6

Introduction to the Autonomic Nervous System and Autonomic Pharmacology

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Introduction

The autonomic nervous system (ANS) includes afferent, central, and efferent components. The efferent component is the general visceral efferent (GVE) system and is subdivided into two primary branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS). More recently, the enteric nervous system is considered a functional component. The ANS plays a critical role in regulating processes required for maintaining physiological homeostasis and responding to acute stressors. Numerous physiological functions are regulated by the ANS including, but not limited to: regulation of heart rate and cardiac contractility; visceral and cutaneous blood flow distribution; gastrointestinal motility and digestion; and urogenital processes. It is virtually impossible to consider physiological regulation without integrating the roles of sympathetic and parasympathetic neural mechanisms into a functional overview, as summarized in the *Primer on the Autonomic Nervous System* (Hamill and Shapiro, 2004):

> The autonomic nervous system (ANS) is structurally and functionally positioned to interface between the internal and external milieu, coordinating bodily functions to ensure homeostasis (cardiovascular and respiratory control, thermal regulation, gastrointestinal motility, urinary and bowel excretory functions, reproduction, and metabolic and endocrine physiology), and adaptive responses to stress (flight or fight response). Thus, the ANS has the daunting task of ensuring the survival and the procreation of the species.

For the most part, physiological processes regulated by the ANS are not under voluntary control and are essential for maintaining physiological regulation under basal or resting conditions, as well as in response to various forms of physical or emotional stress. Changes in the level of afferent and efferent activity in sympathetic and parasympathetic nerves occur primarily independent of conscious or voluntary control, thereby providing the derivation for the name autonomic nervous system (from the Greek: *auto* = self; *nomos* = law).

Sympathetic Nervous System

Sympathetic nerves originate from cell bodies in the intermediolateral cell column of the thoracic (T) and lumbar (L) sections of the spinal cord, synapse in ganglia (more anatomical detail is presented later in this chapter), and project to a wide array of targets (Figure 6.1). The level of activity in sympathetic nerves is regulated at multiple levels of the brain, including hypothalamic and brainstem sympathetic neural circuits (Figures 6.1 and 6.2). The majority of sympathetic nerves demonstrate a tonic or basal level of activity, characterized by the presence of bursts of activity (Claassen et al., 1996). Figure 6.3A shows original traces of directly recorded nerve discharge bursts from four sympathetic nerves (renal, adrenal, splanchnic, lumbar). Direct recordings of sympathetic nerve activity provide an output measure of central sympathetic neural circuits. Changing the level of activity in peripheral sympathetic nerves, by either increasing or decreasing the level of sympathetic nerve discharge (SND), is a primary means by which the SNS regulates physiological function (Kenney, 2014; Kenney et al., 2014). For example, heat stress or hyperthermia increases the level of visceral SND (Figure 6.3B), thereby mediating a redistribution of blood flow away from visceral organs to cutaneous vascular beds. On the other hand, acute increases in arterial blood pressure activate the arterial baroreceptor reflex which abruptly reduces SND (Figure 6.3C), a physiological response that contributes to returning blood pressure to normal levels. In this example (Figure 6.3C) blood pressure was increased by the intravenous administration of the adrenergic agonist drug, phenylephrine hydrochloride, which will be discussed in more detail in Chapter 7.

In many contexts the primary understanding of SNS regulation has focused on the activation of this nervous system as a unit, as in response to critical emergencies

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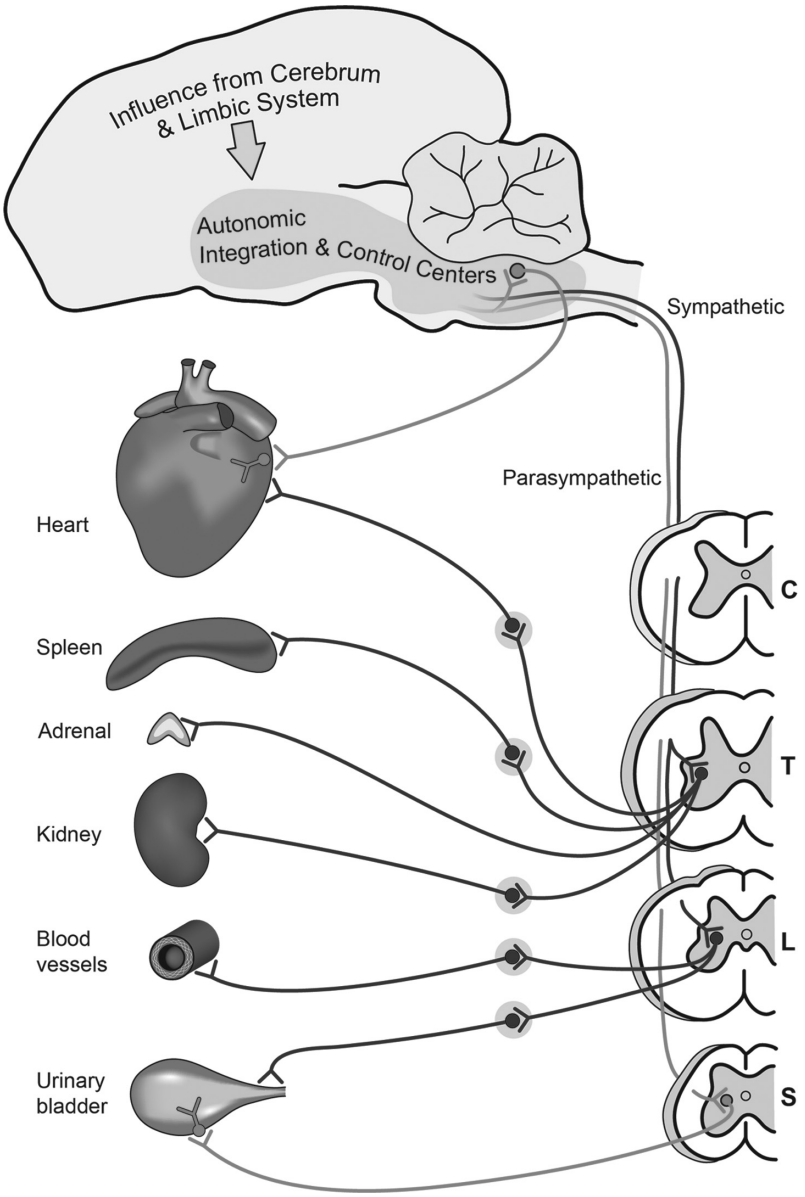

Figure 6.1 Schematic diagram highlighting anatomical features of the autonomic nervous system. Sympathetic preganglionic neurons originate from cell bodies located in the intermediolateral cell column of the thoracic (T) and lumbar (L) sections of the spinal cord, synapse in ganglia located outside the spinal cord, and postganglionic neurons project from the sympathetic ganglia to a wide array of targets. The chromaffin cells of the adrenal medulla are analogous to ganglionic neurons and are innervated by sympathetic preganglionic neurons. Efferent activity in sympathetic nerves is regulated by various integration and control centers located at multiple levels of the supraspinal neuraxis (identified as Autonomic Integration and Control Centers). Presympathetic neurons from these hypothalamic and brainstem sites project to the thoracic and lumbar spinal cord sites where the sympathetic preganglionic cell bodies are located. Parasympathetic preganglionic neurons originate from cell bodies located in brainstem nuclei and in the intermediolateral cell column of the sacral (S) spinal cord. Parasympathetic preganglionic neurons are innervated by nerve endings of preparasympathetic neurons whose cell bodies are found in supraspinal nuclei. Many parasympathetic preganglionic neurons terminate and synapse in intramural ganglia located within the innervated target organs, or in ganglia located outside but near the innervated target organs. C, cervical spinal cord.

or to elicit the "fight-or-flight" response. In these conditions, SNS activation mediates increased heart rate and cardiac contractility, vascular vasoconstriction in skin and viscera with shunting of blood flow to skeletal muscles, hepatic glycogenolysis, bronchiolar and pupillary dilation, and contraction of the spleen. This physiological response profile is mediated by the combined activation of peripheral sympathetic nerves innervating specific target organs (e.g., heart, blood vessels) and the adrenal medulla. This prominent activation state led to the concept that the SNS acts as a unit. However, it is now well-understood that a fundamental regulatory strategy of the SNS involves selectively controlling the level of activity in nerves innervating different targets in response to a number of physiological conditions (i.e., nonuniform regulation of sympathetic nerve activity). For example, acute cold stress or hypothermia increases the level of activity in nerves innervating cutaneous blood vessels but reduces the level of activity in nerves innervating the kidney, providing the neural substrate for reducing blood flow to the periphery and increasing visceral organ blood flow. The ability to selectively regulate the level of activity in sympathetic nerves innervating specific targets provides the neural substrate for producing highly specific physiological response profiles. Physiological responses of selected organs and effector tissues elicited by activation of efferent sympathetic nerves are summarized in Table 6.1. Specific receptor classes and types involved in mediating SNS-induced physiological responses are included in Table 6.1 and are introduced

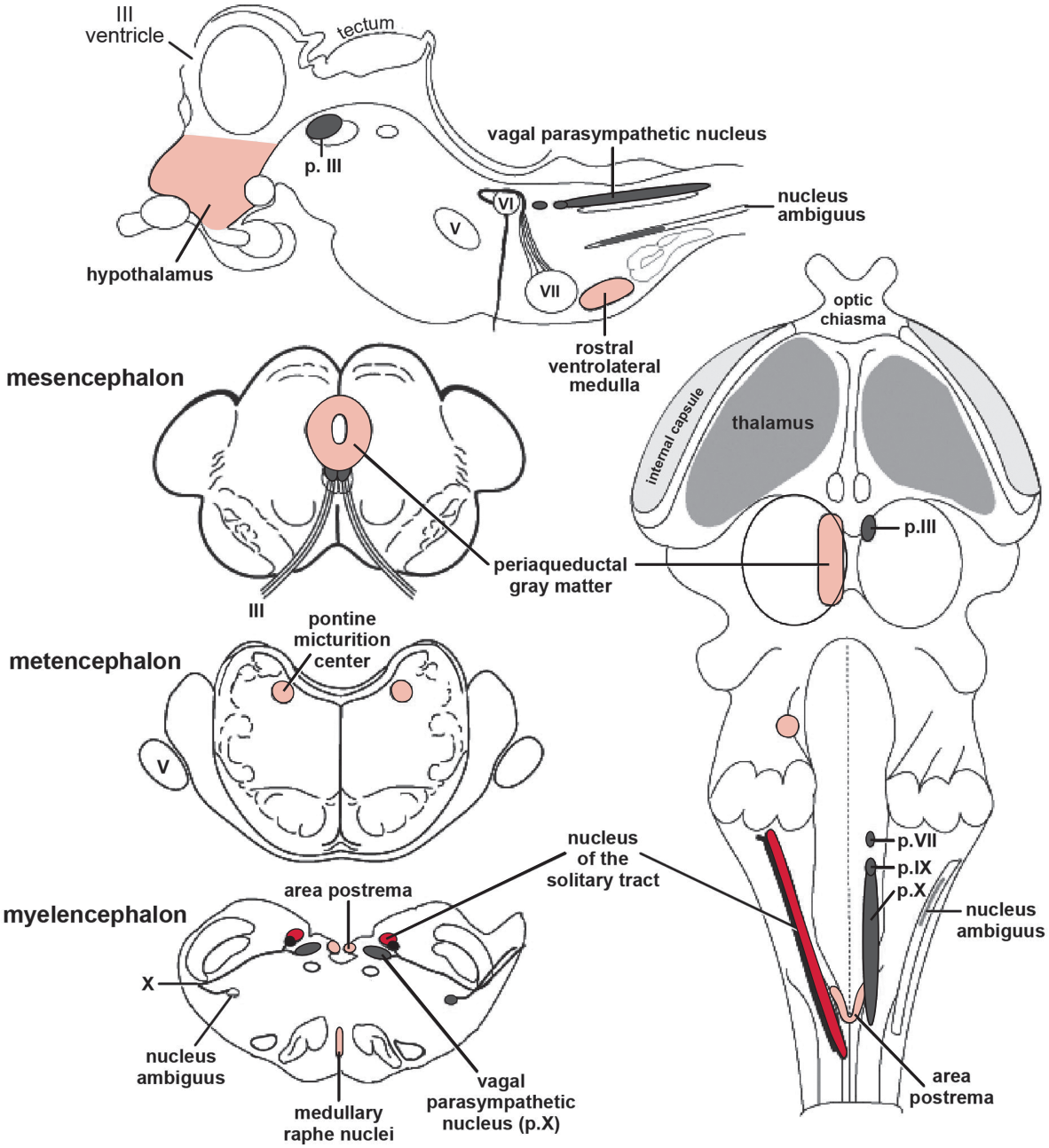

Figure 6.2 Selected autonomic nuclei and centers are shown in transverse (left), dorsal (right), and midsagittal (top) views. Components depicted in light red represent autonomic integration, relay, and/or control centers. The nucleus of the solitary tract, an important visceral sensory nucleus, is red. Brainstem preganglionic parasympathetic nuclei (p.) are shown in dark gray (including a portion of the nucleus ambiguous which provides cardiac visceral efferent neurons). Bilateral structures are shown on one side only in the dorsal view and not all structures are represented in each view to minimize clutter. The hypothalamus is the principle integration and control center of the autonomic nervous system and contains numerous nuclei, which are involved in the regulation of autonomic function. The periaqueductal gray matter surrounds the mesencephalic aqueduct and serves (among other functions) as a relay for visceral control signals from the hypothalamus to hindbrain nuclei. The pontine micturition center (just one of several autonomic control centers in the brainstem which control visceral functions) contains neurons that project to the lumbosacral spinal cord where they excite sacral preganglionic parasympathetic neurons which cause contraction of the urinary bladder wall and inhibit neurons to urinary sphincters (lumbar preganglionic sympathetic and sacral somatic neurons). The rostral ventrolateral medulla and medullary raphe nuclei are major sites of presympathetic neurons that project to preganglionic sympathetic neurons in the thoracolumbar spinal cord. The area postrema (just one of several circumventricular organs which are located in close proximity to the ventricular system of the brain and lack a blood–brain barrier) detects emetic agents in the blood and projects to hindbrain nuclei responsible for controlling emesis; other circumventricular organs (not shown) are likewise susceptible to direct chemosensory stimulation by blood-borne agents and are involved in other aspects of neuroendocrine and autonomic function. Source: Adapted from Fletcher and Brown, 2010.

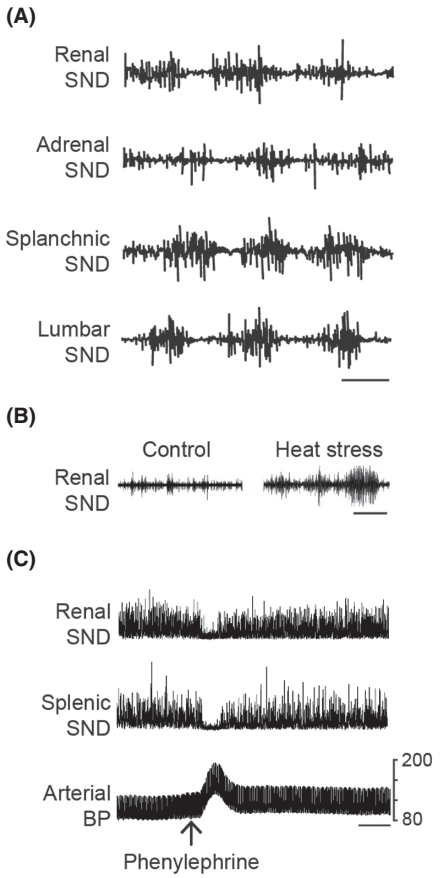

Figure 6.3 **(A)** Traces of sympathetic nerve discharge (SND) recorded under basal conditions from renal, adrenal, splanchnic, and lumbar nerves. Note that at rest sympathetic nerves are characterized by the presence of a tonic level of activity. Horizontal calibration is 100 ms. Source: Adapted from Claassen et al., 1996. **(B)** Traces of renal SND recorded under control conditions and during heat stress. Renal SND was increased from control levels during the period of acute heat stress. Horizontal calibration is 250 ms. Source: Adapted from Kenney, 2014. Reproduced with permission of Elsevier. **(C)** Traces of discharges from renal and splenic sympathetic nerves recorded before, during, and after an acute increase in arterial blood pressure produce by the intravenous administration of the α-adrenergic receptor agonist, phenylephrine hydrochloride. The acute increase in arterial blood pressure and subsequent activation of the arterial baroreceptors elicited a reflex-mediated inhibition of SND. Horizontal calibration is 15 s. Source: Adapted from Kenney, 2014. Reproduced with permission of Elsevier

later in this chapter and considered in more detail in Chapter 7.

Parasympathetic Nervous System

Parasympathetic nerves originate from cell bodies in the brainstem and sacral sections of the spinal cord, and synapse in ganglia (more anatomical detail is presented later in this chapter). The level of activity in parasympathetic nerves is regulated by multiple areas in the brain (Figures 6.1 and 6.2). Parasympathetic nerves innervating many target organs are tonically active and changing the level of activity in peripheral parasympathetic nerves in response to specific physiological stimuli is a primary mechanism by which the PSNS regulates physiological function. Figure 6.4 shows directly recorded cardiac vagal parasympathetic nerve discharge under basal conditions, and in response to an experimentally induced activation of the baroreceptor reflex, which produced an increase in the level of cardiac vagal nerve activity and an associated reduction in heart rate (Simms et al., 2007). The primary functional profile elicited by activation of the PSNS includes initiating and sustaining energy conservation and homeostasis during periods of relative physiological quiescence. In general, increasing the level of activity in parasympathetic nerves reduces heart rate, stimulates gastrointestinal secretions and peristalsis, contracts the body of the urinary bladder, and modulates immune function. Physiological responses of selected organs and effector tissues elicited by activation of efferent parasympathetic nerves are summarized in Table 6.1. Specific receptor classes and types involved in mediating PSNS-induced physiological responses are included in Table 6.1, and are introduced later in this chapter and considered in more detail in Chapter 7.

Many organs and tissues are innervated by both the sympathetic and parasympathetic arms of the ANS, and these targets are described as receiving dual ANS innervation (e.g., heart and urinary bladder in Figure 6.1). In many instances physiological responses produced by activation of parasympathetic or sympathetic nerves to a target tissue or organ that receives dual ANS innervation are functionally antagonistic. That is, if activation of one arm of the ANS inhibits a specific physiological function then activation of the other arm enhances the function. For example, stimulation of cardiac sympathetic nerves increases heart rate whereas activation of cardiac parasympathetic nerves reduces heart rate. However, the presence of a dual ANS innervation to a specific target does not indicate that the physiological function of that target is balanced to the same degree for each arm of the ANS. On the contrary, the basal physiological function of many organs is weighted towards either PSNS or SNS regulation, an effect that is species dependent and can vary depending on the specific physiological situation or pathophysiological state (Box 6.1 Case study). For example, the gastrointestinal system is regulated by the enteric nervous system, along with the SNS and the PSNS. Activation of parasympathetic nerves innervating the gastrointestinal tract and administration of drugs that mimic the PSNS stimulate gastrointestinal functions, whereas it is generally considered that the SNS exerts more of a modulatory effect on gastrointestinal function consistent with the fact that sympathomimetic drugs are not prominently used as GI inhibitory agents

Table 6.1 Physiological responses of selected organs and effector tissues produced by activation of efferent sympathetic (sympathetic stimulation) and parasympathetic (parasympathetic stimulation) nerves. Specific receptor classes and types involved in mediating the physiological responses are included for sympathetic (adrenergic receptors; α and β) and parasympathetic (muscarinic receptors; M) stimulation. Stimulation of sympathetic nerves innervating the adrenal medulla mediates secretion of epinephrine (EPI), an effect involving activation of nicotinic neural (N_N) receptors

Organs/effector tissues	Sympathetic stimulation	Receptor	Parasympathetic stimulation	Receptor
Eye				
Radial muscle, iris	Pupillary dilation	α_1		
Sphincter muscle, iris			Pupillary constriction	M_3, M_2
Ciliary muscle	Slight relaxation	β_2	Contraction	M_3, M_2
Glands of head				
Lacrimal	↑ Secretion (minor effect)	α_1	↑↑ Secretion (major effect)	M_3, M_2
Salivary	↑ Secretion (minor effect)	α_1	↑↑ Secretion (major effect)	M_3, M_2
Lungs				
Bronchiolar smooth muscle	Bronchiolar dilation	β_2	Contraction	$M_2 = M_3$
Heart				
Sinoatrial node	↑ Heart rate	$\beta_1 > \beta_2$	↓ Heart rate	$M_2 >> M_3$
Atria	↑ Contractility/conduction	$\beta_1 > \beta_2$	↓ Contractility/conduction	$M_2 >> M_3$
Atrioventricular node	↑ Automaticity/conduction	$\beta_1 > \beta_2$	↓ Conduction	$M_2 >> M_3$
Ventricle	↑ Contractility/conduction	$\beta_1 > \beta_2$	↓ Contractility	$M_2 >> M_3$
Blood vessels (arteries and arterioles)				
Coronary	Constriction; dilation	α_1, α_2; β_2		
Pulmonary	Constriction; dilation	α_1; β_2		
Skin and mucosa	Constriction	α_1, α_2		
Skeletal muscle	Constriction; dilation	α_1; β_2	Dilation (not due to parasympathetic stimulation)	M_2
Abdominal viscera	Constriction; dilation	α_1; β_2		
Gastrointestinal tract				
Motility	↓ Motility	α_1, α_2, β_1, β_2	↑ Motility	$M_2 = M_3$
Sphincters	↑ Tone	α_1	↓ Tone	M_3, M_2
Secretion	Inhibition	α_2	Stimulation	M_3, M_2
Urinary bladder				
Detrusor muscle	Relaxation	β_2	Contraction	$M_3 > M_2$
Sphincters	Contraction	α_1	Relaxation	$M_3 > M_2$
Sex organs				
Male	Ejaculation	α_1	Erection	M_3
Female			Erection	
Skin				
Sweat glands		α_1		M_3, M_2
Pilomotor muscles		α_1		
Adrenal medulla	Secretion of EPI	N_N		
Kidney				
Renin	↑ Secretion	β_1		
Liver	Glycogenolysis	α_1		
	Gluconeogenesis	β_2		
Splenic capsule	Contraction	α_1		
Autonomic nerves				
Sympathetic nerves				
Autoreceptor	Inhibition of NE release	α_2		
Heteroreceptor			Inhibition of NE release	M_2, M_4
Parasympathetic nerves				
Autoreceptor			Inhibition of ACh release	M_2, M_4
Heteroreceptor	Inhibition ACh release	α_2		

in clinical conditions. Therefore, the gastrointestinal system receives a dual ANS innervation and the physiological responses mediated by these nervous systems are functionally antagonistic. However, the fundamental physiological regulatory processes are weighted towards PSNS dominance. Moreover, in some cases the dual SNS and PNSN innervation to a specific tissue may produce similar yet not identical responses. For example, the salivary glands receive a dual ANS innervation, although activation of the SNS and PSNS do not produce

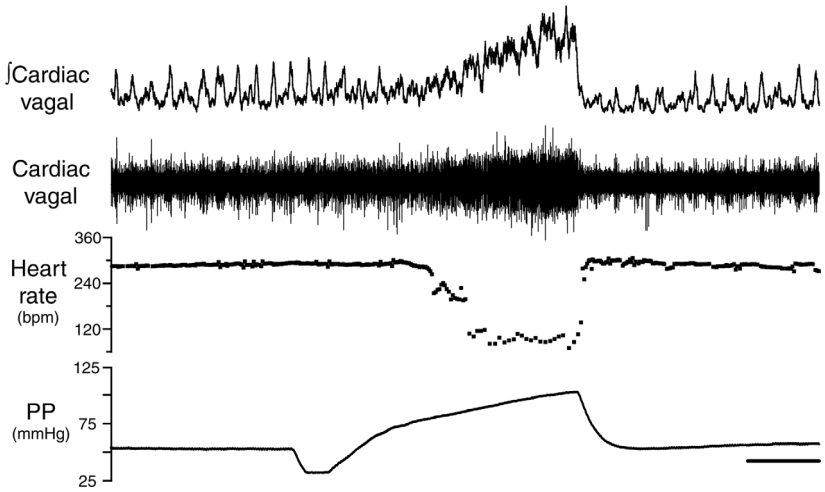

Figure 6.4 Traces of cardiac vagal nerve activity and heart rate recorded before, during, and after activation of the baroreflex produced by experimental manipulation of aortic perfusion pressure (PP). Note the presence of a tonic level of cardiac vagal nerve activity, the increase in vagal nerve activity in response to baroreflex activation, and the expected reflex-mediated reduction in heart rate in response to the increase in cardiac vagal nerve activity. Source: Adapted from Simms, 2007. Reproduced with permission of John Wiley & Sons.

functionally antagonistic responses. Activation of the SNS innervation to the salivary glands produces secretion of amylase and a viscous salivary fluid (secondary to activation of α-adrenergic receptors) whereas activation of PSNS innervation to the salivary glands produces a watery salivary fluid.

