienced stage fright? Performing artists and public speakers have been known to use beta-blockers to control tremor, anxiety, and palpitations before appearances.



Summary

The autonomic nervous system (ANS) controls many of the activities of the heart and lungs; therefore, an understanding of this system is critical. The portions of the ANS that control the heart and lungs are the sympathetic (fight-or-flight) and parasympathetic (sleep-and-eat) branches. Stimulation of the sympathetic branch increases the rate and force of contraction of the heart and bronchodilates the lungs. The opposing parasympathetic branch, when stimulated, will decrease the rate and force of heart contractions and cause bronchoconstriction. Drugs given to “open up the airways” will either stimulate the sympathetic nervous system or block the effects of the parasympathetic nervous system.

Review Questions

- Which branches make up the peripheral nervous system?
 - somatic
 - parasympathetic
 - sympathetic
 - central nervous system
 - I and II
 - I, II, III, and IV
 - IV only
 - I, II, and III
- Indicate whether the following pertain to the sympathetic nervous system (S), parasympathetic nervous system (P), or both (B).
 - ___ fight or flight
 - ___ digestion
 - ___ ACh at preganglion
 - ___ NE
 - ___ ACh at postganglion
- Match synonymous terms in the autonomic nervous system.

___ sympathomimetic	(a) cholinergic
___ parasympathomimetic	(b) anticholinergic
___ sympatholytic	(c) adrenergic
___ parasympatholytic	(d) antiadrenergic
- Bronchodilation can be achieved using which kind(s) of agent?
 - parasympatholytic
 - sympatholytic
 - sympathomimetic
 - parasympathomimetic
 - I and II
 - II, III, and IV
 - III only
 - I and III
- Skeletal muscles are found in
 - blood vessels
 - airways
 - heart
 - diaphragm
- Contrast the two branches of the autonomic nervous system.
- Differentiate afferent and efferent nerve impulses.
- Give the physiologic responses to the following:
 - beta₂ stimulation
 - beta₁ stimulation
 - alpha₁ stimulation
 - beta₂ inhibition
- What would be the anticholinergic response in the eyes, lungs, and heart?
- What would be the adrenergic response in the eyes, lungs, and heart?



Case Study 3–1

Maria Ramirez

Maria Ramirez was excited about starting her academic career leading to a degree in respiratory care. She felt confident she could do the work but was having some difficulty understanding the peripheral nervous system and all its responses. She decided to make it more personally relevant to her life in order to truly learn the material versus massive memorization.

She remembered a time when she was young and attacked by a dog. She clearly remembered her heart racing and her respirations increasing; in fact, she was surprised at how fast her respirations were and yet how easy it was to breathe. Once the incident was over, she remembered feeling her heart rate and breathing slow back down to normal. She also remembered as a teenager taking a low dose medication that actually caused her airways to restrict, giving her a diagnosis of asthma. One final incident she felt related to the study of this chapter was when she had an eye exam and atropine drops were placed in her eyes. She remembered the sunlight hurting her eyes as she walked to her car in sunny Arizona, and she immediately remembered the doctor telling her to wear sunglasses until the effects of the drops wore off. Answer the following that relate to her story and this chapter.

1. During the dog attack, the increase in heart rate and increase in respirations and bronchodilation could best be attributed to _____.
 - (a) sympatholytic response
 - (b) sympathomimetic response
 - (c) parasympathomimetic response
 - (d) parasympatholytic response
2. Heart vitals returning to normal could best be attributed to _____.
 - (a) sympatholytic response
 - (b) sympathomimetic response
 - (c) parasympathomimetic response
 - (d) parasympatholytic response
3. The medication to diagnose asthma can best be attributed to _____.
 - (a) sympatholytic response
 - (b) sympathomimetic response
 - (c) parasympathomimetic response
 - (d) parasympatholytic response
4. The atropine eye drop response of a dilated pupil could best be attributed to _____.
 - (a) sympatholytic response
 - (b) sympathomimetic response
 - (c) parasympathomimetic response
 - (d) parasympatholytic response



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