The ANS also contains extensive afferent (sensory) components that provide neural information regarding the internal physiological environment. The peripheral afferent components, namely the general visceral afferent (GVA) system, generally utilize similar nerve pathways as the efferent components. For example, the vagus nerve and its branches are comprised of approximately 80% afferent fibers (sensory) and 20% efferent fibers (DuBois and Foley, 1936). Afferent pathways conveying peripheral sensory information ultimately project to multiple supraspinal sites, including the hypothalamus and brainstem (e.g., the nucleus of the solitary tract). Integration of neural information at central sites can modulate the level of efferent activity in sympathetic and parasympathetic nerves.

It has often been considered that the ANS operates rather independently of other adaptive systems. However, the functional repertoire of the ANS now includes an important role for both arms of this nervous system in regulating and integrating processes between

Box 6.1 Case Study

An 8-year-old, female, spayed mixed breed dog was presented for acute onset of vomiting and lethargy. Laboratory data were consistent with mild dehydration. Vomiting continued despite treatment with intravenous fluid and antibiotics over the next 24 hours for presumed gastritis. Abdominal radiographs and ultrasound were negative for gastrointestinal foreign body or obstruction. No peristalsis was evident on ultrasound. The vomiting subsided but the patient became progressively more lethargic and unable to ambulate more than a few feet. The patient refused to eat. Fecal incontinence was present secondary to decreased anal sphincter tone. Although the dog was initially able to urinate, the volume of urine she was able to expel progressively decreased over several days until she was unable to void. Photophobia developed and the pupillary light reflex became sluggish. An echocardiogram revealed an ejection fraction of only 14%. The heart rate remained near 85 beats per minute despite this low ejection fraction. A diagnosis of dysautonomia was made (Harkin et al., 2002; Harkin et al., 2009).

Dysautonomia is an idiopathic neurodegenerative disorder characterized by degeneration of neurons in ANS ganglia, which produces marked changes in the function of target organs innervated by the sympathetic and parasympathetic nervous systems (Harkin et al., 2002; Harkin et al., 2009). Due to the widespread innervation of the ANS to numerous tissues and organs, patients with dysautonomia present with alterations in multiple physiological systems, making this disease state difficult to diagnose. Changes in target function are generally manifested based on the usual predominance of sympathetic or parasympathetic tone to a given organ or tissue. For example, under basal conditions, function of the gastrointestinal tract is dominated by a predominance of parasympathetic nerve activity conveyed via the vagus nerve and manifested as enhanced gastrointestinal motility and activity. Therefore, ganglionic degeneration and loss of the PSNS innervation to the gastrointestinal tract is often characterized by reduced smooth muscle tone and motility in patients suffering from dysautonomia.

diverse physiological systems. For example, it is well-established that the ANS plays a role in mediating interactions between the nervous and immune systems, two adaptive systems that have generally been considered to function independently of each other (Kenney and Ganta, 2014).

Multiple experimental methods have been employed for assessing SNS and PSNS contributions to physiological states and pathophysiological conditions including: pharmacological activation or blockade of receptors associated with the sympathetic and parasympathetic nervous systems; molecular approaches involving genomic and proteomic analyses; direct recordings of afferent and efferent activity in sympathetic and parasympathetic nerves; and the use of multiple methods to analyze specific components of directly recorded nerve activity. The collective contributions of these studies have provided essential information regarding the anatomical framework and physiological mechanisms regulating ANS function, thereby providing the backdrop for understanding autonomic pharmacodynamics and the development of specific autonomic drugs.

Anatomy of the Autonomic Nervous System: Overview

The ANS contains supraspinal, spinal, and peripheral (afferent and efferent) components, and is characterized by distinctive anatomical frameworks. The efferent components of both branches of the ANS use chemical neurotransmitters for conveying information between nerve cells (e.g., transmission from preganglionic neurons to postganglionic neurons at ganglionic sites) and from postganglionic neurons to target cells and tissues. Chemical neurotransmission involves the release of small amounts of neurotransmitter molecules from nerve terminals into the synaptic space, diffusion of transmitters across the synaptic space, neurotransmitter molecules binding to specialized receptors (specific receptors are discussed in a subsequent section) located primarily at postsynaptic sites on cells innervated by the ANS, and the subsequent activation or inhibition of intracellular secondary messenger mechanisms. The presence of adrenergic, cholinergic, and nonadrenergic–noncholinergic (NANC) neurons provides the essential substrates for generating and sustaining a diverse array of physiological functions. A fundamental tenet for understanding autonomic pharmacology begins with considering specific anatomical components of the sympathetic and parasympathetic nervous systems, which are described separately in this section.

Sympathetic Nervous System

Multiple sites in the central nervous system (CNS), including forebrain, brainstem, and spinal neural circuits, regulate the level of sympathetic nerve activity (Figure 6.2). The hypothalamus is a principal integration and control center of the ANS. Neurons within hypothalamic nuclei (e.g., the paraventricular nucleus) receive afferent signals from a variety of sources and, in turn, dispatch efferent signals to primary autonomic centers in the brainstem, (e.g., the rostral ventrolateral medulla (RVLM) and the midline medullary raphe nuclei). The axons of brainstem neurons within these centers (i.e., presympathetic neurons) project to sympathetic preganglionic neurons in the spinal cord (the axons of neurons in select hypothalamic nuclei also project to preganglionic neurons directly).

The cell bodies of sympathetic preganglionic neurons are located in the intermediolateral cell column of thoracic and cranial lumbar spinal segments (providing the derivation for the thoracolumbar terminology of the SNS). As mentioned, they are innervated by nerve endings of presympathetic neurons whose cell bodies are located in supraspinal nuclei. Sympathetic preganglionic nerve fibers exit the spinal cord in association with thoracic and lumbar spinal nerves and many sympathetic preganglionic neurons terminate and synapse in paravertebral ganglia located bilaterally on each side of the spinal column (Figures 6.1 and 6.5). Other sympathetic preganglionic neurons terminate and synapse in ganglia that are located closer to target organs, the prevertebral ganglia. Postganglionic sympathetic neurons arise from paravertebral and prevertebral ganglia and project to target organs and tissues (de Lahunta and Glass, 2009; Dyce et al., 2010; Evans and de Lahunta, 2013). The primary neurotransmitter released from preganglionic neurons at sympathetic ganglionic sites is acetylcholine (ACh), and at these sites ACh primarily binds to and activates nicotinic receptors located on the dendrites of postganglionic sympathetic neurons (Figure 6.5). Sympathetic ganglionic nicotinic receptors are classified as nicotinic neural (N_N) receptors. Nerve fibers that synthesize and release ACh are classified as cholinergic fibers; therefore sympathetic preganglionic nerve fibers are described as cholinergic. Norepinephrine (NE) (noradrenaline) is the predominant neurotransmitter released from postganglionic SNS neurons at target organ sites. At these sites NE primarily binds to and activates adrenergic receptors (designated as α and β receptors, as in Figure 6.5). Nerve fibers that synthesize and release NE are classified as adrenergic (or noradrenergic) fibers. Some postganglionic SNS neurons release dopamine (identified as dopaminergic neurons, as in Figure 6.5), which is the immediate metabolic precursor to NE and is an important neurotransmitter in the peripheral vasculature and

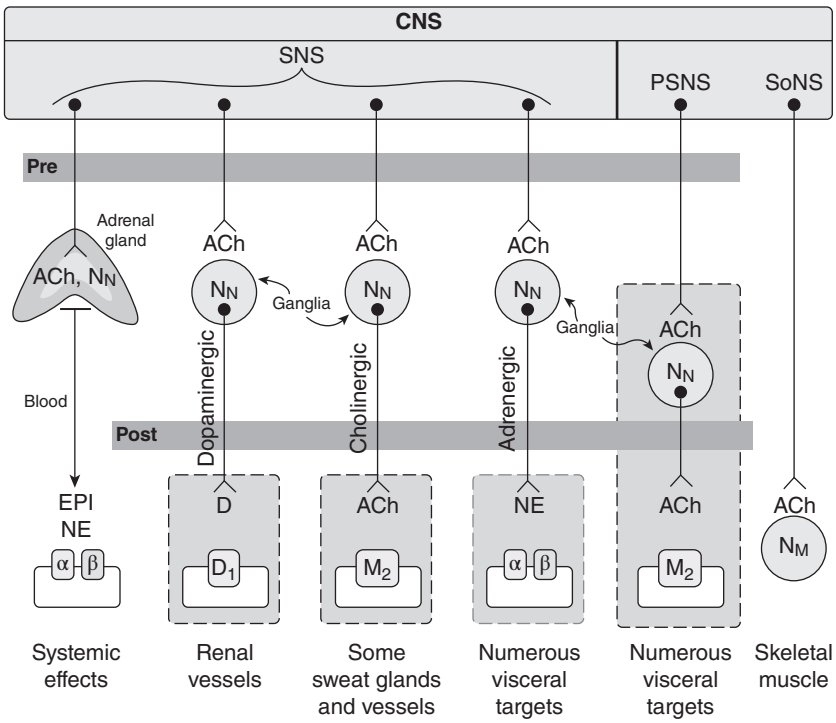

Figure 6.5 Schematic representation of the preganglionic and postganglionic anatomical relationships of nerves contained in the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS). The anatomical substrate of somatic motor nerves (SoNS) is also shown. Only the primary neurotransmitters are shown. ACh is the neurotransmitter released at sympathetic and parasympathetic ganglia and at most parasympathetic neuroeffector junctions. Norepinephrine (NE) is the primary neurotransmitter released at adrenergic sympathetic neuroeffector junctions (see text for exceptions.) "Visceral targets" refers to smooth muscle, cardiac muscle, and glands. Note that some sympathetic postganglionic fibers release acetylcholine or dopamine rather than NE. The adrenal medulla, a modified sympathetic ganglion, is innervated by sympathetic preganglionic fibers and releases epinephrine and NE into the blood. ACh, acetylcholine; D, dopamine; EPI, epinephrine; M, muscarinic receptors; N, nicotinic receptors; NE, norepinephrine.

the CNS (Figure 6.5). Dopamine binds to and activates dopaminergic receptors (designated as D_1, as in Figure 6.5). The chromaffin cells of the adrenal medulla are analogous to ganglionic neurons, are innervated by preganglionic SNS fibers and contain N_N receptors, and synthesize and release epinephrine (EPI) and NE (Figure 6.5). A subgroup of postganglionic SNS neurons release ACh as a neurotransmitter (such as the sympathetic innervation to sweat glands in humans and the sympathetic innervation of skeletal muscle arteries in some species), and these fibers are classified as postganglionic sympathetic–cholinergic fibers (Figure 6.5). The ACh released from postganglionic sympathetic–cholinergic fibers binds to and activates muscarinic receptors (designated as M_2 in Figure 6.5).

Along with NE, cotransmitter molecules or substances are released from many postganglionic SNS fibers at target tissues and organs (Gourine et al., 2009; Burnstock, 2013; Herring, 2015; Ralevic, 2015). ATP has been identified as a cotransmitter along with NE in sympathetic nerves. NE and ATP may be stored in the same vesicles and released together, or may be stored in separate vesicles and regulated as individual entities. The relative contributions of NE and ATP in cell-mediated physiological responses depends on the specific target tissue, species, and neural stimulation parameters. ATP mediates responses via activation of purinergic receptors that are identified as adenosine (P1) receptors and P2X and P2Y receptors. Neuropeptide Y (NPY) can also be released with NE from sympathetic nerves and is an agonist at neurokinin receptors (e.g., Y_1 and Y_2). The primary physiological role of this peptide is to modulate sympathetic neurotransmission at both pre- and postsynaptic sites. Cotransmitters have an important signaling role in the cardiovascular, urogenital, and respiratory systems.

Parasympathetic Nervous System

Like the SNS, multiple CNS sites are involved in regulating efferent parasympathetic nerve outflow, although the integrative central mechanisms are not as thoroughly defined. The hypothalamus is involved in parasympathetic integration and control, and hypothalamic nuclei communicate with brainstem autonomic centers (e.g., the pontine micturition center). The axons of brainstem neurons within these centers (i.e., preparasympathetic neurons) project to parasympathetic preganglionic neurons in the brainstem and spinal cord. The axons of neurons in hypothalamic nuclei may also project to preganglionic neurons directly.

The cell bodies of parasympathetic preganglionic neurons are located in brainstem nuclei (e.g., the parasympathetic nuclei of the oculomotor, facial, glossopharyngeal, and vagus nerves, as well as the nucleus ambiguus) (Figure 6.2), and in the intermediolateral cell column of the sacral spinal cord (Figure 6.1). As mentioned, they are innervated by nerve endings of preparasympathetic neurons whose cell bodies are found in supraspinal nuclei. Preganglionic axons exit the brainstem with their respective cranial nerves (preganglionic parasympathetic

axons from the nucleus ambiguus join the vagus nerve) whereas they exit the sacral spinal cord in association with sacral spinal nerves. The specific placement of preganglionic PSNS cell bodies in the brainstem and sacral spinal cord provides the derivation for the craniosacral terminology of the PSNS. Most parasympathetic preganglionic neurons terminate and synapse in intramural ganglia (terminal ganglia) located within the innervated target organs. Other preganglionic parasympathetic fibers terminate and synapse in ganglia (e.g., ciliary, pterygopalatine, submandibular, otic, and pelvic ganglia) located outside the innervated target organs or on ganglion cells that are characterized by a rather diffuse distribution of cells located near target organs (de Lahunta and Glass, 2009; Dyce et al., 2010; Evans and de Lahunta, 2013). Like the SNS, the primary neurotransmitter released from preganglionic neurons at parasympathetic ganglionic sites is ACh, and at these sites ACh primarily binds to and activates nicotinic receptors located on postganglionic parasympathetic neurons (Figure 6.5). Parasympathetic ganglionic nicotinic receptors are classified as N_N receptors. Postganglioinic parasympathetic neurons arise from parasympathetic ganglia and project to target cells, tissues, and organs. ACh is also the primary neurotransmitter released from postganglionic PSNS neurons at target organ sites, and at these sites ACh primarily binds to and activates muscarinic receptors (designated as M_2 receptors, as in Figure 6.5). As stated previously, nerve fibers that synthesize and release ACh are classified as cholinergic fibers, therefore both preganglionic and postganglionic parasympathetic neurons are cholinergic.

It is common that cotransmitters are released, along with ACh, from many postganglionic PSNS fibers at target tissues and organs (Gourine et al., 2009; Burnstock, 2013; Herring, 2015; Ralevic, 2015). Parasympathetic nerves innervating the urinary bladder release ATP as a cotransmitter and there is evidence that parasympathetic nerves supplying the salivary glands utilize vasoactive intestinal polypeptide as a cotransmitter. Similar to sympathetic nerves, ACh and specific cotransmitters may be stored in the same vesicles and released together, or may be stored in separate vesicles and regulated as individual entities. The relative contributions of ACh, ATP, vasoactive intestinal polypeptide, and other putative neurotransmitters and cotransmitters in cell-mediated physiological responses depends on the specific target tissue, species, and neural stimulation parameters.

Nonadrenergic–Noncholinergic Neurons

Some nerves that project to and innervate effector tissues and organs, generally at anatomical sites that are innervated by autonomic nerves, do not exhibit the histochemical characteristics of cholinergic or adrenergic fibers. These neurons are classified as nonadrenergic–noncholinergic (NANC) fibers. Many of the same molecules/substances identified as cotransmitters in ANS nerves also play a role as neurotransmitters released from NANC nerve endings (e.g., ATP, NPY) (Gourine et al., 2009; Burnstock, 2013; Herring, 2015; Ralevic, 2015). Substantial evidence points to an important role of NANC transmission in the physiological regulation of the GI tract (the enteric nervous system is prominently innervated by cholinergic, adrenergic, and NANC nerve fibers), genitourinary tract, and select blood vessels. For example, nitric oxide (NO), synthesized and released from NANC nerves and endothelial cells, is an important contributor to penile erection (Burnett, 2006; Lasker et al., 2013). NO is produced in NANC neurons by neural NO synthase (nNOS) and in endothelial cells by endothelial NO synthase (eNOS). NO is considered a primary vasoactive neurotransmitter and chemical mediator, and after binding to an intracellular receptor results in the conversion of GTP to cGMP. ACh released from cholinergic nerves can bind to muscarinic receptors on endothelial cells and initiate the formation of NO. NANC neurons may also contain extensive afferent components, which are thought to contribute to the local, reflex regulation of sensory inputs.

Enteric Nervous System

Regulation of the complex physiological processes associated with gastrointestinal physiology, including secretions, motility, and nutrient absorption, are mediated to a large extent by the enteric nervous system, an intrinsic nervous system located in the wall of the gastrointestinal system. The enteric nervous system contains both motor and sensory components and is characterized by the presence of a complex intrinsic neural network that includes the myenteric plexus and the submucosal plexus. Afferent information from nerve endings in the gut wall and mucosa convey chemical, mechanical, and stretch sensory information to the intrinsic neural networks. The enteric neural networks are innervated by preganglionic PSNS nerve fibers and postganglionic SNS nerve fibers. The parasympathetic and sympathetic innervation to the enteric nervous system appears to influence the intrinsic function of this nervous system in a modulatory manner. Sensory fibers in the enteric nervous system also transmit information to sympathetic ganglia and can modulate postganglionic sympathetic nerve outflow (Evans and de Lahunta, 2013). The enteric nervous system is extensively innervated by NANC nerve fibers.

Integrated Steps in SNS and PSNS Neurotransmission

The physiology of ANS function and regulation involves numerous integrated steps, including: regulation of supraspinal and spinal autonomic neural circuits; changing the level of efferent activity in sympathetic and parasympathetic nerves that innervate peripheral organs and tissues; neurotransmitter and neuromodulator synthesis, release, and degradation; chemical transmission from nerve cell to nerve cell (e.g., ganglionic regulation); chemical transmission from nerve cells to target organ sites; receptor-mediated effects; and regulation of activity in afferent nerves. Each of these processes and functions can be manipulated by pharmacological agents, providing multiple sites for drug-mediated changes in ANS regulation and function.

Peripheral Nerve Activity and Transmission of Action Potentials

Central neural circuits are critically involved in generating the basal activity in peripheral sympathetic and parasympathetic nerves, and in altering the level of activity in these nerves in response to internal and external stimuli. The arrival of nerve impulses at axonal terminals initiates a series of physiological processes that culminate with the release of neurotransmitters and cotransmitters into the synaptic cleft. An in-depth discussion regarding fundamental physiological processes involved in the conduction of action potentials along nerve axons, including resting membrane potential, changes in membrane ionic conductances, membrane depolarization, action potential propagation, and membrane repolarization, is beyond the scope of this introductory chapter. Generally, axonal conduction is not markedly influenced by pharmacological interventions, although there are several key exceptions. For example, voltage-sensitive membrane sodium channels are blocked and axonal conduction is inhibited by local anesthetics such as lidocaine, and by tetrodotoxin (puffer fish toxin) and saxitoxin (shellfish toxin).

Neurotransmitter Synthesis, Storage, Release, and Inactivation

Cholinergic Neurons

Cholinergic nerve terminals contain several types of vesicles, including small membrane-bound vesicles that play a key role in ACh storage (Figure 6.6), and larger vesicles that contain biological substances (e.g., ATP) that are cotransmitters released simultaneously along with ACh from cholinergic nerves (Table 6.2).

The synthesis of vesicles is typically completed in neuronal cell bodies and vesicles are relocated to nerve terminals by axonal transport mechanisms. Vesicles contain numerous proteins involved in transport and trafficking processes and an extensive amount of research has been focused on understanding these cellular processes. One important functional group of proteins are termed vesicle-associated membrane proteins (VAMPs), which play a critical role in aligning ACh-containing vesicles with functional release sites on the inner neuronal cell membrane, and in initiating neurotransmitter release. Release sites on the presynaptic plasma membrane contain synaptosomal nerve-associated proteins (SNAPs), which interact with vesicle-associated membrane proteins to facilitate vesicle–plasma membrane fusion and subsequently neurotransmitter release (Figure 6.6). Botulinum toxin interferes with ACh release from cholinergic nerve terminals.

The enzyme choline acetyltransferase (ChAT) synthesizes ACh from acetyl-CoA and choline in the cytoplasm of cholinergic nerves (Figure 6.6). Neurons in the PSNS are characterized by high rates of ACh release, which is mediated by a highly efficient and rapid process of ACh synthesis. Choline is transported across the neuronal membrane from the extracellular space via a sodium-dependent membrane choline transporter (CHT; Figure 6.6), whereas acetyl-CoA is synthesized in mitochondria located in the nerve endings. Choline transport into the cell can be limited by blocking the choline transporter using a group of research drugs called hemicholiniums. Following synthesis in the cytoplasm, ACh is transported into vesicles by a vesicle-associated transporter, which can be antagonized by the research drug vesamicol. Acetylcholine storage in vesicles is characterized by the packaging of "quanta" of ACh molecules (normally 1,000 to 50,000 molecules in each vesicle).

Release of ACh neurotransmitter from vesicles in cholinergic nerves is dependent on the arrival of action potentials at neuronal membrane terminals which activate voltage-gated calcium channels allowing for inward movement of Ca^{2+} into the nerve terminal (Figure 6.6). Calcium initiates processes that are essential for the vesicle membrane fusion with the neuronal membrane, leading to the exocytotic discharge of neurotransmitter into the synaptic cleft. Following release of ACh from cholinergic nerve terminals, ACh molecules may bind to and activate nicotinic (primarily ganglionic sites in the ANS) and muscarinic (primarily cells and tissues at target sites innervated by postganglionic nerves) receptors. Atropine and related alkaloids are muscarinic receptor antagonists whereas chlorisondamine blocks N_N receptors.

Nicotinic and muscarinic receptors are also present at presynaptic sites. Following release of ACh from cholinergic nerve terminals, this neurotransmitter can

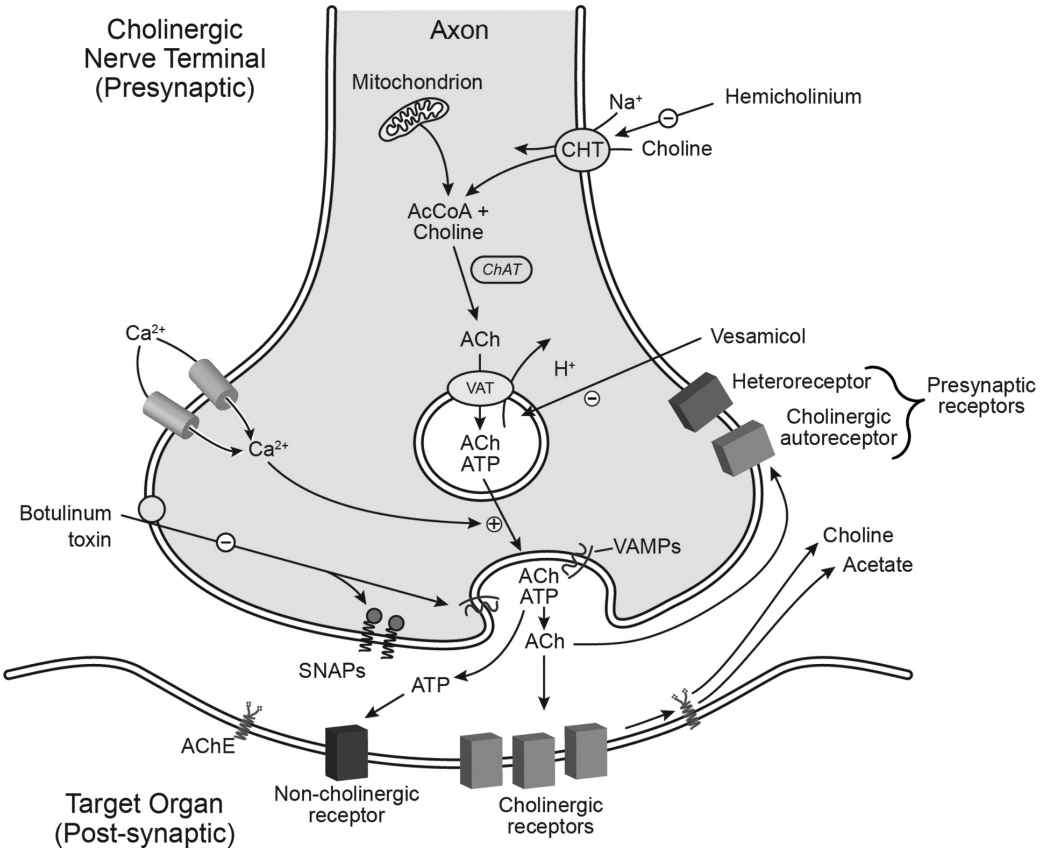

Figure 6.6 Schematic diagram depicting physiological processes at the site of a postganglionic parasympathetic nervous system neuron innervating a target tissue. Processes are described in the text and include: neurotransmitter synthesis, storage, and release; chemical transmission from nerve cells to target organ cells and tissues; neurotransmitter activation of presynaptic receptors; and termination of neurotransmitter action.

bind to and activate presynaptic cholinergic autoreceptors, primarily nicotinic receptors on preganglionic neurons and muscarinic receptors on postganglionic neurons, which in turn attenuate the release of ACh. This physiological process provides a pathway via which the release of ACh from a specific cholinergic neuron is regulated at a local level, an autoregulatory process. Cholinergic receptors also function as heteroreceptors, that is ACh released from cholinergic nerve terminals can bind to nicotinic or muscarinic receptors located on the presynaptic terminals of adjacent neurons, such as sympathetic nerve terminals, and inhibit the release of neurotransmitters from these neurons, such as NE from postganglionic sympathetic neurons.

As stated previously, cotransmitter molecules or biological substances are released along with ACh at target sites innervated by postganglionic parasympathetic neurons. Physiological functions of PSNS cotransmitters include modulating the presynaptic release of ACh, producing synergistic actions with ACh, and activating different postjunctional cells. In general, PSNS cotransmission at synaptic sites provides increased pharmacological and physiological finesse in the regulation of target tissue responses.

The binding of ACh to cholinergic receptors is transient and ACh located in the synaptic space is inactivated by acetylcholinesterase (AChE) (Figure 6.6), an enzyme that rapidly hydrolyzes ACh into choline and acetate. AChE is located in close proximity to the synaptic cleft at most cholinergic synapses, including postganglionic parasympathetic neuroeffector sites, and is present in autonomic ganglia, cholinergic nerves, and at neuromuscular junctions. The distribution of ACh released from cholinergic neurons is localized because AChE is efficient at terminating the action of ACh at synaptic sites. The amount of ACh available at synaptic sites, and subsequently its functional activity, can be enhanced by drugs and chemicals that block AChE (e.g., acetylcholinesterase agents). AChE is found in other body tissues, including red blood cells.

Adrenergic Neurons

Many animal species synthesize and secrete three endogenous catecholamines: NE, EPI, and dopamine. Biochemical steps in the synthesis of catecholamines are shown in Figure 6.7. Catecholamine synthesis is initiated by the conversion of phenylalanine to tyrosine by the enzyme phenylalanine hydroxylase. The enzyme tyrosine

Table 6.2 Autonomic nervous system receptor types, typical anatomical locations, and their primary mechanisms of action

Receptor name	Typical locations/tissue	G-Protein	Cellular responses
Cholinoceptors			
Muscarinic M_1	CNS; enteric nervous system; glands; sympathetic postganglionic neurons	$G_{q/11}$	Activation of PLC, IP_3 and DAG, ↑ intracellular calcium
Muscarinic M_2	CNS; heart; smooth muscle; select presynaptic sites	$G_{i/o}$	Activation of K^+ channels, adenylyl cyclase inhibition, and ↓ cAMP
Muscarinic M_3	CNS; heart; glands; smooth muscle	$G_{q/11}$	Activation of PLC, IP_3 and DAG
Muscarinic M_4	Prominently expressed in the CNS; vagal nerve terminal	$G_{i/o}$	Activation of K^+ channels, adenylyl cyclase inhibition, and ↓ cAMP
Muscarinic M_5	CNS; vascular endothelium	$G_{q/11}$	Activation of PLC, IP_3 and DAG
Nicotinic N_N	SNS and PNS autonomic ganglia; postganglionic neurons; presynaptic nerve terminals		Depolarization of postganglionic SNS and PNS neurons, ↑ ionic permeability (Na^+, K^+)
Nicotinic N_M	Somatic nervous system; neuromuscular junction		Depolarization and skeletal muscle contraction, ↑ cation permeability
Adrenoceptors			
α_{1A}	Vascular smooth muscle; urogenital smooth muscle; reproductive organs; CNS	G_q	Activation of PLA_2, PLC, IP_3 and DAG, ↑ intracellular calcium
α_{1B}	Vascular smooth muscle; spleen; liver; CNS	G_q	Activation of PLA_2, PLC, IP_3 and DAG, ↑ intracellular calcium
α_{1D}	Platelets; CNS	G_q	Activation of PLA_2, PLC, IP_3 and DAG, ↑ intracellular calcium
α_{2A}	Presynaptic adrenergic nerve terminals; CNS; brainstem and spinal cord sites; postganglionic SNS neurons; autonomic ganglia; platelets	G_i/G_o	Inhibition of adenylyl cyclase, ↓ cAMP
α_{2B}	Vascular smooth muscle; CNS; liver; kidney	G_i/G_o	Inhibition of adenylyl cyclase, ↓ cAMP
α_{2C}	CNS	G_i/G_o	Inhibition of adenylyl cyclase, ↓ cAMP
β_1	Heart; kidney; juxtaglomerular cells; CNS; presynaptic sites on adrenergic and cholinergic nerve terminals	G_s	Stimulation of adenylyl cyclase, ↑ cAMP
β_2	Smooth muscle (bronchial, vascular, bladder); heart; liver; skeletal muscle	G_s	Stimulation of adenylyl cyclase, ↑ cAMP
β_3	Adipose tissue	G_s	Stimulation of adenylyl cyclase, ↑ cAMP
Dopamine receptors			
D_1 (DA_1), D_5	CNS; kidney; vascular smooth muscle	G_s	Stimulation of adenylyl cyclase, ↑ cAMP
D_2 (DA_2), D_3, D_4 D_5	CNS; smooth muscle; presynaptic nerve terminals	G_i/G_o	↓ Intracellular cAMP; ↑ K^+ currents

CNS, central nervous system; SNS, sympathetic nervous system; PNS, parasympathetic nervous system; PLC, phospholipase C; PLA, phospholipase A; IP_3, inositol-1, 4, 5-triphosphate; DAG, diacylglycerol; cAMP, cyclic AMP.

hydroxylase converts tyrosine to dihydroxyphenylalanine (dopa), and this enzymatic step is considered the rate-limiting step in catecholamine synthesis. Dopa is decarboxylated by the enzyme L–aromatic amino acid decarboxylase (dopa decarboxylase) to form dihydroxyphenylethylamine (dopamine), which is transported into and stored in granules. In some neurons and neuronal systems, including select peripheral postganglionic sympathetic neurons and neurons in several CNS sites (e.g., mammalian extrapyramidal system), catecholamine synthesis terminates with dopamine. These neurons release dopamine as the primary neurotransmitter and are identified as dopaminergic neurons. Dopamine–β-hydroxylase mediates the conversion of dopamine to NE, and this conversion is the terminal enzymatic step in catecholamine synthesis in postganglionic SNS neurons and in some CNS neurons. The chromaffin cells of the adrenal medulla synthesize and release EPI and NE. In some adrenal medullary cells the terminal step in the biosynthesis of catecholamines involves conversion of dopamine to NE, whereas in other cells NE is released from the granules and is converted to EPI within the cytoplasm by phenylethanolamine *N*-methyltransferase, and subsequently re-enters the chromaffin granules prior to release from the adrenal medulla. EPI (~80%; NE, ~20%) is the primary catecholamine released from the adrenal medulla. The enzymatic conversion of NE to EPI also occurs in select CNS sites. The level of catecholamines contained in the cytoplasm is closely regulated by two physiological

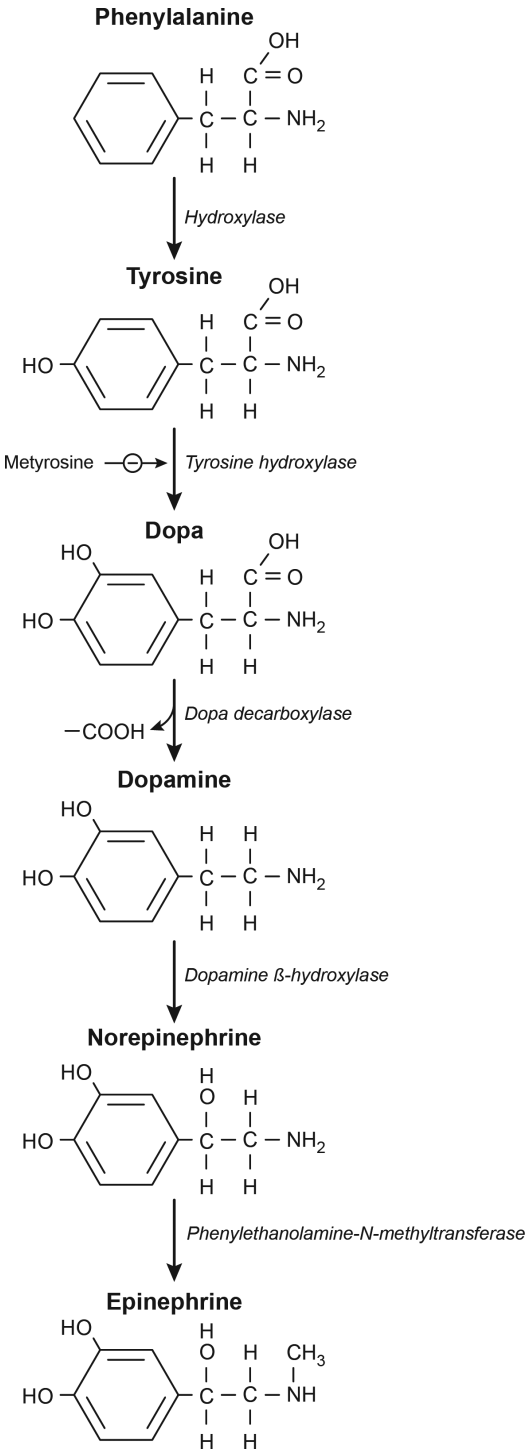

Figure 6.7 Biosynthesis of catecholamines. The rate-limiting step is the conversion of tyrosine to dopa by the enzyme tyrosine hydroxylase. Generally, postganglionic sympathetic nervous system neurons do not contain the enzyme, phenylethanolamine-*N*-methyltransferase (PMNT), therefore, the enzymatic conversion of dopamine to norepinephrine is the final step in catecholamine biosynthesis in these neurons. The enzymatic conversion of norepinephrine to epinephrine by PMNT occurs primarily in the adrenal medulla and in specific central nervous system sites.

processes: inactivation by the neuronal mitochondrial enzyme monoamine oxidase (MAO); and transportation of cytoplasmic NE into granules by the vesicular monoamine transporter. NE, EPI, dopamine, and serotonin are all transported by monoamine transporters and reserpine inhibits this process and leads to depletion of the amount of stored neurotransmitter.

The exocytic process of releasing neurotransmitters and cotransmitters from granules contained in adrenergic nerve endings is initiated by arrival of an action potential at the nerve terminal (Figure 6.8), is calcium dependent, and is similar in many aspects to the release of ACh from cholinergic nerves. Although NE is the primary neurotransmitter released from postganglionic sympathetic nerves, there are several cotransmitters that can be simultaneously released, including ATP, NPY, and other peptide molecules. These additional neurotransmitters or neuromodulators may be costored with NE or may be stored in separate vesicles. The functions of cotransmitters in synaptic neurotransmission are varied and multifactorial and may include direct postsynaptic receptor effects, modulation of receptor effects of other adrenergic neurotransmitters or cotransmitters, and alteration of the presynaptic release of neurotransmitters or neuromodulators.

Following release from postganglionic sympathetic nerve terminals, NE molecules can bind to and activate adrenergic receptors located on postsynaptic cells and tissues, as well as activate presynaptic adrenergic receptors located on the postganglionic nerve terminal from which the catecholamine was released (Figure 6.8). α_2-adrenergic receptors (with a specific emphasis on the α_{2A}-adrenergic receptor subtype) are the primary presynaptic receptors that, when activated, mediate an autoregulatory response to inhibit transmitter release at selected postganglionic SNS nerve terminals. The release of NE from postganglionic SNS neurons can also be reduced by several of the cotransmitters that are released simultaneously with NE. Conversely, the release of NE from postganglionic SNS neurons can be augmented by activation of presynaptic β_2-adrenergic receptors. Adrenergic receptors located on the presynaptic terminals of adjacent neurons, such as nearby parasympathetic nerve terminals, can function as heteroreceptors. For example, NE released from postganglionic sympathetic nerve terminals can bind to adrenergic receptors located on parasympathetic nerve terminals and inhibit ACh release. Similarly, the activation of heteroreceptors located on sympathetic nerve terminals, such as the binding of ACh to muscarinic receptors expressed on postganglionic SNS neurons, can inhibit the release of catecholamines from sympathetic nerve terminals.

As a physiological strategy to reduce overstimulation of adrenergic receptors secondary to neuronal release

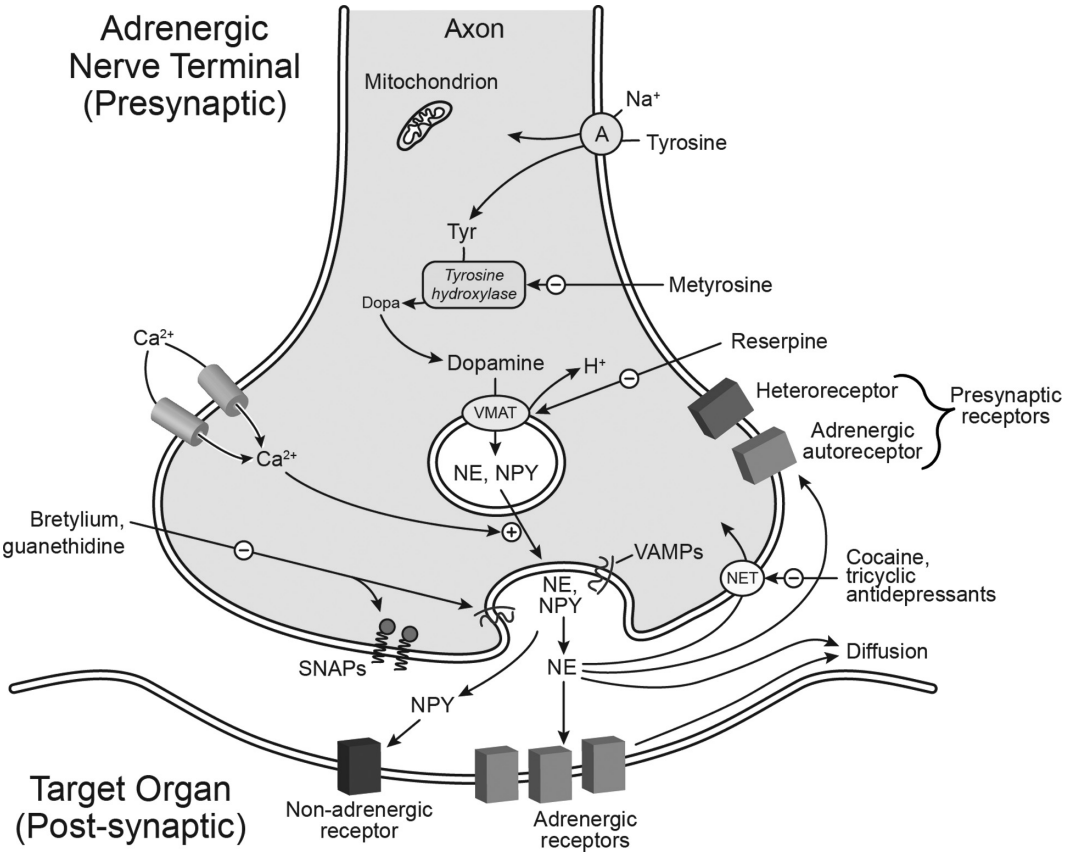

Figure 6.8 Schematic diagram depicting physiological processes at the site of a postganglionic sympathetic nervous system neuron innervating a target tissue. Processes are described in the text and include: neurotransmitter synthesis, storage, and release; chemical transmission from nerve cells to target organ cells and tissues; neuronal reuptake of neurotransmitter; neurotransmitter activation of presynaptic receptors; and termination of neurotransmitter action.

of NE, the amount of NE contained in the synapse is tightly regulated. Elimination of synaptic NE and/or termination of NE synaptic activity occurs via three physiological processes. First, NE can be metabolized by the enzyme catechol-*O*-methyltransferase (COMT) that is located at postsynaptic cell membrane-associated neuroeffector sites. Second, NE (as well as other similar molecules) can be transported back into postganglionic sympathetic nerve terminals (or nearby glial cells) by an active norepinephrine transporter (NET, also termed uptake 1 or reuptake 1) reuptake system that is present in axonal membranes (Figure 6.8). In a similar process, synaptic dopamine can be taken back into dopaminergic cells by a membrane dopamine transporter. NE that has been transported back into the neuron may be recycled and placed in granules or undergo metabolic breakdown via mitochondrial MAO. Inhibition of NET, mediated by cocaine and tricyclic antidepressant drugs, results in an increase in the level of NE in the synaptic cleft and enhanced receptor-mediated effects. Third, NE can diffuse away from the synaptic cleft and be metabolized in the plasma or liver, or excreted in the urine. Hepatic COMT is critically involved in the metabolism of endogenous circulating and administered catecholamines. It is generally considered that the reuptake of synaptic NE into adrenergic nerve terminals and the diffusion of NE from synaptic areas and subsequent enzymatic degradation are the primary processes involved in terminating NE activity. Metabolism of endogenous catecholamines by MAO and COMT involves numerous pathways (Figure 6.9).

Autonomic Receptors

Multiple experimental interventions (including structure–activity analyses, binding of isotope-labeled ligands, pharmacokinetic and pharmacodynamic analyses of specific autonomic agonists and antagonists, and molecular biological and proteomic analyses) have been used to identify and characterize receptors involved in ANS regulation. These include nicotinic and muscarinic cholinergic receptors, as well as alpha, beta, and dopaminergic adrenergic receptors (Wilson-Pauwels et al., 1997; Yamada and Ito, 2001; Abrams and Andersson, 2007; Yoshimura et al., 2008; Andersson,

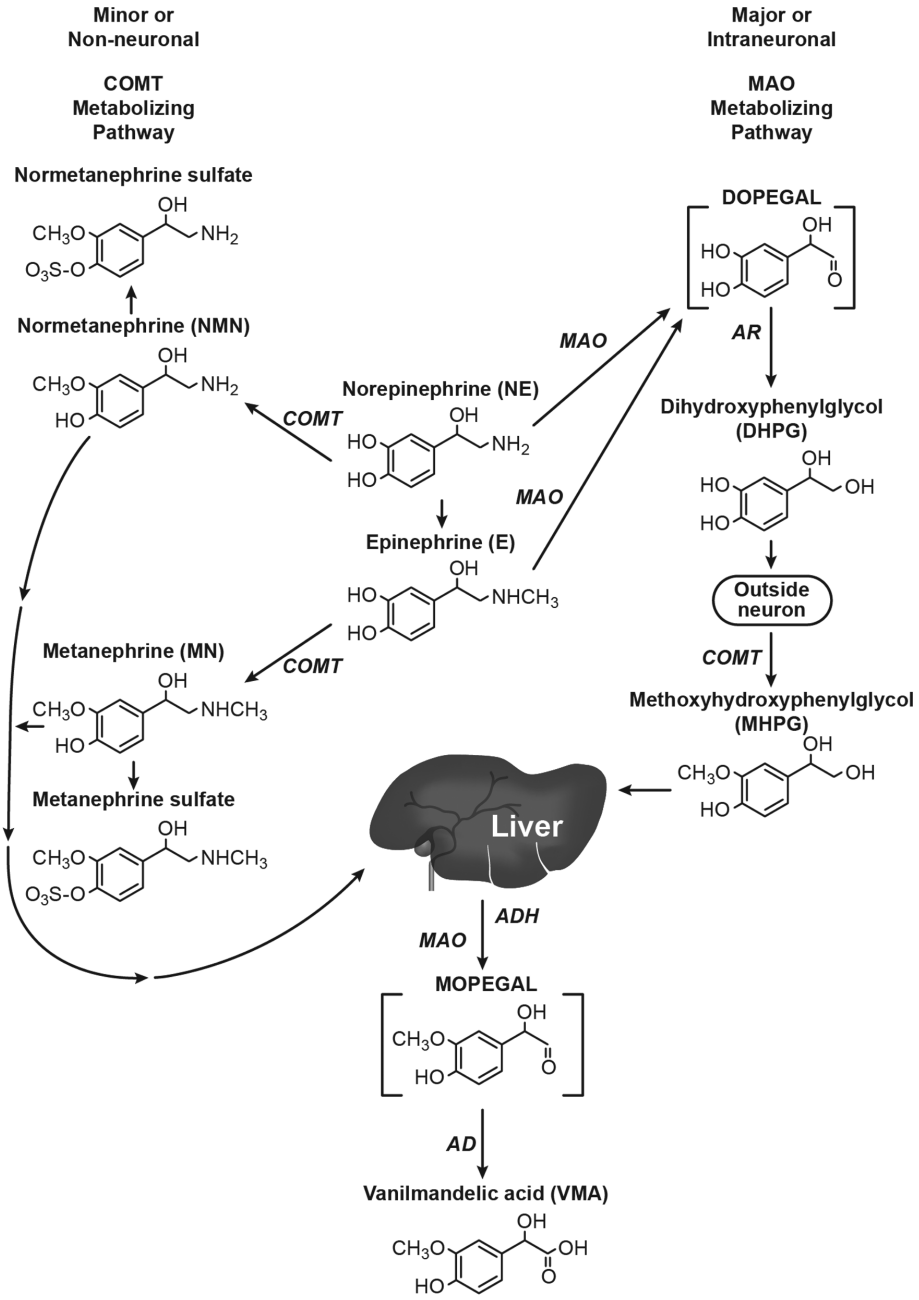

Figure 6.9 Flow diagram illustrating the metabolism of norepinephrine and epinephrine by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). Source: Adapted from Oeltmann 2004. Reproduced with permission of Elsevier.

2011; Cazzola et al., 2012; Lei, 2014; Herring, 2015). Specific receptor information is summarized in Table 6.2 (receptors/sites/G proteins/secondary messengers) and described in subsequent sections.

Cholinergic Receptors

As stated previously, ACh is the primary agonist at two types of cholinergic receptors (the term cholinoceptor is often used interchangeably): nicotinic and muscarinic. These receptors were named according to the alkaloids (nicotine and muscarine) that were identified to be agonists at the respective receptors.

Nicotinic Receptors: Anatomical Location, Receptor Subtypes, and Signal Transduction

Peripherally located autonomic N_N receptors are present on postganglionic neurons in autonomic ganglia (intramural, prevertebral, and paravertebral) and mediate neurotransmission from preganglionic to postganglionic neurons in both arms of the ANS. N_N receptors are also present on adrenal medullary chromaffin cells and mediate neurotransmission from preganglionic SNS neurons to adrenal medullary chromaffin cells. Nicotinic receptors are widely distributed in the CNS and are present in nonneuronal tissues. Nicotinic muscle (N_M) receptors are critically involved in mediating signal transmission at

the neuromuscular junction and are an essential component of the somatic nervous system (SoNS) (Figure 6.5).

Nicotinic receptors are ligand-gated ion channels and contain five homologous subunits organized around a central pore (Stokes et al., 2015). Activation of these receptors initiates a rapid increase in cellular permeability to selective cations (Na^+ and Ca^{2+}); cell membrane depolarization; and excitation of postganglionic ANS neurons, adrenal medullary chromaffin cells, or skeletal muscle fibers (Stokes et al., 2015).

As previously discussed, in addition to their anatomical location at postsynaptic sites on effector cells, nicotinic receptors are located at presynaptic sites. Activation of these receptors influences the release of neurotransmitters from neurons at peripheral sites and in the CNS.

Muscarinic Receptors: Anatomical Location, Receptor Subtypes, and Signal Transduction

Muscarinic receptors are located predominately at postsynaptic target sites innervated by postganglionic parasympathetic nerves such as the heart, glands, urinary bladder, and gastrointestinal tract, thereby establishing a pivotal role for these receptors in the functionality of the PSNS. Five subtypes of muscarinic receptors have been identified, each associated with a different gene, and many of the physiological functions associated with PSNS activation are mediated by muscarinic$_2$ (M_2) and muscarinic$_4$ (M_4) receptors. Muscarinic receptor subtypes are located in distinct peripheral anatomic locations (Table 6.2) and demonstrate differential specificities to various agonists and antagonists.

Muscarinic receptors are G protein-coupled receptors (GPCRs), and activation of these receptors may elicit an excitatory or inhibitory response (Calebiro et al., 2010; Jalink and Moolenaar, 2010; Ambrosio et al., 2011; Vischer et al., 2011; Latek et al., 2012; Duc et al., 2015). A fundamental mechanism mediating the capability of the PSNS to produce an assortment of physiological response profiles arises from the fact that specific muscarinic receptors couple primarily to specific G proteins. Muscarinic receptor subtypes M_1, M_3, and M_5 couple through $G_{q/11}$, whereas M_2 and M_4 receptors couple to G_i and $G_{0.}$ Specificity in the intracellular response profiles following activation of specific muscarinic receptors are the result of G protein-mediated effects on the generation of second messengers and on the activity of ion channels (Table 6.2).

As described previously, and in addition to their anatomical location at postsynaptic sites on effector cells innervated by postganglionic PSNS neurons, muscarinic receptors are located at presynaptic and perisynaptic sites and activation of these receptors influences the release of neurotransmitters from neurons at peripheral sites and in the CNS.

Adrenergic Receptors

The endogenous catecholamines NE and EPI are agonists at α- and β-adrenergic receptors (also termed adrenoceptors), whereas dopamine, the metabolic precursor of NE, is a primary agonist at dopaminergic receptors.

Adrenergic Receptors: Anatomical Location, Receptor Subtypes, and Signal Transduction

The concept of distinct adrenergic receptors (α and β) as determined by their relative responsiveness to specific receptor agonists was first proposed in a classic paper authored by Ahlquist (1948). There are two types of α-adrenergic receptors; α_1 and α_2. Each type contains specific receptor subtypes, designated as α_{1A}, α_{1B}, and α_{1D}; and α_{2A}, α_{2B}, and α_{2C}. There are three primary types of β-adrenergic receptors, β_1, $\beta_{2,}$ and $\beta_{3,}$ and two primary types of dopaminergic receptors, dopamine$_1$, D_1, and dopamine$_2$, D_2.

α- and β-adrenergic receptors are expressed predominately at target sites innervated by postganglionic sympathetic nerves, and their placement is characterized by a substantial degree of anatomical specificity (adrenergic types and designated tissue locations are summarized in Table 6.2). β-adrenergic receptors are expressed in the heart (primarily β_1), urinary bladder (primarily β_2 and β_3), liver (primarily β_2), kidney (primarily β_1); and in bronchial (primarily β_2), uterine (primarily β_2 and β_3), and vascular (primarily β_2) smooth muscle. It is often considered that vascular smooth muscle β_2-adrenergic receptors are not innervated by postganglionic sympathetic nerve fibers and circulating catecholamines released from the adrenal medulla are the primary endogenous agonists for these receptors. β-adrenergic receptors regulate many physiological functions including: heart rate and cardiac contractility; renin release; smooth muscle relaxation; and numerous metabolic events in adipose, skeletal muscle, and hepatic cells (see Table 6.1). α_1-adrenergic receptors are expressed in numerous tissues and organs including vascular smooth muscle, radial muscle of the iris, and smooth muscle in the genitourinary system. It is generally considered that α_1-adrenergic receptors are in close proximity to postganglionic sympathetic nerve endings, and NE released from these neurons is a primary endogenous agonist for these receptors. α_2-adrenergic receptors are expressed in a variety of cells and tissues including: vascular smooth muscle; thromobocytes; endothelial cells that synthesize and release nitric oxide; CNS sites; and on the terminals of postganglionic sympathetic nerve fibers.

Adrenergic receptors (α and β) are G protein-coupled receptors that link to G proteins (Calebiro et al., 2010; Jalink and Moolenaar, 2010; Ambrosio et al., 2011; Vischer et al., 2011; Latek et al., 2012; Duc et al., 2015).

A fundamental mechanism underpinning the capability of the ANS to produce various types of physiological response profiles arises from the fact that specific adrenergic receptors couple primarily to specific G proteins. For example, α_1 receptors couple to G_q, α_2 receptors couple to G_i, and β-adrenergic receptors couple to G_s. Specificity in the intracellular response profiles following activation of specific adrenergic receptors are the result of G protein-mediated effects on the generation of second messengers and on the activity of ion channels (Table 6.2).

As stated above, α_2-adrenergic receptors are expressed on the terminals of sympathetic nerve fibers, and NE released from postganglionic sympathetic neurons may interact with α_2-adrenergic receptors located at presynaptic sites to reduce NE release. The α_{2A}-adrenergic receptor subtype is considered to play an important role in this autoregulatory function. α-adrenergic receptors, especially α_2 receptors, can also be classified as heteroreceptors. For example, NE released from postganglionic sympathetic nerve fibers can modulate ACh release by activating α_2-adrenergic receptors that are expressed on parasympathetic neurons.

Dopamine mediates numerous physiological effects in the CNS and at peripheral targets, including the vasculature in many visceral organs. The D_1 receptor is generally associated with stimulation of adenylyl cyclase and increased cAMP, which may mediate the vasodilatory effects of dopamine in the renal and splanchnic circulations. On the other hand, activation of D_2 receptors has been shown to inhibit adenylyl cyclase activity, open potassium channels, and decrease calcium influx. D_2 receptors are expressed on the terminals of postganglionic sympathetic nerve fibers, and activation of these presynaptic dopaminergic receptors can produce the inhibition of NE from these nerve terminals.

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7

Adrenergic Receptor Agonists and Antagonists

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Classification of Adrenergic Agonists

The sympathetic nervous system (SNS) influences the regulation of most organ systems and plays a critical role in regulating physiological homeostasis under basal conditions and in response to acute and sustained stressors. Changes in physiological function are initiated and sustained by altering the level of efferent sympathetic nerve outflow, which in turn affects the release of norepinephrine (NE) from postganglionic nerve terminals. Sympathetic nerve activity mediates NE release from nerve terminals, and the released NE binds to and activates adrenergic receptors located on postsynaptic effector tissues and at presynaptic sites. In a similar fashion, central activation of sympathetic nerve activity directed to the adrenal medulla initiates the release of epinephrine (EPI) and some NE from this gland, which circulates in the blood and binds to and activates adrenergic receptors in target tissues.

Drugs that mimic the pharmacological and physiological actions of the endogenous catecholamines are classified as sympathomimetic drugs, that is their effects are mediated by activation of adrenergic receptors located on effector cells and tissues. One framework for classifying the functionality of adrenergic receptor agonists is centered on their general pharmacological mechanism of action (Figure 7.1). Three classifications are often considered. The first group, which includes the endogenous catecholamines (e.g., NE and EPI) and many sympathomimetic drugs (e.g., phenylephrine, dobutamine), are classified as direct agonists. These neurotransmitters and drugs bind directly to and activate adrenergic receptors (Figure 7.1). Many adrenergic agonists used in clinical medicine are direct adrenergic receptor agonists. A second group is classified as indirect-acting agonists because they mediate physiological responses via a pharmacological mechanism of action that involves increasing the synaptic levels of endogenous catecholamines, thereby enhancing the availability of endogenous catecholamines to bind to adrenergic receptors. This effect can be achieved by three different mechanisms of action: (i) reducing the metabolic breakdown of catecholamines by pharmacologically blocking or antagonizing endogenous enzymes involved in the metabolism of NE and EPI (e.g., monoamine oxidase inhibitors); (ii) inhibiting the physiological processes involved in the reuptake of NE from the synaptic space into postganglionic sympathetic nerve terminals (e.g., cocaine and tricyclic antidepressants); and (iii) enhancing the release of catecholamines from postganglionic sympathetic nerve terminals (e.g., tyramine). Some drugs (e.g., ephedrine) demonstrate the capability to directly activate adrenergic receptors as well as augment the release of NE from adrenergic nerve terminals, and these drugs are classified as mixed-acting adrenergic agonists (Figure 7.1). In a conceptual context, the physiological responses produced by direct, indirect, and mixed-acting agonists are similar to responses produced by activating central sympathetic neural circuits, increasing the level of efferent sympathetic nerve outflow, and inducing the release of NE from postganglionic sympathetic nerves.

Sympathomimetic Amines and Structure–Activity Relationships

The capacity of sympathomimetic drugs to produce physiological responses consistent with functional patterns produced by SNS activation depends on the similarity of the chemical structure of sympathomimetic drugs to that of NE and EPI. The parent compound of sympathomimetic amines is β-phenylethylamine, which consists of a benzene ring and an ethylamine side chain. Chemical substitutions can be made on the aromatic ring, on the α and β carbons atoms, and on the terminal amino group to produce compounds with sympathomimetic activity.

The endogenous adrenergic receptor agonists EPI, NE, and dopamine, as well as the synthetic sympathomimetic isoproterenol, contain a hydroxyl group on the 3 and 4 positions of the benzene ring. The 3,4-dihydroxybenzene structure is also known as catechol; therefore sympathomimetic amines that contain this nucleus are known as

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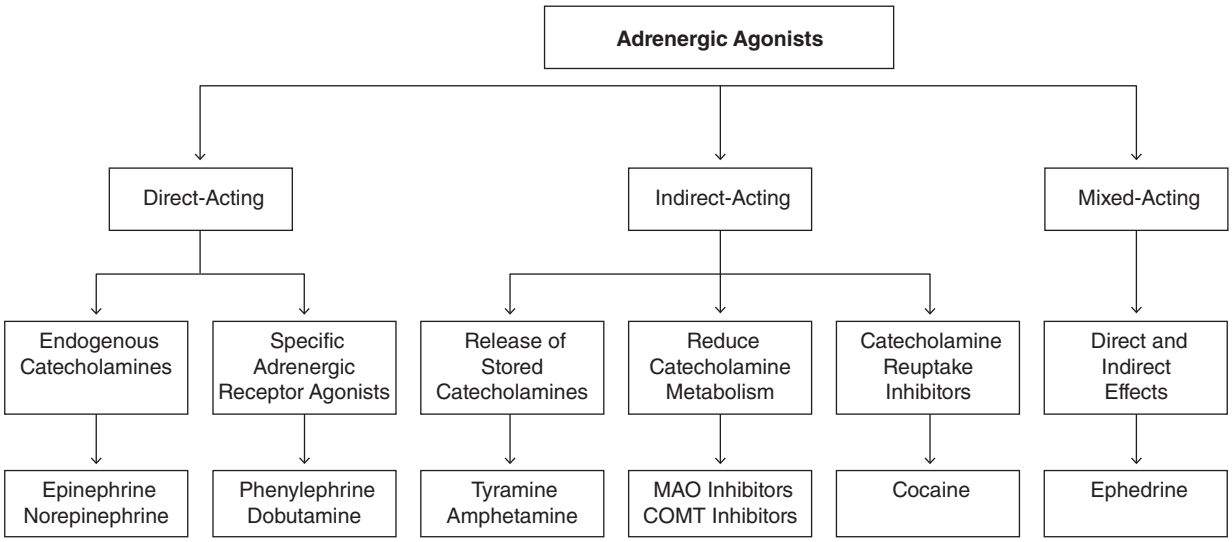


Figure 7.1 Framework for classifying the functionality of catecholamines and sympathomimetics based on pharmacological mode of action, that is direct agonists, indirect agonists, and mixed agonists. COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

catecholamines. For the most part, the catechol nucleus is required for maximum α- and β-adrenergic receptor potencies, and modifications in phenylethylamine mediate changes in the affinity of drugs for specific adrenergic receptors, and affect the intrinsic ability to activate these receptors. Removal of one or both hydroxyl groups from the aromatic ring reduces β-adrenergic receptor activity. For example, phenylephrine, a specific α_1-adrenergic receptor agonist, is identical in structure to EPI, a mixed α-β-adrenergic receptor agonist, except for the lack of one hydroxyl group on the ring (Table 7.1). Substitution on the β-carbon atom of the side chain produces a compound with reduced central nervous system (CNS) effects, whereas substitution on the α-carbon atom produces a drug that is generally more resistant to oxidation by monoamine oxidase (MAO). The α- and β-agonistic properties of various drugs are affected by alkyl substitutions on the amino group. Collectively, this information supports the idea that pharmacological profiles of specific agonists differ depending upon chemical structure. The chemical structures and related pharmacological characteristics of the endogenous catecholamines and several adrenergic drugs are summarized in Table 7.1.

Activation of Adrenergic Receptors and Cell Signaling

Physiological responses produced by catecholamines and sympathomimetic drugs are initiated by the binding of agonists to adrenergic receptors located on the cell surface (Wilson-Pauwels et al., 1997; Yamada and Ito, 2001; Cazzola et al., 2012; Lei, 2014; Herring, 2015). Adrenergic receptors are *G* protein-coupled receptors

Table 7.1 Chemical structures of catecholamines and selected sympathomimetic drugs

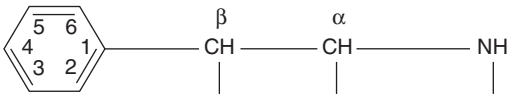
Drug		β	α	
β-phenylethylamine	…	H	H	H
β-phenylethanolamine	…	OH	H	H
Catecholamines				
Dopamine	3-OH, 4-OH	H	H	H
Norepinephrine	3-OH, 4-OH	OH	H	H
Epinephrine	3-OH, 4-OH	OH	H	CH_3
Isoproterenol	3-OH, 4-OH	OH	H	$CH(CH_3)_2$
Noncatecholamines				
Phenylephrine	3-OH	OH	H	CH_3
Tyramine	4-OH	H	H	H
Ephedrine	…	OH	CH_3	CH_3

Table 7.2 Adrenergic receptor types and subtypes, selected agonist and antagonist drugs, primary G proteins involved in mediating cellular responses to activation of specific adrenergic receptors, and typical intracellular effects secondary to adrenergic receptor ligand binding

Receptor	Agonist	Antagonist	G Protein	Effects
α_1-Adrenergic	Phenylephrine	Prazosin	G_q	Activation of PLA_2, PLC, ↑ IP_3 and DAG; common to all
α_{1A}		Tamsulosin		
α_{1B}				
α_{1D}				
α_2-Adrenergic	Dexmedetomidine	Yohimbine Atipamezole	G_i	Inhibition of adenylyl cyclase, ↓ cAMP; common to all
α_{2A}				
α_{2B}				
α_{2C}				
β-Adrenergic	Isoproterenol	Propranolol	G_s	Stimulation of adenylyl cyclase, ↑ cAMP; common to all
β_1	Dobutamine	Atenolol		
β_2	Terbutaline	Butoxamine		
β_3	Mirabegron			
Dopaminergic	Dopamine			
D_1	Fenoldopam		G_s	Stimulation of adenylyl cyclase, ↑ cAMP
D_2	Bromocriptine		G_i	↓ cAMP

PLC, phospholipase C; PLA, phospholipase A; IP_3, inositol-1,4,5-triphosphate; DAG, diacylglycerol; cAMP, cyclic AMP.

(GPCRs) (Calebiro et al., 2010; Jalink and Moolenaar, 2010; Ambrosio et al., 2011; Vischer et al., 2011; Latek et al., 2012; Duc et al., 2015). G proteins are classified by their specific subunits, and select G proteins regulate specific effector proteins and interact with select molecular pathways. Membrane and intracellular processes associated with GPCRs have been previously introduced in Chapter 6.

The β-adrenergic receptor family is composed of three different subtypes (β_1, β_2, and β_3). Activation of β receptors, regardless of subtype, results in stimulation of adenylyl cyclase and increased cAMP, mediated via the stimulatory coupling protein G_s (Table 7.2). β-adrenergic receptors (β_1, β_2, and β_3) are expressed in numerous tissues and organs (Table 7.3), although for a given tissue a specific receptor subtype may be more prominently

Table 7.3 Anatomical distribution of adrenergic receptor subtypes and general physiological effectors produced in response to activation of specific adrenergic receptors

Receptor	Tissue	Response
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Splenic capsule	Contraction
	Urethral smooth muscle	Contraction
α_2	Postsynaptic CNS neurons	Numerous sites
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Selected vascular smooth muscle	Contraction
β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Smooth muscle relaxation
	Liver	Gluconeogenesis
β_3	Fat cells	Activates lipolysis
D_1	Vascular smooth muscle	Dilates select blood vessels
D_2	Autonomic nerve terminals	Modulates neurotransmitter release from nerve terminals

expressed when compared with other receptor subtypes, thereby providing the tissue or organ with a relatively specific β-adrenergic subtype signature. For example, cardiac functions, such as increased heart rate and enhanced cardiac contractility, are medicated to a prominent extent by activation of cardiac β_1-receptors, whereas relaxation of bronchial smooth muscle involves activation of bronchial smooth muscle β_2-adrenergic receptors.

β-adrenergic receptors are expressed in smooth muscle at multiple anatomical sites, including: pulmonary airways (β_2 receptors), vascular smooth muscle (β_2 receptors), and the detrusor muscle of the bladder (β_2 and β_3 receptors). Activation of β receptors in these tissues mediates smooth muscle relaxation contributing to bronchodilation, vasodilation of vascular smooth muscle with accompanying reduced vascular resistance, and relaxation of the bladder body. Smooth muscle relaxation secondary to activation of β-adrenergic receptors may be mediated via processes that include the phosphorylation of myosin light-chain kinase to an inactive form. In many species the innervation of vascular smooth muscle β_2-adrenergic receptors by postganglionic sympathetic nerves is rather sparse, suggesting that the primary activation of these receptors is mediated by circulating EPI released from the adrenal medulla. β-adrenergic receptors (generally thought to be β_2 receptors) are also located at presynaptic sites on postganglionic nerve terminals and, in general, activation of presynaptic β_2-adrenergic receptors facilitates the release of NE.

The α_1-receptor family includes three subgroups: $\alpha_{1A,}$ $\alpha_{1B,}$ and $\alpha_{1D.}$ Binding of an agonist to α_1-adrenergic receptors, regardless of subtype, activates phospholipase C, mediated via activation of a G_q coupling protein, which leads in many cases to the formation of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol, and multiple functional effects including the release of intracellular Ca^{2+} stores (Table 7.2). Although the distribution (Table 7.3) and activation of different α_1-adrenergic receptor subtypes provides the substrate for a diverse profile of physiological responses, the functional signature of α_1-adrenergic receptor activation is smooth muscle contraction, including contraction of vascular smooth muscle, the radial muscle of the iris (iris dilator muscle), and smooth muscle in the genitourinary system. Generally, α_1-adrenergic receptors located in vascular smooth muscle are in close proximity to postganglionic sympathetic nerve endings, therefore they are considered innervated vascular receptors.

The α_2-receptor family includes three subgroups: $\alpha_{2A,}$ $\alpha_{2B,}$ and $\alpha_{2C.}$ In many targets the physiological responses to activation of α_2 receptors involves the coupling of these receptors to the inhibitory regulatory protein G_i (Table 7.2), resulting in inhibition of adenylyl cyclase activity and reduced intracellular cAMP levels. It is known that other signaling pathways, separate from the inhibition of adenylyl cyclase, are involved in mediating intracellular processes to α_2-receptor activation. α_2-adrenergic receptors are expressed in a variety of cells and tissues (Table 7.3), including vascular smooth muscle, thromobocytes, endothelial cells, and in the CNS. α_2-adrenergic receptors are located on the terminals of postganglionic sympathetic nerve fibers, and activation of these presynaptic adrenergic receptors by endogenous catecholamines and other sympathomimetics reduces NE release from nerve terminals.

By binding to and activating specific receptors at both central and peripheral sites, the endogenous catecholamine dopamine produces numerous physiological effects. Activation of the dopamine$_1$ (D_1) receptor is generally associated with increased cAMP, whereas activation of dopamine$_2$ (D_2) receptors can inhibit adenylyl cyclase activity.

Adrenergic Receptor Selectivity and Tissue Distribution

Overview

The breadth and diversity of (i) adrenergic receptor types and subtypes, (ii) G-proteins, and (iii) second messenger systems provides the cellular and molecular substrate for mediating the myriad number of physiological responses produced by activation of the SNS. In addition, many adrenergic receptor agonists demonstrate a level of selectivity for specific adrenergic receptors. An individual endogenous catecholamine or sympathomimetic drug may exhibit a higher affinity or selectivity for one or more subtypes of adrenergic receptors. Receptor selectivity provides an important framework for understanding target organ effects of endogenous catecholamines and sympathomimetic drugs. However, receptor selectivity for a given agonist is generally not absolute; that is, at higher concentrations a given drug or catecholamine may interact with and activate other subtypes or classes of adrenergic receptors, providing the functional basis for considering a spectrum of relative receptor affinities for most adrenergic agonists. Examples of relative receptor affinities for endogenous catecholamines of select adrenergic drugs are listed in Table 7.4. EPI is an agonist at α_1-, α_2-, β_1-, and β_2-adrenergic receptors, whereas NE is an agonist at α_1-, α_2-, and β_1-adrenergic receptors, with less potent effects on β_2-adrenergic receptors. Isoproterenol is a β_1- and β_2-adrenergic receptor agonist whereas phenylephrine is a selective α_1-adrenergic receptor agonist (Table 7.4).

The anatomical location of specific adrenergic receptor types and subtypes plays a key role in mediating the functional/physiological responses produced by a given

Table 7.4 Classification of adrenergic receptor agonists and their relative selectivity for specific adrenergic receptors

Agonists	Receptor selectivity
Alpha agonists	
Phenylephrine	$\alpha_1 > \alpha_2 >>>>> \beta$
Dexmedetomidine, Medetomidine, Xylazine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, Terbutaline	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$

drug or catecholamine. Pharmacological interactions between specific agonists and adrenergic receptors, as well as the profile of physiological responses produced by agonist–receptor interactions, are diverse and dynamic and are influenced by a number of factors, including: the tissue distribution of adrenergic receptors; the number of adrenergic receptors expressed at specific sites; interactions between the sympathetic and parasympathetic nervous systems at target sites; specific pathophysiological and disease states; the background level of sympathetic nerve activity; and levels of endogenous catecholamines and/or sympathomimetic drugs. Regarding the latter, prolonged exposure of adrenergic receptors to specific agonists reduces the responsiveness of these receptors to agonist activation, producing a progressive attenuation in the tissue's capacity to facilitate physiological responses. This physiological phenomenon is known as desensitization of adrenergic receptors. Multiple cellular and molecular mechanisms likely play a role in mediating adrenergic receptor desensitization, including changes in the number of adrenergic receptors and in intracellular signaling mechanisms.

Cardiovascular Responses to Adrenergic Receptor Agonists: Effects of Adrenergic Receptor Selectivity and Distribution

The pivotal contributions of adrenergic receptor selectivity and tissue distribution in mediating physiological responses to sympathomimetic drugs can be highlighted by comparing the effects of specific endogenous catecholamines and sympathomimetic drugs on various physiological regulatory systems, including cardiovascular regulation. In this section the cardiovascular effects (blood pressure, heart rate, myocardial contractility, cardiac output) produced by the administration of phenylephrine (selective α_1-adrenergic receptor agonist), NE and EPI (endogenous catecholamines), and isoproterenol (β_1- and β_2-adrenergic receptor agonist) are compared, with an emphasis on integrating and explaining how differences in their affinity or selectivity for specific α- and β-adrenergic receptors, and the primary anatomical location of specific adrenergic receptors, contribute to the

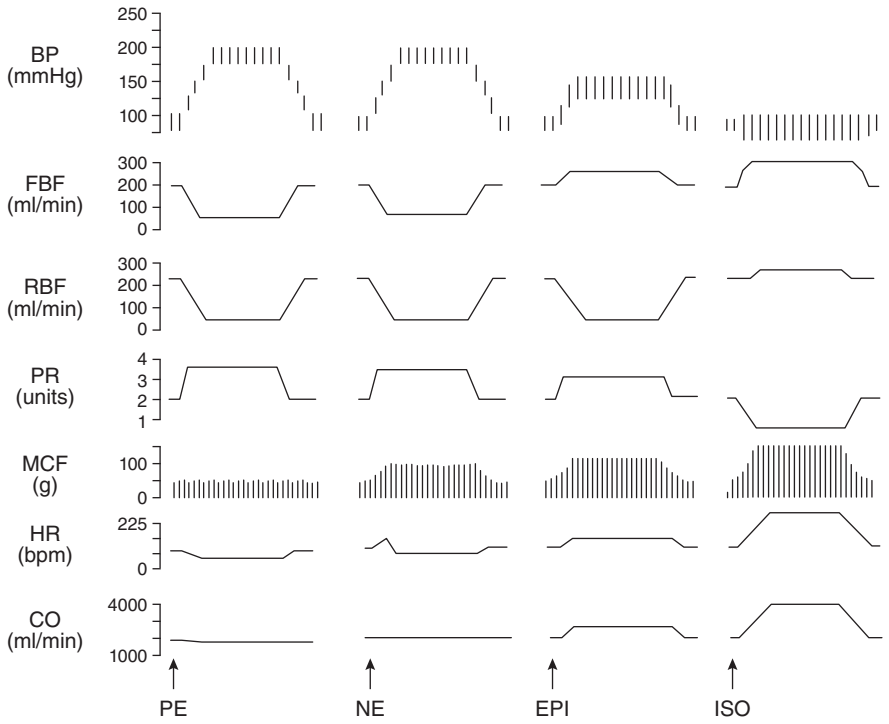


Figure 7.2 Schematic showing cardiovascular effects in response to the intravenous administration of four adrenergic agonists (phenylephrine (PE), norepinephrine (NE), epinephrine (EPI), and isoproterenol (ISO)) characterized by different relative receptor affinity profiles. Schematic representations of approximate equivalent doses of these endogenous catecholamines and sympathomimetic amines on blood pressure (BP), femoral blood flow (FBF), renal blood flow (RBF), peripheral vascular resistance (PR), myocardial contractile force (MCF), heart rate (HR), and cardiac output (CO). See text for explanation of the cardiovascular responses.

Table 7.5 Selected adrenergic receptors that play a role in cardiovascular regulation, their primary distributions in the vasculature and heart, general cardiovascular responses produced by their activation, and the selectivity of agonists (EPI, NE, ISO, and PE) for the specific adrenergic receptors

Receptor	Tissue	Physiological response	Agonist selectivity
α	Blood vessels	Vasoconstriction	PE; EPI > NE >>> ISO
β_1	Heart	Augmented inotropic and chronotropic effects	ISO > EPI ≥ NE
β_2	Blood vessels	Vasodilation	ISO > EPI >>> NE

EPI, epinephrine; ISO, isoproterenol; NE, norepinephrine; PE, phenylephrine.

observed cardiovascular responses (Figure 7.2). Arterial blood pressure is determined by the flow of blood through a vessel, which is ultimately determined by cardiac output and by the diameter or tone of that vessel, represented as peripheral vascular resistance. Information regarding the specific adrenergic receptors that play a role in cardiovascular regulation, their primary anatomical distributions in the vasculature and heart, the specific cardiovascular responses produced by their activation, and the order of potency of EPI, NE, isoproterenol, and phenylephrine are summarized in Table 7.5. This information provides the background required for explaining differences in cardiovascular response profiles to specific adrenergic agonists (Figure 7.2). In the examples described in this section each of the adrenergic receptor agonists have been administered as bolus injections over a short period of time.

Phenylephrine is a potent and selective agonist at α_1-adrenergic receptors. α_1-receptors are expressed in numerous vascular beds (e.g., visceral organs, skin, and skeletal muscle) and their activation by phenylephrine administration produces vasoconstriction of arterial smooth muscle, which in turn increases peripheral vascular resistance and reduces femoral blood flow and renal blood flow (Figure 7.2). In addition, phenylephrine administration produces venoconstriction, which reduces venous capacitance and increases venous return. The increase in arterial blood pressure is primarily due to the marked α_1-mediated increase in peripheral vascular resistance. The abrupt increase in arterial blood pressure secondary to phenylephrine administration activates the arterial baroreflex, which elicits a reflex-mediated increase in cardiac vagal nerve activity and a reduction in heart rate (bradycardia). α_1-receptors are not prominently expressed on cardiac cells involved in the regulation of cardiac rate or myocardial contractility; therefore phenylephrine administration does not elicit substantial direct effects on heart rate or cardiac output. However, from an integrative perspective phenylephrine administration does affect several of the physiological indices involved in the regulation of cardiac output, including: increased peripheral vascular resistance and afterload; increased venous return to the heart; and reduced heart rate via activation of the baroreflex.

Norepinephrine is an agonist at α-adrenergic (α_1 and α_2) and β_1-adrenergic receptors (and to a much lesser extent to β_2-adrenergic receptors). Activation of vascular α_1-adrenergic receptors by NE increases peripheral vascular resistance, as evidenced by decreases in femoral and renal blood flow (Figure 7.2). In addition, NE administration produces venoconstriction, which reduces venous capacitance and increases venous return. The activation of α_2-adrenergic receptors in vascular smooth muscle produces vasoconstriction and likely contributes to NE-induced increases in peripheral vascular resistance. β_1-adrenergic receptors are expressed in the heart, and activation of cardiac β_1-receptors by NE produces positive inotropic (increased cardiac contractility) and chronotropic (increased rate) effects. The increase in arterial blood pressure is mediated by combined vascular (α-adrenergic receptor-mediated vasoconstriction) and cardiac (increased cardiac output due to activation of β_1-adrenergic receptor) effects. The marked NE-induced increase in arterial blood pressure activates the arterial baroreflex, which elicits a reflex-mediated increase in cardiac vagal nerve activity and a reduction in heart rate. The reflex bradycardia does not necessarily lead to a reduction in cardiac output because of the direct effect of NE to activate cardiac β_1-receptors and increase myocardial contractility and stroke volume.

Epinephrine is a potent agonist at α-adrenergic (α_1 and α_2) and β-adrenergic (β_1 and β_2) receptors, and activation of vascular β_2-adrenergic receptors produces vasodilation. Therefore, EPI administration produces vasoconstriction and reduces blood flow in vascular beds that contain high concentrations of α-adrenergic receptors (e.g., visceral organs, cutaneous vessels), accounting for the EPI-induced reduction in renal blood flow (Figure 7.2). Some targets, such as the smooth muscle in the arterial vasculature supplying skeletal muscle, contain both β_2- and α-adrenergic receptors, and EPI-induced activation of β_2 receptors produces vascular vasodilation, whereas EPI-induced activation of α-adrenergic receptors produces vasoconstriction. In general, skeletal muscle vascular beds are often characterized by reduced peripheral vascular resistance in response to EPI administration (demonstrated as increased femoral blood flow in Figure 7.2), whereas EPI produces

α-adrenergic receptor-mediated vasoconstriction in visceral vascular beds. Due to the competing vasoconstrictor and vasodilatory effects of EPI, the increase in peripheral vascular resistance to EPI administration is generally not as robust as that observed in response to NE administration (Figure 7.2). EPI is a prominent cardiac stimulant and activation of cardiac β_1-adrenergic receptors increases cardiac contractility, heart rate, and cardiac output. The initial effect of EPI administration is often characterized by a rapid increase in cardiac output (cardiac β_1-receptor activation), a marked increase in peripheral vascular resistance mediated by the activation of visceral α-adrenergic receptors, and an increase in arterial blood pressure, which in turn may elicit a baroreflex-mediated increase in cardiac vagal nerve activity and a transient reduction in heart rate. Subsequent activation of β_2-adrenergic receptors as EPI is distributed to peripheral sites, such as skeletal muscle vascular beds, attenuates increases in peripheral vascular resistance and arterial blood pressure.

Isoproterenol is a potent, nonselective β_1- and β_2-adrenergic receptor agonist that exerts little effect on α-adrenergic receptors; therefore blood pressure responses to this β-adrenoceptor agonist are a function of its effects on cardiac and peripheral vascular β-adrenergic receptors. The vascular response profile to isoproterenol administration is characterized by vascular vasodilation, an increase in blood flow to vascular beds that contain a high density of β_2-adrenergic receptors (skeletal muscle, as supported by the increase in femoral blood flow), modest β_2-adrenergic receptor-mediated vasodilation in visceral vascular beds (e.g., renal blood flow), and reduced peripheral vascular resistance (Figure 7.2). Because isoproterenol lacks affinity for α-adrenergic receptors, there is no pharmacological-induced vascular smooth muscle contraction; therefore isoproterenol produces a marked reduction in peripheral vascular resistance. Isoproterenol is a potent cardiac stimulant. Isoproterenol activation of cardiac β_1-adrenergic receptors increases cardiac output by increasing heart rate, mediated by direct activation of the sinus node, and by increasing contractility of myocardial cells. It is generally considered that β_1-adrenergic receptors are the predominate type of myocardial β-adrenergic receptor. Mean arterial blood pressure is typically reduced in response to isoproterenol secondary to the marked reduction in peripheral vascular resistance, despite the accompanying increase in cardiac output.

Comparing cardiovascular responses to specific catecholamines and select sympathomimetic drugs supports the concept that relative receptor affinity, direct receptor effects, receptor distribution, and intrinsic reflex adjustments are key components for predicting drug-associated physiological response profiles for a variety of organs and regulatory systems.

Clinical Applications of Adrenergic Receptor Agonists

As stated previously, adrenergic receptors are distributed widely throughout many tissues and organ systems, and activation of these receptors facilitates a myriad of physiological responses. Selected clinical applications of sympathomimetics in specific conditions are described in this section as a framework for characterizing the pharmacodynamic effects of these drugs.

Adrenoceptor Agonists and Respiratory Physiology

A 15-year-old Quarter Horse mare presented with the clinical complaint of cough and increased abdominal effort during the expiratory phase of respiration. Physical examination revealed a heart rate of 44 beats per minute (normal; 36–44 beats per minute) and a respiratory rate of 20 breaths per minute (normal; 12–24 breaths per minute). Thoracic auscultation revealed increased bronchovesicular sounds and expiratory wheezes in all lung fields. In addition to an increased respiratory effort, the mare demonstrated prominent nostril flare (wide open nostrils) with expiration. Arterial blood gas analysis indicated hypoxemia as demonstrated by an arterial partial pressure of oxygen ($Pa0_2$) of 66 mmHg.

Based on the clinical findings, an immediate treatment protocol included the administration of aerosolized albuterol (selective β_2-adrenergic receptor agonist) (Rush et al., 1999). β_2-adrenergic receptors are present in bronchial smooth muscle, and activation of these receptors by β_2-agonists results in relaxation of bronchial smooth muscle and bronchodilation (Boushey, 2007; Cunningham, 2007). Approximately 10 minutes after albuterol administration, thoracic auscultation had improved substantially. Continued therapy included corticosteroid with albuterol, which was maintained over the course of 72 hours and the arterial partial pressure of oxygen level ($Pa0_2$) improved to 97 mmHg (Cornelisse et al., 2004; Boushy, 2007). In addition to improved oxygen delivery, the mare exhibited an improved respiratory effort demonstrated by resolution of her expiratory effort and nasal flare. The owner indicated the horse lived in a small pen with a round bale of hay that was stored outdoors.

This patient is suffering from recurrent airway obstruction, an allergic form of airway disease (Cunningham, 2007; Ainsworth and Cheetham, 2010). The condition is similar to asthma in humans. Airway obstruction results from hypersensitivity reaction to molds located in the forage. Following inhalation of molds, airway inflammation is induced in the form of neutrophil inflammation with marked mucous accumulation and airway smooth muscle contraction (Ainsworth and Cheetham,

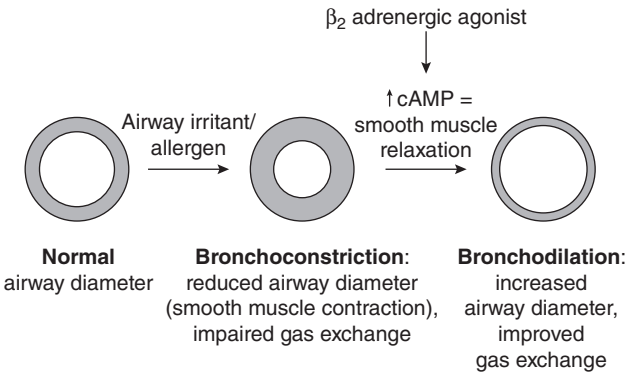


Figure 7.3 Airway irritants produce bronchoconstriction mediated via activation of inflammatory cascades and the parasympathetic nervous system (PSNS). The PSNS is responsible for maintaining baseline airway tone and activation of bronchial muscarinic receptors produces contraction of bronchial smooth muscle. Administration of a β_2-adrenergic receptor agonist and subsequent activation of bronchial smooth muscle β_2-adrenergic receptors increases intracellular cAMP levels with subsequent activation of cAMP-dependent protein kinase A, resulting in relaxation of bronchial smooth muscle.

2010). Therapeutic goals for affected individuals involve environmental management to reduce mold exposure and bronchodilation through the use of β_2-adrenergic receptor therapy. Corticosteroid therapy is aimed at reducing the hypersensitivity reaction (neutrophilic) to aerosolized allergens (Boushey, 2007; Ainsworth and Cheetham, 2010).

Control of bronchial smooth muscle tone depends on the integration of signals from several types of receptors that respond to chemical, mechanical, and physical stimuli (Cunningham, 2007; Guyton and Hall, 2011). The parasympathetic nervous system is responsible for maintaining baseline airway tone and activation of bronchial muscarinic receptors produces contraction of bronchial smooth muscle. On the other hand, activation of bronchial smooth muscle β_2-adrenergic receptors increases intracellular cAMP levels with subsequent activation of cAMP-dependent protein kinase A, which results in relaxation of bronchial smooth muscle (Figure 7.3).

Epinephrine and isoproterenol are potent bronchodilators, whereas NE exerts less of an effect due to its limited affinity for β_2-adrenergic receptors (Boushey, 2007). Several selective β_2-adrenergic receptor agonists are available for use in veterinary patients. Terbutaline is commonly used for small animal patients, can be administered parenterally or orally, and is useful for the treatment of airway constriction in dogs and cats (Boushey, 2007). In equine patients albuterol can be administered as a short-acting (1–2 hour) aerosolized bronchodilator for conditions that involve airway obstruction (bronchoconstriction) (Rush et al., 1999). Clenbuterol is an alternate bronchodilator prepared for oral administration as a syrup. A significant advantage of clenbuterol is a longer duration of action (12 hours). Clenbuterol is FDA approved for use in horses with airway constriction. It should be noted that clenbuterol is illegal for use in food-producing animals (Boushey, 2007; Ainsworth and Cheetham, 2010).

Sympathomimetics can be administered parenterally or by aerosol formulation to achieve rapid and effective bronchodilation for the treatment of allergic reactions or status asthmaticus. The selective β_2-adrenergic receptor agonists do not elicit the same number of additional physiological responses as do EPI and isoproterenol (Boushey, 2007; Guyton and Hall, 2011).

Arterial Blood Pressure Regulation and Sympathomimetics

A male Labrador retriever presented with a cranial cruciate rupture and was prepared for surgery. The patient was premedicated with hydromorphone, anesthesia was induced with propofol, and was maintained with isoflurane (volatile anesthetic) in oxygen. During the 20 minutes after initiation of isoflurane administration, systolic blood pressure gradually decreased from an initial level of 100 mmHg to 75 mmHg. The depth of anesthesia was determined to be appropriate, the heart rate was 92 beats/minute and the patient was normovolemic. What pharmacological interventions might be appropriate to treat the arterial hypotension in this patient?

When choosing a drug to treat hypotension, potential causes of the reduction in arterial blood pressure need to be considered. Isoflurane is a potent vasodilator, even at subanesthetic doses, and a reduction in peripheral vascular resistance is the predominant mechanism for the decrease in blood pressure. In addition, although cardiac output is preserved at low-dose isoflurane, the maintenance of surgical anesthesia for the type of surgery described for this condition may require higher doses of isoflurane, which are known to reduce cardiac output secondary to direct depressant effects on myocardial contractility. Under the conditions of this clinical case the isoflurane-induced hypotension would most effectively be ameliorated by a drug that can mediate increases in systemic vascular resistance and cardiac output; therefore, sympathomimetics that activate both α_1- and β_1-adrenergic receptors would be considered.

The drugs most frequently selected for treatment of hypotension in veterinary medicine under the described clinical situation would include dopamine, ephedrine, and dobutamine. Dopamine is an agonist at DA_1 receptors and the intravenous administration of low-dose dopamine (approximately, 0.5 to 2 μg/kg/min) promotes vasodilation of numerous vascular beds, including the renal and splanchnic vasculatures, an effect

that would not be consistent with the express purpose of reversing isoflurane-induced hypotension. However, dopamine demonstrates complex, dose-dependent adrenergic receptor agonist properties. At moderate infusion rates (2 to 10 μg/kg/min) dopamine activates cardiac β_1-receptors, leading to increases in cardiac contractility, heart rate, and cardiac output. At higher rates of infusion (10 to 20 μg/kg/min), dopamine activates vascular α_1-adrenergic receptors, leading to vasoconstriction and increased peripheral vascular resistance. At the higher dose, dopamine remains an agonist at cardiac β_1-adrenergic receptors; therefore, high-dose dopamine infusion increases peripheral vascular resistance and enhances cardiac contractility, positioning dopamine as a suitable choice for isoflurane-induced hypotension. Dopamine has a short half-life and is given by a constant-rate intravenous infusion.

Ephedrine is a noncatecholamine drug that is an agonist at α_1-, β_1-, and β_2-adrenergic receptors, and can also induce the release of NE from postganglionic sympathetic nerve terminals. The cardiovascular effects of ephedrine have been shown to be dose dependent in isoflurane-anesthetized dogs (Wagner et al., 1993). Low-dose ephedrine (0.1 mg/kg) produces transient yet substantial increases in mean arterial pressure, cardiac index, and stroke volume, as well as decreases in heart rate and systemic vascular resistance. These data suggest that low-dose ephedrine may activate primarily cardiac β_1- and vascular β_2-adrenergic receptors. At a higher dose (0.25 mg/kg) ephedrine induces more marked and sustained increases in mean arterial pressure, cardiac index, and stroke volume, and also mediates an increase in systemic vascular resistance, suggesting that higher doses of ephedrine likely activates vascular α_1-adrenergic receptors. The combined cardiovascular effects produced by high-dose ephedrine make this drug an effective treatment option for isoflurane-induced hypotension.

Although at clinical doses dobutamine can act as an agonist at β_2- and α_1-adrenergic receptors, for the most part this drug demonstrates a relative selectivity for β_1-adrenergic receptors, especially those subserving changes in myocardial contractility (rather than cardiac rate). Thus, dobutamine administration increases myocardial contractility, cardiac index, and stroke volume. In this regard, dobutamine is particularly useful in treating low cardiac output flow states such as congestive heart failure or dilated cardiomyopathy. However, the rather modest agonistic properties at α_1-adrenergic receptors, at least in dogs, often make the use of dobutamine a less effective treatment option for isoflurane-induced hypotension (Rosati et al., 2007).

Epinephrine, NE, and phenylephrine are additional sympathomimetics that can increase arterial blood pressure, although they are not generally used under the conditions of isoflurane-induced hypotension. However, EPI is effective in life-threatening circumstances such as asystole or anaphylaxis. EPI is a potent cardiac stimulant and vasoconstrictive agent and can reverse the marked hypotension and cardiac irregularities associated with anaphylactic shock. Blood pressure responses to a given infusion rate of EPI are often associated with a substantial degree of interpatient variability; therefore, arterial blood pressure must be carefully monitored with EPI administration. EPI is a potent renal vasoconstrictor and can result in significant decreases in renal blood flow at higher doses. Additionally, some inhalation anesthetics, predominately halothane, can sensitize the heart to catecholamines. EPI decreases the refractory period and the heart is more susceptible to ventricular arrhythmias.

Because of its potent α_1-adrenergic receptor agonistic activity, NE is used clinically in hypotensive situations. NE administration induces marked constriction of arteries and veins and is used to support vascular resistance in circumstances such as vascular collapse secondary to sepsis. Like EPI, it is a potent constrictor of renal and mesenteric vascular beds, which may ultimately lead to decreased perfusion of those organ systems. Administration of selective α_1-adrenergic agonists, such as phenylephrine, produce peripheral vasoconstriction and are used in circumstances where cardiac output is adequate such as the hypotension resulting from spinal or epidural local anesthesia and subsequent block of sympathetic nerves.

Adrenergic Drugs and Urinary Incontinence

Adrenergic receptors are expressed at numerous sites in the urinary tract including the ureters (β_2 receptors), detrusor muscle of the bladder body (β_2 and β_3 receptors), bladder base (α_1 receptors), and the internal urethral sphincter (α_1 receptors). Stimulation of sympathetic nerves innervating these sites or activation of these receptors secondary to administration of sympathomimetics produces smooth muscle relaxation of the bladder body via β_2-adrenergic receptors (and β_3 receptors), and smooth muscle contraction at the bladder base and the internal urethral sphincter by activation of α_1-adrenergic receptors. The latter mechanism is the basis for treatment of urinary incontinence in veterinary patients using the α_1-adrenergic receptor agonists.

Urethral sphincter incompetence is the most common cause of acquired urinary incontinence in female dogs and cats. A single daily dose of phenylpropanolamine results in an increase in urethral pressure values and improved urinary continence in most affected dogs (Claeys et al., 2001). As expected, phenylpropanolamine administration can produce significant increases in arterial blood pressure, mediated by activation of vascular smooth muscle, and a baroreflex-mediated compensatory decrease in heart rate (Carofiglio et al., 2006). The consequences of phenylpropanolamine-induced

increases in systemic vascular resistance and afterload should be considered when prescribing this drug for urinary incontinence.

Clinical Applications of Sympathomimetic-Induced Vasoconstriction

Drugs that are selective α-adrenergic agonists, or have potent α-adrenergic activity and minimal β_2-adrenergic effects, can cause significant vasoconstriction and are used for a number of clinical applications. These include the addition of EPI to local anesthetics to delay removal of the anesthetic from the site of injection, thereby prolonging its effect; the reduction of local perfusion to affect hemostasis in areas such as the nose or mouth; and the treatment of hypotension secondary to marked vasodilation but in the presence of normal or increased cardiac output, a response profile that occurs after sympathetic nerve blockade with spinal or epidural anesthesia.

α_1-adrenergic receptors are expressed on the smooth muscle of the splenic capsule and SNS activation to this target produces smooth muscle contraction, as does administration of sympathomimetics such as phenylephrine. Splenic smooth muscle contraction discharges red blood cells into the circulation and reduces the size of the spleen. Reduction of splenic size produced in response to the intravenous administration of the α_1-adrenergic selective receptor agonist phenylephrine is often used as part of the therapy for treatment of nephrosplenic entrapment in horses. This condition occurs when the left ventral and dorsal colon migrate between the spleen and the body wall and become entrapped over the nephrosplenic ligament, resulting in an obstruction of the large colon (Hardy et al., 2000). Phenylephrine administration reduces splenic area and thickness, and may increase the success of nonsurgical correction (Hardy et al., 1994). As expected, phenylephrine infusion increases peripheral vascular resistance and arterial blood pressure, and produces a marked baroreflex-mediated reduction in heart rate. The use of phenylephrine as a treatment option for nephrosplenic entrapment has been implicated in producing life-threatening internal hemorrhage in aged horses, and the use of this sympathomimetic as a treatment modality in older horses should be carefully considered (Frederick et al., 2010).

Peripheral and Central Sites Mediate Cardiovascular Responses to α_2-Receptor Activation

Circulating catecholamines do not readily cross the blood–brain barrier; however, certain sympathomimetic agents can gain access to the CNS and activate adrenergic receptors found in the brain and spinal cord. α_2-adrenergic receptor agonists (e.g., xylazine, detomidine, medetomidine, and dexmedetomidine) are routinely used in veterinary patients for sedation and analgesia. The sedative and analgesic effects of these agents are consistent with activation of central neural receptors and pathways. Accompanying the clinically desired sedative and analgesic effects are pronounced cardiovascular and sympathetic neural changes in response to administration of α_2-adrenergic selective receptor agonists (Kenney et al., 2014). The cardiovascular responses provide a window for characterizing physiological responses produced by activation of peripheral and central α_2-adrenergic receptor subtypes.

The α_2-adrenergic receptor family includes three subgroups: $\alpha_{2A,}$ $\alpha_{2B,}$ and $\alpha_{2C.}$ α_2-adrenergic receptors are present in vascular smooth muscle, on the terminals of postganglionic sympathetic nerve fibers, and in the central nervous system, including in the brainstem. The intravenous administration of selective α_2-adrenergic receptor agonists produce a biphasic cardiovascular profile, an initial transient hypertension followed by a longer lasting hypotension. The following description of the biphasic cardiovascular response is based on the intravenous administration of dexmedetomidine, and is representative of responses induced by α_2-adrenergic selective receptor agonists.

Activation of α_2-adrenergic receptors by intravenous dexmedetomidine administration produces vasoconstriction of arterial smooth muscle, which increases peripheral vascular resistance and produces an immediate increase in arterial blood pressure. It is thought that the dexmedetomidine-induced contraction of vascular smooth muscle is mediated by activation of α_{2B}-adrenergic receptors. The abrupt increase in arterial blood pressure activates the arterial baroreflex, which elicits a reflex-mediated increase in cardiac vagal nerve activity and a reduction in heart rate. Circulating dexmedetomidine rapidly gains access to CNS α_2-adrenergic receptors and activation of brainstem receptors produce inhibition of sympathetic nerve outflow and activation of parasympathetic nerve outflow. It is thought that the central neural effects of dexmedetomidine on sympathetic and parasympathetic neural circuits are mediated by activation of α_{2A}-adrenergic receptors. The dexmedetomidine-induced hypotensive response is mediated by the sustained reduction in sympathetic nerve outflow, as well as the sustained increase in parasympathetic nerve outflow, which mediates a reduction in heart rate.

Ophthalmology and Adrenergic Agonists

A 9-year-old golden retriever presented with cloudy lenses and the owner reported the animal had decreased vision. The ophthalmic examination revealed bilateral

advanced immature cataracts. To facilitate intraoperative mydriasis (pupillary dilation), the selective α_1-adrenergic receptor agonist, phenylephrine, is used in dilation protocols for dogs prior to cataract surgery. α_1-adrenergic receptors are expressed on the radial dilator muscle of the iris (iris dilator muscle) and on conjunctival blood vessels. SNS activation to this target causes mydriasis, as does α_1-adrenergic receptor activation by sympathomimetics such as phenylephrine. Following topical application, phenylephrine produces contraction of the smooth muscle of the conjunctival blood vessels and contraction of the iris dilator muscle, causing blanching of the conjunctival vasculature and pupillary dilation, respectively. Topical phenylephrine should be used with caution in small patients due to the potential for phenylephrine to enter the systemic circulation and induce arterial hypertension secondary to activation of peripheral vascular α_1-adrenergic receptors (Pascoe et al., 1994). Phenylephrine is commercially available in 2.5% and 10% solutions.

A dilute solution of phenylephrine may also be used in the neuroanatomic localization of Horner's syndrome, an oculosympathetic palsy (Webb and Cullen, 2013). After application of a dilute solution of phenylephrine to both eyes in unilateral postganglionic Horner's syndrome, the affected pupil should dilate within 20 minutes and other clinical signs (ptosis, enophthalmia, and third eyelid elevation) will improve or completely resolve.

Apraclonidine and brimonidine are α_2-agonists that have intraocular pressure lowering effects in humans, secondary to increasing the outflow of aqueous humor from the eye. These medications are not recommended for veterinary patients due to systemic side effects and lack of significant intraocular pressure lowering effects (Miller and Rhaesa, 1996; Gelatt and MacKay, 2002).

Use of β-Adrenergic Agonists in Food Production

Beta-adrenergic receptor agonists (βAA) have been used as growth promotion agents for livestock in the United States since 1999 when ractopamine hydrochloride was approved in swine (FDA, 1999). Since that time, ractopamine has been approved for use in cattle and turkeys and a second βAA, zilpaterol, was approved for use in cattle in the United States, Mexico, Canada, and South Africa (FDA, 2003; FDA, 2006). Ractopamine is primarily a β_1-adrenergic receptor agonist with some β_2-receptor activity. Zilpaterol is primarily a β_2-adrenergic receptor agonist. It is also important to note that not all βAA are approved for use in food animals. In the United States, it is illegal to feed a βAA or any other drug in a manner that is inconsistent with its labeling as approved by the FDA. Extra-label drug use is strictly prohibited. These drugs are fed at the end of the animals feeding period only. The use of these drugs in food animals is further discussed in Chapter 52.

The muscle growth in response to βAA treatment appears to be a true muscle hypertrophy, such that muscle fibers increase in diameter due to increased protein synthesis and decreased protein degradation without the incorporation of additional DNA from satellite cells (Yang and McElligott, 1989). However, with longer duration of βAA administration the rate of hypertrophy cannot be maintained without additional DNA and the responsiveness to the βAA is dampened and the accretion of skeletal muscle decreases. The response of muscle cells to βAA stimulation is highly dependent on receptor presence, which is influenced by animal maturity and receptor density, which can be reduced with chronic βAA administration. Additionally, the muscle hypertrophy within the carcass is not evenly distributed, as skeletal muscles that are used for locomotion, which typically have an increased blood supply, have a greater degree of hypertrophy compared to apaxial muscles (Hilton et al., 2010). Muscle fiber types are also differentially affected by β_2AA administration as the increase in muscle fiber diameter is greater in type IIA fibers compared with type I fibers. Beta receptor specificity of skeletal muscle varies between species used for food production. Ruminants tend to have an increased number of β_2-adrenergic receptors than other species. The distribution of subtypes of receptors also varies with the age of the animal, with a more pronounced response to β_2AA in yearling cattle, when compared to calves or fetal responses (Beermann, 2002; Johnson et al., 2014).

Glycogenolysis is increased by βAA stimulation of muscle (Etherton, 1994). Glycogenolytic effects are induced by the phosphorylation of glycogen phosphorylase, which converts glycogen, an intracellular stored form of glucose, to monomeric glucose-6-phosphate. Glucose-6-phosphate is a substrate source for glycolysis, or anaerobic respiration, resulting in the production of ATP and pyruvate. Pyruvate will then enter the Krebs cycle and undergo aerobic respiration, assuming that enough cellular oxygen is available. If the cell is in a hypoxic state, pyruvate will be converted to lactate by lactate dehydrogenase. Lactate will then accumulate and be removed from the cell via blood circulation. The end result of βAA-mediated glycogenolysis is to make an energy source stored within the muscle cell rapidly available.

In adipose cells, βAA promote lipolysis associated with stimulating triacylglycerol hydrolysis and inhibiting lipogenesis stimulated through the β-receptor–G protein–cAMP–PKA pathway (Lafontan et al., 1988; Bergen, 2001; Johnson et al., 2014). The βAA-induced increase in cAMP results in the phosphorylation of acetyl-CoA carboxylase inhibiting the de novo biosynthesis of fatty acids. The net response of adipose tissue

to βAA is lipolytic and causes a release of fatty acids, which may be used as an energy source by conversion to acetyl-CoA (Blum and Flueckiger, 1988; Johnson et al., 2014). High concentrations of acetyl-CoA can inhibit conversion of pyruvate to acetyl-CoA, forcing pyruvate to be metabolized to lactate by lactate dehydrogenase and potentially increasing metabolic acidosis in cases where lactic acidosis is present, such as hypoxic situations (Haffner and Kendall, 1992).

β-adrenergic receptor agonists exert significant cardiovascular effects as described earlier in this section. The use of ractopamine and zilpaterol has been shown to increase heart rate in cattle, with the most significant increase at the beginning of the feeding period.

Adrenergic-Receptor Antagonists

The physiological effects produced by activation of the SNS or the administration of sympathomimetic drugs can be diminished by blocking adrenergic receptors (adrenoceptor antagonists), decreasing the amount of NE released presynaptically, or suppressing sympathetic outflow from central sympathetic neural circuits. Drugs that inhibit the interaction of NE, EPI, and other sympathomimetics with α- and β-adrenergic receptors are termed adrenergic receptor antagonists or adrenoceptor antagonists.

Adrenergic receptor antagonists demonstrate selectivity and specificity for the various adrenergic receptors, and drugs are classified based on their antagonism of α- or β-adrenergic receptors. Antagonism of peripheral dopaminergic receptors is of little clinical relevance in veterinary medicine at the present time. Blockade of dopaminergic receptors in the CNS have significant clinical relevance and these drugs are discussed in Chapter 9. The relative selectivity for adrenergic receptor antagonists are presented in Table 7.6.

Table 7.6 Classification of adrenergic receptor antagonists and their relative selectivity for specific adrenergic receptors

Drugs	Receptor selectivity
Alpha antagonists	
Prazosin, Terazosin, Doxazosin	$\alpha_1 >>>> \alpha_2$
Phenoxybenzamine	$\alpha_1 > \alpha_2$
Phentolamine	$\alpha_1 = \alpha_2$
Atipamezole, Yohimbine, Tolazoline	$\alpha_2 >> \alpha_1$
Mixed antagonists	
Carvedilol	$\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$
Beta antagonists	
Propranolol, Timolol	$\beta_1 = \beta_2$
Metoprolol, Atenolol, Esmolol, Betaxolol	$\beta_1 >>> \beta_2$

Alpha-Adrenergic Receptor Antagonists

Alpha-adrenoceptor antagonists are a chemically heterogeneous and structurally diverse group of drugs. Some of the more clinically relevant groups include β-haloethylamine alkylating agents (e.g., phenoxybenzamine), imidazoline analogs (e.g., phentolamine and tolazoline), piperazinyl quinazolines (e.g., prazosin), and indole derivatives. These drugs are predominantly competitive antagonists at α-adrenergic receptors, with the exception of phenoxybenzamine which irreversibly binds to the α-adrenergic receptor. The relative receptor affinity of individual α_1- and α_2-receptor antagonists varies markedly, and recent research advances have developed drugs that discriminate among the receptor subtypes. Additionally, the phenothiazine tranquilizers (e.g., acepromazine) demonstrate substantial α-adrenergic receptor blocking effects, but since this is generally considered a side effect of these drugs, as opposed to an indication for their use, these drugs will not be discussed in this chapter.

Cardiovascular Effects

Some of the most significant clinical and therapeutic effects, particularly of the α_1-antagonists, target the cardiovascular system. Systemic administration of α_1-adrenergic receptor antagonists produces dilation of both arterial and venous vessels, resulting in reduced blood pressure secondary to decreases in peripheral vascular resistance. As expected, administration of α_1-adrenergic receptor antagonists block or eliminate the vasoconstriction and blood pressure responses produced by exogenous administration of sympathomimetic drugs or neurotransmitters. For example, increases in peripheral vascular resistance and subsequent elevations in blood pressure produced by phenylephrine (selective α_1-adrenergic receptor agonist) administration are completely eliminated by pretreatment with an α_1-adrenergic antagonist. Following pretreatment with an α_1-adrenergic receptor antagonist, increases in peripheral vascular resistance to NE administration are eliminated, which markedly attenuates NE-induced increases in arterial blood pressure despite its effect to activate cardiac β_1-adrenergic receptors and increase heart rate and cardiac contractility. Furthermore, following pretreatment with an α_1-adrenergic receptor antagonist, administration of EPI may induce a reduction in peripheral vascular resistance and marked vasodilation mediated by activation of β_2-adrenergic receptors, resulting in decreased levels of arterial blood pressure. This effect is known as EPI reversal and can occur not only with exogenous administration of the sympathomimetic following administration of an α_1-adrenergic receptor antagonist, but may also occur when administering an α_1-adrenergic

receptor antagonist to a patient with high circulating levels of EPI.

Noncardiovascular Effects

Activation of sympathetic nerves innervating the urethra produces contraction of urethral smooth muscle by activation of α_1-adrenergic receptors. α_1-adrenergic receptor antagonists decrease resistance to urine flow. α_{2B}-adrenergic receptors have a role in platelet aggregation; however, the clinical significance of blocking these receptors and the role it might play in antiaggregant therapy is not well understood. α_2-adrenergic receptors inhibit insulin secretion from pancreatic islet cells and antagonism of these receptors may stimulate insulin release. Other effects produced by α-adrenergic receptor antagonists include protrusion of the third eyelid, miosis, and nasal stuffiness. α_2-adrenergic receptor agonists are frequently used to provide sedation and analgesia to veterinary patients, and there are several α_2-adrenergic receptor antagonists, that can reverse the sedation mediated by the α_2-adrenergic receptor agonists. Specific physiological effects of available α_2-adrenergic receptor antagonists will be discussed under the section on specific agents.

Specific Agents and Clinical Uses

Nonselective α_1-α_2-Antagonists

Phenoxybenzamine and phentolamine are examples of α-adrenergic antagonists with effects at both α_1- and α_2-adrenergic receptors. There are few clinical indications for the use of phentolamine in veterinary medicine and formulations of this drug are no longer consistently available in the United States.

Phenoxybenzamine binds covalently to α-adrenergic receptors and produces an irreversible block. Restoration of physiological responses to activation of α-adrenergic receptors following phenoxybenzamine administration requires the synthesis of new α-adrenergic receptors. The α-adrenergic antagonistic effects of phenoxybenzamine are more substantial with α_1- than α_2-adrenergic receptors. Phenoxybenzamine demonstrates a variety of other pharmacological effects including inhibiting the reuptake of NE at presynaptic nerve terminals and acting to various degrees as an antagonist at histamine, acetylcholine, and serotonin receptors. The predominant, and perhaps only, use of phenoxybenzamine in veterinary medicine is to manage the symptoms of catecholamine excess in the treatment of patients with a pheochromocytoma (Herrera et al., 2008; Agrawal et al., 2014).

Phenothiazine tranquilizers are also potent, nonselective α-adrenergic receptor antagonists. The CNS effects of these drugs underlie their use as tranquilizers; however, the decrease in peripheral vascular resistance secondary to antagonism of α-adrenergic receptors is clinically significant and should be considered when selecting these drugs for tranquilization or anesthetic premedication. Similarly, the tetracylic antidepressant trazodone, used for its sedative properties in dogs, can antagonize α_1-adrenergic receptors.

Selective α_1-Antagonists

Prazosin is a competitive antagonist with a marked selectivity for the α_1-adrenergic receptor. Historically, prazosin has been used for the treatment of hypertension or to reduce afterload in patients with heart failure, but there are now more efficacious therapies. Currently, prazosin is used to decrease resistance to urine flow in the proximal and prostatic urethra in dogs with functional urethral obstruction, prostatic hyperplasia, and idiopathic vesicourethral reflex dyssynergia, or to facilitate voiding in animals with upper motor neuron bladders (detrusor–external sphincter dyssynergia) due to spinal trauma or intervertebral disc disease (Fischer et al., 2003; Haagsman et al., 2013). The efficacy of this drug in the treatment of urethral obstruction in cats is debated because smooth muscle is confined to the proximal third of the cat urethra, whereas urethral obstructions in these animals generally occur in the distal urethra, which is composed of skeletal muscle (Hetrick and Davidow, 2013; Lulic et al., 2013). Terazosin, doxazosin, and alfuzosin are reversible α_1-adrenergic receptor antagonists with similar physiological effects to prazosin, but with different pharmacokinetic profiles. Specific information regarding the use of these drugs in veterinary patients is limited.

Tamsulosin and silodosin are α_1-adrenergic receptor antagonists that demonstrate a degree of α_1-adrenergic receptor subtype selectivity. Tamsulosin is a second-generation α_1-adrenergic receptor antagonist that was developed with the goal of decreasing the frequency of orthostatic hypotension. Tamsulosin has a higher affinity for α_{1A} and α_{1D} receptors than for the α_{1B} subtype. The α_{1A}-adrenergic receptor subtype is a primary adrenergic receptor subtype in the urethra and prostate of humans and dogs, whereas the α_{1B}-adrenergic receptor subtype is a principal subtype in vascular smooth muscle in these species (Kobayashi et al., 2009). Silodosin is a third-generation, highly selective α_{1A} receptor antagonist. Dogs with and without prostatic hyperplasia demonstrated similar effects between silodosin and tamsulosin on decreasing intraurethral pressure, but silodosin had less of an effect on blood pressure (Kobayashi et al., 2009). Silodosin suppresses phenylephrine-induced increases in intravesical ureteral pressure in dogs and may facilitate passage of distal ureteral stones (Kobayashi et al., 2010). Although orthostatic hypotension is not as clinically significant in veterinary patients, the potential for effects on peripheral vasculature when using these drugs should be considered.

Selective α_2-Antagonists

Yohimbine, tolazoline, and atipamezole are α_2-adrenergic receptor antagonists that are used to reverse the sedative effects of α_2-adrenergic agonists such as xylazine, medetomidine, dexmedetomidine, detomidine, and romifidine. Reversal of α_2-agonist-mediated sedation and off-label therapy of certain drug intoxications are currently the only therapeutic indications for these drugs in veterinary medicine.

Yohimbine was the prototype for selective α_2-adrenergic receptor antagonists and is an indolealkylamine alkaloid that is found in the bark of the tree *Pausinystalia yohimbe* and in *Rauwolfia* root. Yohimbine also demonstrates a degree of antagonistic activity at serotonin receptors. Yohimbine is used in veterinary patients to reverse sedation from α_2-adrenergic agonists, although less frequently in small animal patients since the introduction of atipamezole. The efficacy of yohimbine for reversal of xylazine sedation in cattle is variable.

Tolazoline belongs to the synthetic group of competitive α_2-adrenergic receptor antagonists known as the imidazoline derivatives. Tolazoline is a mixed α_1- and α_2-adrenergic receptor antagonist, and the approved product, Tolazine Injection, is licensed for reversing xylazine in horses. This product is used off-label to reverse other α_2-adrenergic agonists in equids, such as detomidine, and for the reversal of α_2-agonist sedation in other large animal species and wildlife, where the cost of atipamezole may be a concern (Powell, 1998). The use of tolazoline or other α_2-adrenergic receptor antagonists to reverse detomidine sedation is incomplete and transient.

Atipamezole is an α_2-adrenergic receptor antagonist with an imidazole structure and a binding affinity and α_2/α_1 selectivity ratio much higher than those of yohimbine or tolazoline. Atipamezole is not selective for subtypes of α_2-adrenergic receptors (Pertovaara et al., 2005). Atipamezole was originally approved to reverse the sedative and analgesic effects of medetomidine hydrochloride. Atipamezole rapidly reverses sedation induced by α_2-adrenoceptor agonists, at one-tenth the dose required for yohimbine. Atipamezole at clinically relevant doses causes few cardiovascular effects despite the potential increase in NE following blockade of presynaptic α_2-adrenergic receptors. Atipamezole reverses the bradycardic effects produced by α_2-adrenergic receptor agonists. Atipamezole has been used off-label in dogs to treat intoxication by imidazoline decongestants (e.g. oxymetazoline, tetrahydrozoline, xylometazoline) that are α_2-adrenoceptor agonists used topically for relief of nasal congestion or conjunctival redness. Atipamezole has also been used off-label to treat intoxication from the insecticide/acaricide, amitraz, which is an α_2-adrenergic receptor agonist (Bahri, 2008).

Clinical Use of α-Adrenergic Receptor

It is not uncommon for small animal patients to develop a urethral obstruction, a condition that is often relieved with a urethral catheter. Unfortunately, recurrence of urethral obstruction following removal of the urinary catheter is a frequent complication (Hetrick and Davidow, 2013). Activation of sympathetic nerves to the bladder facilitates relaxation of the bladder body smooth muscle through activation of β_2- and β_3-adrenergic receptors, and enhances contraction of the smooth muscle of the proximal urethra by activation of α_1-receptors.

Urethral spasm is thought to play a role in urethral obstruction recurrence and drugs that mediate urethral smooth muscle relaxation by α_1-adrenergic receptor blockade are a useful component of postobstruction therapy. The two most frequently used drugs in veterinary medicine are phenoxybenzamine and prazosin. Prazosin has a higher α_1-adrenergic receptor affinity, and administration of prazosin to dogs results in a greater reduction of urethral pressure than phenoxybenzamine (Fischer et al., 2003).

Important limitations to the use of α_1-adrenergic receptor antagonists for urethral relaxation are the cardiovascular effects. Vascular smooth muscle tone is reduced with α_1-adrenergic receptor blockade and significant decreases in systolic, diastolic, and mean arterial blood pressure can occur. Newer selective α_1-adrenergic receptor antagonists, such as silodosin, have less of an effect on blood pressure than nonselective antagonists like prazosin, but clinical data for use of α_{1A} selective antagonists in veterinary medicine at this point is limited.

Beta Adrenergic Receptor Antagonists

Beta-adrenergic receptor antagonists are used widely in human medicine because of their efficacy in the treatment of hypertension, ischemic heart disease, congestive heart failure, and certain cardiac arrhythmias. While some of these clinical entities are also indications for the use of β-adrenergic antagonists in veterinary patients, the routine use of β-blockers in veterinary medicine remains somewhat controversial based on the relative dearth of information determining the clinical efficacy of these drugs in veterinary patients.

β-adrenergic receptor antagonists are structurally similar to catecholamines and competitively reduce receptor occupancy by catecholamines and other β-adrenergic agonists. Most of the available drugs are pure antagonists; however, there are several that are partial β-adrenergic receptor agonists (e.g., pindolol and acebutolol). These drugs can cause partial activation of β receptors, although not to the level of full agonists such as EPI, and inhibit the activation of β-adrenergic receptors in the presence of high levels of EPI and NE. This effect of some β-adrenergic antagonists is often

Table 7.7 Pharmacodynamic characteristics of adrenergic receptor antagonists commonly used in veterinary medicine

Drugs	β-Receptor selectivity	α_1-Receptor block	Intrinsic sympathetic activity	Local anesthetic activity
Atenolol	β_1	No	No	No
Betaxolol	β_1	No	No	Slight
Carvedilol	None	Yes	No	No
Celiprolol	β_1	No	Yes	No
Esmolol	β_1	No	No	No
Metoprolol	β_1	No	No	Yes
Pindolol	None	No	Yes	Yes
Propranolol	None	No	No	Yes
Sotalol	None	No	No	No
Timolol	None	No	No	No

referred to as intrinsic sympathetic activity (ISA). Drugs with ISA maintain slight basal stimulation of the β_1- and β_2-adrenergic receptors, and this modest β-mediated activity may prevent profound bradycardia or negative inotropy in the resting heart, constriction of bronchioles, or up-regulation of β-adrenergic receptors that can result from long-term therapy with β-adrenergic receptor antagonists. Whether there are clinical advantages or indications for using a drug with ISA remains unclear.

Some β-adrenergic antagonists exhibit membrane-stabilizing activity, similar to local anesthetics, and other β-adrenoceptor blockers are classified as inverse agonists (e.g., carvedilol). Receptors exist in a conformational equilibrium between inactive and active states and this equilibrium shifts with the binding of a ligand. Inverse agonists favor the inactive conformation and will decrease the propensity of the receptor to assume a conformation that is required for stimulation of cAMP, thereby reducing the constitutive activity of the β-adrenergic receptor (Khilnani and Khilnani, 2011).

β-adrenergic receptor antagonists are frequently categorized by their affinity for β-adrenergic receptor subtypes, presence or absence of ISA, and their membrane stabilization effects (Table 7.7). Drugs differ in their relative affinities for β_1 and β_2 receptors. Some have higher affinity for β_1- than for β_2-adrenergic receptors, but none of the clinically available drugs are completely specific for a given β-adrenergic receptor, and the ultimate clinical effect will be dose dependent.

Cardiovascular Effects

The antagonism of β-adrenergic receptors can substantially affect cardiovascular regulation, although there are numerous factors that can influence these responses, including: species differences, human and animal differences, the presence of background cardiovascular disease, and the specific antagonist administered. General cardiovascular effects are reviewed here. Antagonism of cardiac β-adrenergic receptors slows atrioventricular conduction, and produces negative inotropic and chronotropic effects, which may mediate a reduction in cardiac output (Muir et al., 1996). Beta-blocking drugs when administered chronically may reduce blood pressure in hypertensive patients, although they generally do not reduce blood pressure in normotensive patients. It is important when reviewing the effects of individual drugs to distinguish between effects in normal subjects and subjects with cardiovascular disease. Increased peripheral vascular resistance is often an acute effect observed following administration of β-adrenergic receptor antagonists, an effect that is mediated in part by blockade of vascular β_2 receptors. However, with long-term use of β-adrenergic receptor antagonists, peripheral vascular resistance returns to initial values or decreases in patients with hypertension. The mechanism for this response is not well understood, but may involve an effect on the release of renin from the juxtaglomerular apparatus. Activation of the SNS innervation to the kidney increases renin release via activation of β_1-adrenergic receptors, and this effect is reduced with β-adrenergic receptor blockade. In addition, some β-blockers, such as labetalol and carvedilol, also demonstrate antagonistic properties at α_1-adrenergic receptors, which may contribute to a reduction in peripheral vascular resistance.

Pulmonary Effects

Nonselective β-adrenergic receptor antagonists will block β_2-adrenergic receptors in bronchial smooth muscle leading to bronchoconstriction and increased airway resistance. In normal subjects this effect is minimal but in patients with asthma or chronic obstructive pulmonary disease it can be life-threatening. The implications of this in veterinary medicine have not been explored. With regards to recurrent obstructive pulmonary disease, aerosol administration of propranolol or atenolol during an acute airway obstruction can reduce dynamic compliance, whereas during clinical remission the drugs may exert little effect. The clinical indications for the use of β-adrenergic receptor antagonists in equine patients are few, and the effects of β-adrenergic receptor antagonists in cats with feline lower airway disease have not been studied.

Effects on the Eye

Topical administration of β-adrenergic receptor antagonists reduce intraocular pressure by blocking NE released from sympathetic nerve endings from acting on β-adrenergic receptors located on the ciliary epithelium, thereby mediating a decrease in aqueous humor production.

Metabolic and Endocrine Effects

β-adrenergic receptor antagonists inhibit the activation of lipolysis and glycogenolysis produced by catecholamines and sympathomimetic drugs. Nonselective β-adrenergic receptor antagonists may delay recovery from hypoglycemia in patients with type 1 diabetes mellitus, an effect that appears to be less severe in type 2 diabetic patients. β_1-selective adrenergic receptor antagonists are less likely to inhibit the recovery of blood glucose levels from an acute bout of hypoglycemia.

Specific Drugs

Beta-adrenergic receptor antagonists are classified as nonselective β-adrenergic receptor antagonists (first generation), β_1-selective receptor antagonists (second generation), and nonselective or subtype selective β-adrenergic receptor antagonists with additional cardiovascular actions unrelated to β-adrenergic receptor blockade (third generation). The receptor specificity and other nonadrenergic-related effects of several β-adrenergic receptor antagonists are summarized in Table 7.7. Clinically relevant information for many of these drugs is lacking due to the fact that relatively few controlled trials have been completed in animals with naturally occurring disease. Drugs that have been used most frequently in veterinary patients include propranolol, atenolol, esmolol, metoprolol, and carvedilol.

Nonselective β-adrenergic Receptor Antagonists

Propranolol is the prototype nonselective β-adrenergic receptor antagonist and in veterinary medicine has historically been used in the treatment of tachyarrhythmias, hypertension, hypertrophic and obstructive cardiomyopathies, and to treat the cardiovascular consequences of thyrotoxicosis or pheochromocytoma. Propranolol is a competitive antagonist with no intrinsic sympathomimetic activity. It does have membrane-stabilizing activity, but the therapeutic significance of this is not well defined.

Propranolol is well absorbed from the gastrointestinal tract following oral administration, is lipophilic, and demonstrates a large volume of distribution. However, this drug undergoes extensive hepatic metabolism, therefore its bioavailability is low. With the development of more selective β-adrenergic receptor antagonists, the use of propranolol is rarely indicated.

Selective β_1-Adrenergic Receptor Antagonists

Metoprolol is a selective β_1-adrenergic receptor antagonist that exhibits no intrinsic sympathomimetic activity. Metoprolol has a large volume of distribution and undergoes extensive oxidative metabolism in the liver, with less than 10% excreted unchanged in the urine. The elimination half-life of metoprolol in small animals is much shorter than that reported in people. Atenolol is a selective β_1-adrenergic receptor antagonist with no intrinsic sympathomimetic activity, a half-life that is longer than that of metoprolol, a large volume of distribution, and is characterized by minimal hepatic metabolism. Esmolol is an ultra-short-acting β_1-adrenergic receptor subtype selective antagonist with a half-life of about 10 minutes. Steady-state concentrations are quickly achieved during continuous intravenous infusions and its effects are terminated rapidly when the infusion is discontinued.

Third-Generation Nonselective Antagonists

Carvedilol is a nonselective β-adrenergic receptor antagonist and demonstrates modest α_1-adrenergic receptor antagonist properties. Carvedilol attenuates oxygen free radical-initiated lipid peroxidation and has antiproliferative effects. Carvedilol demonstrates membrane-stabilizing activity but no ISA. Carvedilol is rapidly absorbed following oral administration and is extensively metabolized.

Clinical Uses of β-Adrenergic Receptor

Acquired Cardiac Disease in Dogs

Studies in heart failure patients have demonstrated that β-adrenergic receptor antagonism with β_1-selective antagonists or the third-generation antagonist, carvedilol, reduce mortality and/or hospitalization and increase quality of life (Packer et al., 1996; Bristow, 1997). Initially the use of β-adrenergic receptor antagonists in the treatment of heart failure was avoided due to their negative inotropic effects, and the potential for bradycardia, cardiac failure, hypotension, and bronchospasm. However, the availability of more β_1-adrenergic receptor selective drugs or those with additional nonadrenergic related cardiac effects have reduced the potential for some of these complications.

Chronic valvular heart disease, specifically chronic mitral valvular disease, is the most common cause of heart disease and congestive heart failure in dogs, followed by dilated cardiomyopathy (DCM). Neuroendocrine mechanisms that occur during the development of heart failure include stimulation of the SNS, activation of the renin–angiotensin system, and release of vasopressin. High circulating concentrations of NE are evident in dogs with clinical chronic degenerative atrioventricular valve disease (Ware et al., 1990) and in

experimental models of mitral valve regurgitation (MR) (Tsutsui et al., 1994). Increased cardiac sympathetic nerve activity precedes the increase in circulating NE in subjects with primary MR. Although beneficial in the early stages to preserve inotropy, chronic sympathetic activation and elevated catecholamine levels can lead to cardiac hypertrophy and remodeling, myocyte necrosis, chronically elevated heart rate, elevated afterload, and cardiac arrhythmias. A protective adaptation of down-regulation of β_1-adrenoceptors has been described. One of the proposed mechanisms of systolic dysfunction seen with primary MR from chronic mitral valve disease (CMVD) is related to the increased sympathetic activity which results in a reduction of the number of cardiomyocytes and the number of contractile elements within each cardiomyocyte.

It has been proposed that β-adrenergic receptor antagonists might be a beneficial therapy in dogs with CMVD. One study reported a significant improvement of the left ventricular function in dogs with experimentally induced MR treated with the β antagonist atenolol (Nemoto et al., 2002). The administration of atenolol resulted in a decrease in cardiac interstitial NE in the experimental dogs. However, in a retrospective study of dogs with acquired DCM or CMVD, metoprolol administration was associated with no significant differences in cardiac dimensions as measured with echocardiography (Rush et al., 2002).

The effects of orally administered carvedilol were studied prospectively in dogs with mitral valve disease (Marcondes-Santos et al., 2007). The primary end points involved quality of life and sympathetic activation with secondary end points involving echocardiographic variables. The study period was 3 months and there was concurrent administration of benazepril or benazepril and digoxin depending on the severity of disease. The dogs treated with carvedilol had improvement in quality of life scores and a modest reduction in systolic blood pressure. Carvedilol did not improve the sympathetic activation and echocardiographic variables over the 3 months of treatment. Similarly, in a prospective study of dogs with DCM, there was no difference in echocardiographic and neurohormonal variables in the group treated with carvedilol. Additionally, there was no difference in owner-perceived quality of life (Oyama et al., 2007).

Administration of β-adrenergic antagonists is reported to initially worsen hemodynamics and contractile function in dogs with experimental MR. Acute decompensation has been reported in people and dogs with heart failure immediately after initiation of therapy (Kittleson and Hamlin, 1981; Fung et al., 2003). More recently, the phosphodiesterase III inhibitor, pimobendan, has shown clear benefits in dogs with CMVD or DCM and the use of β antagonists in these patients is now seldom indicated (Haggstrom et al., 2008; O'Grady et al., 2008).

Hypertrophic Cardiomyopathy and Ventricular Outflow Obstruction

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in cats and a significant percentage of cats with HCM will develop dynamic obstruction of the left ventricular outflow tract (LVOT). HCM and hypertrophic obstruction cardiomyopathy (HOCM) are characterized by concentric ventricular hypertrophy, dysfunction during diastole, and elevation of left ventricular end–diastolic pressure and left atrial pressure. Obstruction of the LVOT can be due to a single cause or a combination of causes that include asymmetric ventricular septal hypertrophy and anterior (cranial) motion of the mitral valve during systole (SAM).

The most commonly prescribed medications used to reduce dynamic LVOT obstruction in cats with HCM are β-adrenergic receptor antagonists, particularly atenolol. Echocardiographic evaluation of cats with HCM or HCOM given a single dose of atenolol revealed decreases in heart rate, peak velocity in the LVOT, systolic fractional shortening, and left atrial size. Atenolol consistently reduced, and in some cases relieved, LVOT obstruction (Blass et al., 2014). There are conflicting reports on the prognostic importance of SAM in cats with HCM and whether treatment with atenolol should be instituted in preclinical HCM remains controversial. It would be predicted that the negative chronotropic and inotropic effects would reduce peak velocity of blood flow at the LVOT which would, theoretically, decrease the force on the mitral valve leaflets against the septum and delay the development of SAM. The negative inotropic effect would decrease systolic fractional shortening and the potential for dynamic obstruction from the hypertrophied ventricular septum.

Subaortic stenosis (SAS) in dogs is a congenital cardiac abnormality that causes varying degrees of LVOT obstruction. The disease is characterized by an abnormal ridge of fibrous tissue below the aortic valve which results in a decreased cross-sectional area of the LVOT. The severity of disease and prognosis varies depending on the degree of stenosis and the subsequent pressure gradient across the stenosis. Dogs with a pressure gradient of less than 50 mmHg are considered to have mild disease, those with a gradient of 50–80 mmHg are classified as having moderate disease, and severe stenosis would be that which creates a gradient greater than 80 mmHg. Dogs with mild or moderate SAS are considered to have a good prognosis and no treatment is recommended unless symptomatic. Dogs with severe SAS have been empirically treated with beta blockers, most commonly atenolol. However, in a recent retrospective review, beta blocker treatment did not

influence survival in dogs with severe SAS (Eason et al., 2014).

Cardiac Arrhythmias

Beta-adrenergic receptor antagonists are categorized as Class II antiarrhythmics and are used for treating supraventricular and ventricular tachyarrhythmias. β-adrenergic receptor blockade increases the atrioventricular nodal refractory period and slows ventricular response rates in atrial flutter and fibrillation, and reduces ventricular ectopic beats, particularly those precipitated by catecholamines. The β-adrenergic receptor antagonist sotalol has antiarrhythmic effects involving ion channel blockade and prolongs the action potential and extends the refractory period (class III antiarrhythmic).

Ocular Disease

Timolol maleate is a nonselective β-adrenergic receptor antagonist that lowers intraocular pressure by decreasing aqueous humor production. In normal dogs and cats, topical application of timolol results in reduction of intraocular pressure in the treated eye and the contralateral eye, as well as miosis in the treated eye in cats and in the treated and contralateral eye in dogs (Wilkie and Latimer, 1991a, 1991b). Timolol maleate is available in a 0.25% and 0.5% solution and dosing is every 12 hours. In general, the 0.25% solution is recommended for small dogs and in cats due to the possibility of systemic absorption of the drug and systemic effects. Potential systemic side effects of topical timolol include bradycardia, cardiac arrhythmias, heart block (β_1-adrenergic receptor blockade), and pulmonary effects such as exacerbation of asthma and bronchospasm (β_2-adrenergic receptor blockade). Topical timolol should be avoided in patients with cardiac or pulmonary disease. Betaxolol is a β_1-selective receptor antagonist, which has been shown to significantly delay the onset of glaucoma in dogs with primary closed angle glaucoma (Miller et al., 2000).

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8

Cholinergic Pharmacology: Autonomic Drugs

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Acetylcholine (ACh) is the primary neurotransmitter at autonomic ganglia, parasympathetic neuroeffector junctions, some sympathetic neuroeffector junctions, somatic neuromuscular junctions, the adrenal medulla (Figure 8.1 provides examples of each of these innervations), and certain regions of the central nervous system (CNS). In this chapter, drugs that influence postganglionic parasympathetic neuroeffector junctions and autonomic ganglia are examined.

Parasympathomimetic Agents

Cholinergic is used to describe nerve fibers that synthesize and release ACh without distinction as to anatomic site of action (Figure 8.2). Parasympathomimetic is used specifically to describe an ACh-like effect on effector cells innervated by postganglionic neurons of the parasympathetic nervous system (PSNS). The spectrum of responses to parasympathomimetic drugs is not entirely restricted to PSNS effects, and may include cholinergic actions throughout the body (Barnes and Hansel, 2004; Brown and Taylor, 2006; Westfall and Westfall, 2006).

Based on mechanism of action, drugs that produce parasympathomimetic effects can be divided into two major groups (Figure 8.3): direct-acting agents, which like ACh activate cholinergic receptors located on effector cells; and cholinesterase inhibitors, which allow endogenous ACh to accumulate and thereby intensify and prolong its action (Brown and Taylor, 2006). Similar compounds are also used as antiparasitics and insecticides, and anesthetics, areas fully described in later chapters of this text.

Cholinergic Receptors

Acetylcholine is the principal endogenous agonist at two primary types of cholinergic receptors, nicotinic and muscarinic. Nicotinic neural (NN) receptors associated with the autonomic nervous system (ANS) are present on postganglionic neurons in autonomic ganglia and mediate neurotransmission from preganglionic to postganglionic neurons in both the sympathetic nervous system (SNS) and the PSNS. NN receptors are also present on adrenal medullary chromaffin cells and mediate neurotransmission from preganglionic SNS neurons to adrenal medullary chromaffin cells. Nicotinic muscle (NM) receptors are involved in mediating signal transmission at the neuromuscular junction and are an essential component of the somatic nervous system. Nicotinic receptors are ligand-gated ion channels and contain five homologous subunits organized around a central pore (Stokes et al., 2015). Activation of these receptors initiates: a rapid increase in cellular permeability to selective cations (Na^+ and Ca^{2+}); cell membrane depolarization; and excitation of postganglionic ANS neurons, adrenal medullary chromaffin cells, or skeletal muscle fibers (Stokes et al., 2015).

Muscarinic receptors are located predominately at postsynaptic sites, such as the heart, gastrointestinal tract, glands, and urinary bladder, which are innervated by postganglionic parasympathetic nerves. Five subtypes of muscarinic receptors have been identified and many of the physiological functions associated with PSNS activation are mediated by muscarinic2 (M2) and muscarinic4 (M4) receptors. Muscarinic receptors are G protein-coupled receptors (GPCRs), and activation of these receptors may elicit an excitatory or inhibitory response (Calebiro et al., 2010; Jalink and Moolenaar, 2010; Ambrosio et al., 2011; Vischer et al., 2011; Latek et al., 2012; Duc et al., 2015).

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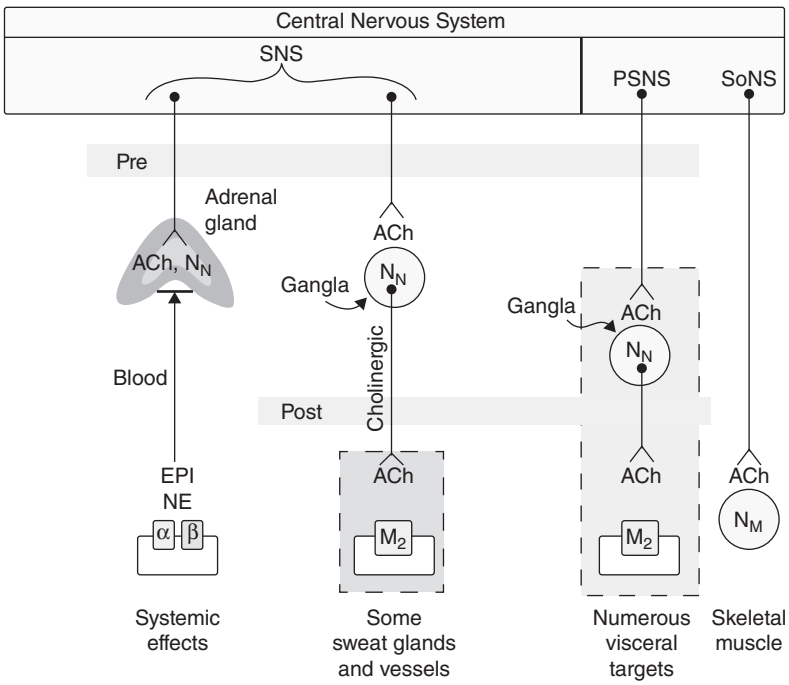

Figure 8.1 Schematic representation of the preganglionic and postganglionic anatomical relationships of nerves contained in the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS). The anatomical substrate of somatic motor nerves (SoNS) is also shown. Only the primary neurotransmitters are shown. Acetylcholine (ACh) is the neurotransmitter released at sympathetic and parasympathetic ganglia and at most parasympathetic neuroefffector junctions. "Visceral targets" refers to cardiac muscle, glands, and bladder smooth muscle. Note that some sympathetic postganglionic fibers release ACh. The adrenal medulla, a modified sympathetic ganglion, is innervated by sympathetic preganglionic fibers and releases epinephrine and NE into the blood. ACh, acetylcholine; EPI, epinephrine; M, muscarinic receptors; NN, nicotinic receptors; NE, norepinephrine.

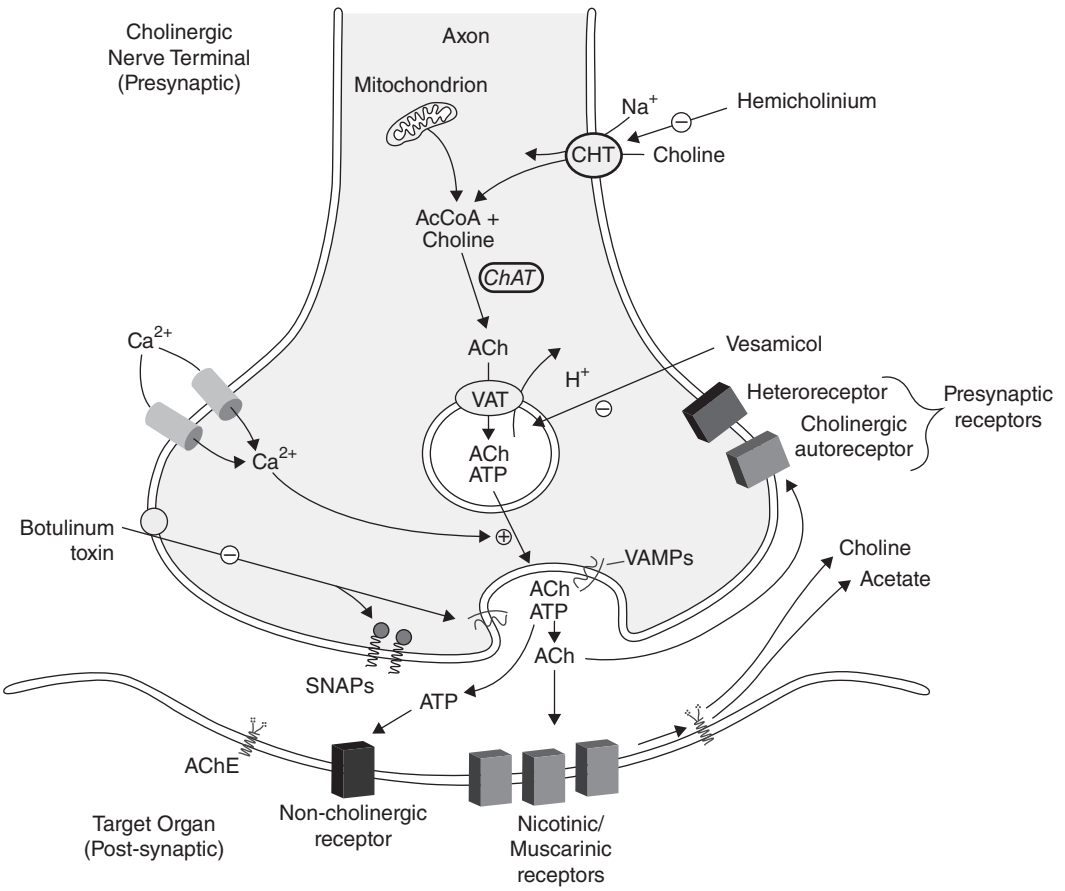

Figure 8.2 Schematic diagram depicting physiological processes at the site of a cholinergic nerve terminal innervating a target tissue. Processes have been described previously in Chapter 6. Cholinergic neurons synthesize and release ACh and this endogenous neurotransmitter binds to and activates nicotinic and muscarinic receptors. ACh, acetylcholine; AcCoA, acetyl-CoA; ChAT, choline acetyltransferase; CHT, choline transporter; SNAP, synaptosomal nerve-associated protein; VAT, vesicle-associated transporter; VAMP, vesicle-associated membrane protein.

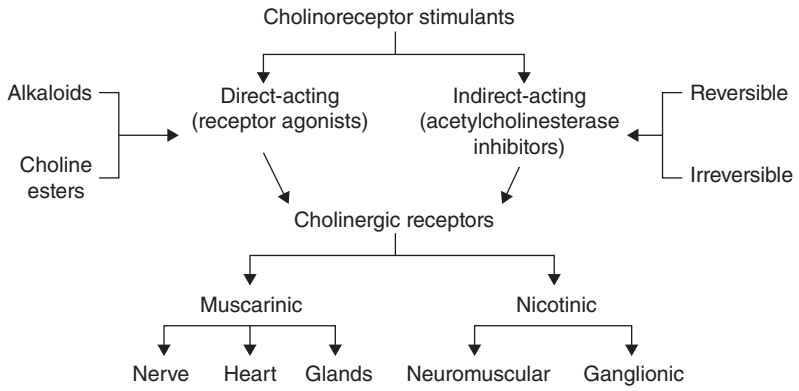

Figure 8.3 Schematic summarizing primary cholinergic receptor stimulants, muscarinic and nicotinic receptors, and target tissues.

Direct-acting Parasympathomimetic Agonists

General Characteristics

Direct-acting parasympathomimetic agonists consist of choline esters, including ACh and numerous synthetic esters, and cholinomimetic alkaloids. Methacholine, carbachol, and bethanecol are primary choline derivatives, whereas muscarine, pilocarpine, and arecoline are primary cholinomimetic alkaloids. Pharmacological effects of ACh and related choline esters and alkaloids are mediated by activation of cholinergic receptors located on cells innervated by cholinergic nerves and, in some cases, on cells that lack cholinergic innervation. Direct-acting agonists act directly on receptors and do not depend upon endogenous ACh for their effects. In general, the physiological responses of selected organs and effector tissues elicited by activation of efferent parasympathetic nerves, as well as direct-acting parasympathomimetic agonists, are similar (Table 8.1). However, the pharmacological characteristics of direct-acting parasympathomimetic agonists demonstrate nonuniform susceptibility to metabolism by cholinesterases, differential relative affinity for muscarinic and nicotinic receptors, and specificity in target organ effects (Table 8.2).

Structure–Activity Relationships

Direct-acting cholinergic agonists contain structural groupings that allow interaction of the agent with cholinergic receptors and result in similar membrane and cellular responses to those caused by ACh. Chemical structures of several choline esters and cholinomimetic alkaloids are shown in Figures 8.4 and 8.5.

Choline esters contain a quaternary nitrogen atom to which three methyl groups are attached. Except for some naturally occurring cholinomimetic alkaloids, a quaternary nitrogen moiety is usually required for a direct potent action on cholinergic receptors. The quaternary nitrogen group carries a positive charge and this cationic group electrostatically binds with a negatively charged (anionic) site of the cholinergic receptor.

Receptive macromolecules (i.e., cholinergic receptors and cholinesterases) that recognize and bind ACh have, in addition to the anionic site, a region that combines

Table 8.1 Effects of direct-acting cholinergic receptor stimulants

Organ	Tissue	Response
Eye	Sphincter muscle, iris	Pupillary constriction
	Cillary muscle	Contraction
Glands	Salivary, lacrimal	↑↑ Secretion
Lung	Bronchial muscle	Contraction
	Bronchial glands	Stimulation
Heart	Sinoatrial node	↓ Heart rate
	Atria	↓ Contractility/conduction
	Atrioventricular node	↓ Conduction
	Ventricles	↓ Contractility (slight)
Blood vessels	Selected arteries	Dilation
Gastrointestinal tract	Motility	↑ GI Muscle Contraction
	Sphincters	↓ Tone
	Secretion	Stimulation
Urinary bladder	Detrusor muscle	Contraction
	Sphincters	Relaxation

Table 8.2 Scope of cholinergic receptor activating properties of some choline esters

	Agonistic properties						
	Susceptibility to cholinesterase		Muscarinic receptors				
	True	Pseudo	CV	GI	UB	E	Nicotinic receptors
Acetylcholine	+++	+++	+++	+++	++	+	+++
Methacholine	+	–	+++	++	++	+	±
Carbachol	–	–	+	+++	+++	++	+++
Bethanechol	–	–	±	+++	+++	++	–

CV, cardiovascular; GI, gastrointestinal; UB, urinary bladder; E, eye.

with the ester component of ACh (Hucho et al., 1991). In cholinesterase, this region is called the esteratic site and its combination with the carboxyl group results in hydrolysis of the ester. Hydrolysis of ACh does not occur upon its interaction with a receptor, however, and the ester-attracting region of the receptor is called the esterophilic site (Inestrosa and Perelman, 1990; Taylor, 1991, 2006a; Massoulie et al., 1993). ACh is structurally arranged so that it combines with the esterophilic and anionic sites of both nicotinic and muscarinic receptors and acetylcholinesterases (Hucho et al., 1991).

ACh is the prototypical cholinergic agent and activates both nicotinic and muscarinic receptors. Acetyl-β-methylcholine (methacholine) is identical in structure to ACh except for the substitution of a methyl group on the β-carbon atom of the choline group. This structural change yields a compound that is primarily a muscarinic receptor agonist lacking significant nicotinic effects when given in usual dosages. Further, it is more active on the cardiovascular system than on the GI tract. Duration of action of methacholine is considerably longer than that of ACh.

Carbachol and bethanechol each have a carbamyl group substituted for the acetic moiety of ACh, and bethanechol also has a β-methyl group. Both of these agents are almost completely resistant to inactivation by the cholinesterases. Their duration of action is therefore considerably longer than that of ACh. Carbachol is active at both muscarinic and nicotinic receptor sites, whereas bethanechol is primarily a muscarinic agonist. Unlike methacholine, both these drugs are somewhat more active on smooth muscles of the GI tract and urinary bladder than on cardiovascular function. Pharmacological characteristics of these choline esters are presented in Table 8.2.

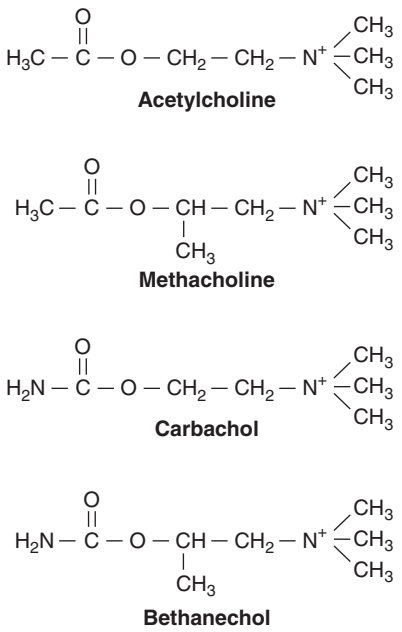

Figure 8.4 Molecular structures of primary choline esters.

Acetylcholine: Prototypical Cholinergic Agonist

Pharmacological Mechanisms and Effects

ACh is the prototypical cholinergic agonist and therefore provides a foundation for understanding the pharmacological effects of other cholinomimetic drugs. The

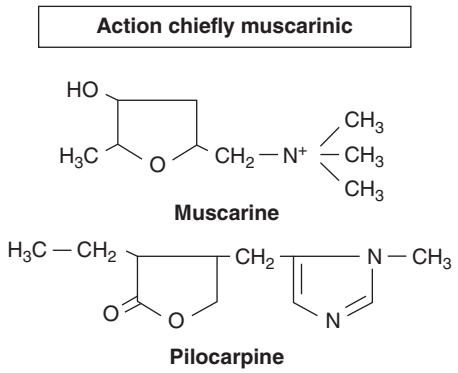

Figure 8.5 Molecular structures of several cholinomimetic alkaloids.

biosynthesis, neuronal release, cellular activities, and inactivation of endogenous ACh were discussed in Chapter 6. Although an essential ANS neurotransmitter, ACh is not used therapeutically for at least two reasons. First, muscarinic and nicotinic receptors are located at numerous tissue sites and therefore no selective therapeutic response to ACh can be achieved. Second, its duration of action is quite brief because it is rapidly inactivated by the cholinesterases. Several derivatives of ACh are more resistant to hydrolysis by cholinesterase and have a somewhat greater selectivity in their sites of action (Table 8.2).

Since ACh is a mixed nicotinic–muscarinic agonist, different physiological response profiles can be produced by administration of this agent, depending upon the relative dominance of muscarinic (parasympathomimetic) or nicotinic actions. These effects can be differentiated by use of small and large doses of ACh and by using selective cholinergic blocking drugs. In general, parasympathomimetic effects dominate with small doses, whereas with large doses nicotinic effects can be elicited. Use of cholinergic blocking drugs and small and large doses of ACh to differentiate muscarinic and nicotinic effects of ACh is shown in Figure 8.4. This figure is discussed in more detail in the following section regarding cardiovascular effects mediated by ACh administration.

Target Organ Effects of ACh

Cardiovascular: Intravenous (IV) administration of small amounts of ACh (5– 10 μg/kg) induces a brief but rapid fall in systolic and diastolic blood pressures, due to a decrease in peripheral resistance resulting from dilation of blood vessels. Most blood vessels receive little or no parasympathetic innervation, and muscarinic receptors located at these sites are noninnervated. Muscarinic receptors mediating dilation of blood vessels are located on the endothelium rather than on the smooth muscle, and the smooth muscle relaxation in response to ACh administration involves the production and release of nitric oxide (Furchgott and Zawadzki, 1980; Lowenstein et al., 1994).

Somewhat larger doses of ACh (10–30 μg/kg) produce pronounced muscarinic effects; therefore, marked reductions in peripheral resistance, heart rate, and blood pressure are observed. Atrial myocardial cells contain muscarinic receptors associated with vagal fibers, and activation of these receptors by ACh produces negative chronotropic and inotropic effects. Generally, the chronotropic effects predominate. In addition to its pronounced slowing effect on heart rate, ACh exerts important effects on impulse conduction.

With high doses (50–100 μg/kg) muscarinic effects of ACh on postganglionic effector cells are accentuated. Profound hypotensive and bradycardic responses are observed. Large doses of ACh produce, in addition to muscarinic (i.e., parasympathomimetic) effects, stimulation of the nicotinic receptors in autonomic ganglia (both parasympathetic and sympathetic) and the adrenal medulla. These effects are particularly evident when the muscarinic receptors of the parasympathetic neuroeffector junctions are blocked by atropine (nonselective muscarinic receptor antagonist). Under these circumstances large doses of ACh stimulate nicotinic receptors of both sympathetic and parasympathetic ganglia. However, because the muscarinic receptors of the parasympathetic neuroeffector junctions are blocked by atropine, the ACh released from postganglionic parasympathetic nerves does not bind to and activate the target organ muscarinic receptors. Under this condition, sympathomimetic responses will be evident, including increased arterial blood pressure, tachycardia, and other typical sympathetic-mediated effects. These effects can be blocked by use of appropriate adrenergic blocking drugs or by use of a ganglionic blocking agent (Figure 8.6).

Nonvascular smooth muscle: ACh stimulates smooth muscle of the urinary bladder and uterus to contract (Chapple et al., 2002). Bronchiolar smooth muscle is also contracted by ACh, resulting in decreased airway diameter (Barnes and Hansel, 2004; Fisher et al., 2004). The smooth muscle effects of ACh are due to muscarinic receptor activation.

Gastrointestinal system: Gastrointestinal motility and secretions are enhanced by ACh in a manner similar to that mediated by stimulation of the PSNS innervation to the gastrointestinal system. These effects may be difficult to detect with small doses because duration of action of ACh is brief owing to rapid destruction by cholinesterase. Larger doses markedly increase secretions and peristaltic movements of the GI tract.

Central nervous system: ACh does not readily cross the blood–brain barrier, therefore CNS effects are not observed when usual dosages are administered. However, intraarterial ACh injection into cerebral arteries or the direct application of ACh into the CNS produces central neural excitation. Both muscarinic and nicotinic receptors are present in the CNS (Krnjevic, 2004).

Adrenal medulla: The adrenal medulla is functionally analogous to autonomic ganglia, and nicotinic receptors located on adrenal medullary chromaffin cells are innervated by preganglionic sympathetic nerve fibers. These receptors are stimulated by ACh to cause release of epinephrine and norepinephrine from chromaffin cells into the circulation. This effect contributes to the overall nicotinic-mediated sympathomimetic effect evoked by large doses of ACh in the presence of muscarinic receptor blockade.

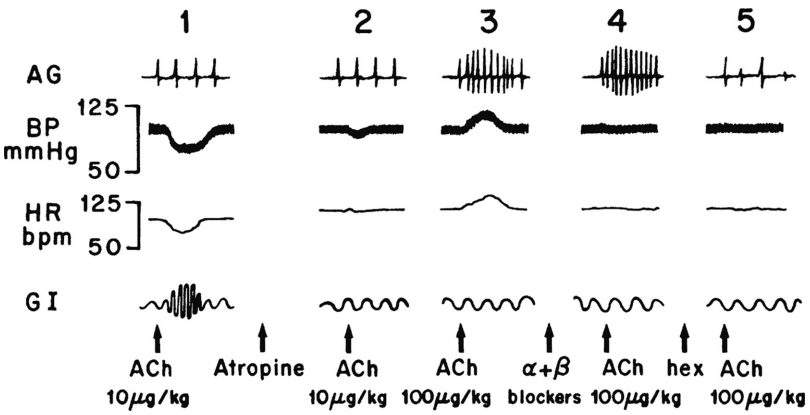

Figure 8.6 Muscarinic and nicotinic effects of acetylcholine (ACh) on blood pressure, heart rate, intestinal motility, and autonomic ganglionic action potentials in an anesthetized dog. Schematic reproductions: (1) A small dose of ACh (10 mg/kg) administered intravenously causes hypotension, bradycardia, and intestinal contractions caused by direct stimulation of muscarinic receptors of blood vessels, heart, and intestinal smooth muscle, respectively. These effects are brief because of rapid destruction of ACh by cholinesterase. (2) Atropine blocks the muscarinic receptors and thereby prevents the effects seen in (1). (3) Large doses of ACh (100 mg/kg) stimulate, in addition to muscarinic receptors, nicotinic receptors of parasympathetic and sympathetic ganglionic neurons, causing an increase in frequency and amplitude of ganglionic action potentials. Although all autonomic ganglia are activated, impulses arising from parasympathetic ganglia do not reach their effector cells because of blockade of parasympathetic postganglionic neuroeffector junctions by atropine. Sympathomimetic responses (pressor effect and tachycardia) result. (4) Impulses arising from sympathetic ganglia are prevented from reaching their effector cells by adrenergic blocking drugs; however, ganglionic nicotinic receptors are still activated by ACh. (5) Hexamethonium (hex) blocks nicotinic receptors of ganglia and thereby inhibits the nicotinic ganglionic stimulating effect of ACh and reduces ganglionic action potentials. AG, action potentials of autonomic ganglionic neuron; BP, systemic blood pressure; HR, heart rate; GI, intestinal peristaltic waves.

Choline Esters: Methacholine, Carbachol, and Bethanecol

Pharmacological Mechanisms and Effects

The pharmacological effects of methacholine, carbachol, and bethanecol are similar to the parasympathomimetic effects produced by ACh administration, and therefore are consistent with the physiological responses evoked by the activation of postganglionic parasympathetic nerves. However, the physiological response profiles produced by different choline esters are not identical, and vary in relative selectivity for one organ system or another (Table 8.2).

Methacholine is a synthetic choline ester that produces cardiovascular effects similar to those produced by ACh, but has a longer duration of action and its primary agonistic activity is at muscarinic receptors. Carbachol is active at both muscarinic and nicotinic receptors, and nicotinic neural receptors are particularly sensitive to carbachol. The pharmacological scope of activity of bethanecol is similar to that of methacholine and carbachol. Unlike carbachol, however, bethanecol is primarily a muscarinic agonist and has little stimulant effects on nicotinic receptors.

Target Organ Effects

Cardiovascular: Methacholine is more active on the cardiovascular system than on the GI or urinary tracts. The opposite selectivity is seen with carbachol and bethanechol. Intravenous administration of methacholine, like ACh, produces a depressor response and slowing of heart rate caused by activation of muscarinic receptors located on blood vessels and in the heart. Cardiac rhythm is altered by methacholine, and the atrioventricular node is particularly sensitive to this agent. Carbachol evokes blood pressure changes similar to, but less pronounced, than those produced by methacholine, whereas bethanechol administration produces considerably less effects on cardiovascular function.

Gastrointestinal system: Carbachol and bethanecol are relatively more active on the gastrointestinal and urinary tracts than on the cardiovascular system. Methacholine administration affects gastrointestinal function, but only in large doses. Carbachol is a potent GI stimulant and increases salivation and peristaltic movements of the gastrointestinal system.

Nonvascular smooth muscle: Carbachol causes contraction of bronchiolar smooth muscle, resulting in a decreased airway. The urinary bladder is contracted by carbachol and bethanechol. Effects of carbachol and bethanechol on smooth muscle are mediated by activation of muscarinic receptors.

Clinical Uses

There are few clinical indications for the use of these cholinergic agonists in veterinary medicine. Bethanechol

has been used to promote bladder contraction in paraplegic dogs and cats with the goal to prevent over distension and detrusor muscle atony (Schubert, 2015). The use of bethanechol to promote detrusor muscle contraction for treatment of detrusor sphincter dysynergia, in conjunction with diazepam and prazosin to decrease urethral sphincter tone, has been reported (Jeyraja et al., 2010; Chandrasekar et al., 2013). The only clinical use for carbachol is as the ophthalmic solution Miostat®, which is administered at the end of cataract surgery to cause miosis.

Cholinomimetic Alkaloids: Pilocarpine, Muscarine, and Arecoline

Pharmacological Mechanisms and Effects

Pilocarpine, arecoline, and muscarine are plant alkaloids that are rather selective parasympathomimetic agents (i.e., their cholinomimetic activity is exerted primarily at muscarinic sites with minimal nicotinic effects). These cholinomimetic alkaloids evoke their parasympathomimetic effects by direct activation of muscarinic receptors.

Target Organ Effects

Pilocarpine is particularly effective in stimulating flow of secretions from exocrine glands, including; salivary, mucous, gastric, and digestive pancreatic secretions. As with ACh, it causes contraction of GI smooth muscle, thereby increasing smooth muscle tone and peristaltic activity. Of considerable importance, pilocarpine has a potent constrictor effect on the pupil.

Arecoline activates muscarinic receptors located at numerous targets including; glands, smooth muscles, and myocardium, and produces the usual parasympathomimetic effects. It is similar to pilocarpine in scope of activity.

Clinical Uses

Pilocarpine hydrochloride is available as a 1%, 2%, and 4% ophthalmic solution (see Chapter 49). Topical pilocarpine causes miosis and lowers the intraocular pressure. Although pilocarpine has been recommended historically to treat glaucoma, the topical irritation caused by this medication can be severe, making the medication poorly tolerated by most patients. Newer antiglaucoma medications are generally less irritating, and thus are recommended more commonly. Pilocarpine can be used to treat cases of neurogenic keratoconjunctivitis sicca in dogs. In order for pilocarpine to be effective there must be some normal functioning lacrimal tissue, and it is unlikely to increase tear production in cases of absolute keratoconujunctivitis sicca (Giuliano, 2013). Oral administration of pilocarpine should be performed with caution in small patients due to the increased risk of toxic systemic effects and death. Alternatively, a dilute pilocarpine solution (0.125% or 0.25%) can be applied directly to the eye to stimulate tear production. Pilocarpine can be used for pharmacological testing and neuroanatomic localization of mydriasis caused by dysfunction of the parasympathic nervous system. Ocular application of dilute pilocarpine solution (0.05%) in dogs with dysautonomia will cause rapid constriction of the pupil in less than 45 minutes compared to unaffected animals (O'Brien and Johnson, 2002). The rapid miosis is secondary to the degeneration of the postganglionic neurons, which leads to hypersensitivity of the denervated muscle to cholinergic drugs. In dogs with mydriasis due to a lack of parasympathic innervation of the iris sphincter muscle (internal ophthalmoplegia), the sphincter muscle will be hypersensitive to topical application of a dilute (0.1%) pilocarpine solution.

Cholinesterase Inhibitors

Pharmacological Mechanisms and Effects

Cholinesterase inhibitors (anticholinesterase agents) inactivate or inhibit acetylcholinesterase (AChE) and pseudocholinesterase, increasing the level of synaptic ACh, and intensifying the activity of endogenous ACh. Because cholinesterase inhibitors enhance the actions of endogenous ACh at all cholinergic receptors, their scope of activity is not limited to parasympathomimetic effects but can include cholinomimetic actions throughout the body (Taylor, 2006b). Effects of cholinesterase inhibitors can be reliably predicted by considering the anatomic location of cholinergic nerves and the respective physiological processes they modulate at target cells and tissues. Parasympathomimetic (muscarinic) effects of these agents are equivalent to the effects associated with activation of postganglionic parasympathomimetic nerves. Cholinesterase inhibitors also cause intensification of ACh activity at nicotinic sites.

Physostigmine, neostigmine, and edrophonium are examples of anticholinesterase drugs that produce a reversible inhibition of cholinesterase, whereas organophosphate compounds produce an irreversible inhibition. Although there is considerable distinction between these two groups of anticholinesterases, their pharmacological effects are similar because of a common mechanism of action. The pharmacological effects of cholinesterase inhibitors can be explained almost entirely by their characteristic inhibitory action on AChE. This results in decreased hydrolysis of neuronally released ACh and intensification of its action at cholinergic receptors. Neostigmine and some other quaternary nitrogen anticholinesterase agents exert some direct effects (either agonistic or antagonistic) on cholinergic receptors in addition to inhibition of cholinesterase.

Structure–Activity Relationships

The enzymatic interactions of AChE, ACh, and cholinesterase inhibitors can be summarized as follows (Inestrosa and Perelman, 1990; Taylor, 1991, 2006a; Massoulie et al., 1993). AChE contains two active sites that recognize specific parts of the ACh molecule: (i) an anionic (negatively charged) region where electrostatic binding occurs with the cationic nitrogen of the choline moiety; and (ii) an esteratic site where the carboxyl portion of the acetyl ester binds to it by covalent bonding. After ACh–AChE interaction occurs, the choline portion is split off, leaving the acetylated esteratic site. Acetic acid is rapidly formed as water reacts with the acetyl group, and the enzyme is thereby reactivated (Wilson, 1954).

Neostigmine, physostigmine, and other carbamate derivatives interact with the anionic and esteratic sites of the enzyme, thereby preventing ACh from affixing to the enzyme. Neostigmine and physostigmine are believed to be hydrolyzed in a manner similar to but much slower than that of ACh (Wilson et al., 1960). Although the rate of combination of inhibitor with AChE is only a few times slower than the analogous combination of ACh with the enzyme, the rate of hydrolysis is much faster for ACh. Therefore, neostigmine and related drugs are reversible cholinesterase inhibitors as a result of their actions as competitive substrates that are hydrolyzed at a much slower rate than the endogenous substrate ACh (Taylor, 1991, 2006a; Massoulie et al., 1993).

Edrophonium is a simple alcohol bearing one quaternary ammonium group. Edrophonium binds to the anionic site of cholinesterase by electrostatic attachment and at the esteratic site by hydrogen bonding. The action of edrophonium is brief because a covalent bond is not formed (Keegan, 2015).

Organophosphate compounds interact with AChE at the esteratic site and form an extremely stable enzyme–inhibitor complex that does not undergo significant spontaneous disassociation. The esteratic site is persistently phosphorylated, and recovery of cholinesterase activity is dependent upon de novo synthesis of new enzyme.

Reversible Inhibitors: Physostigmine, Neostigmine, Edrophonium, Pyridostigmine

Pharmacological Mechanisms and Target Organ Effects

As stated previously, these drugs produce their effects by combining with cholinesterase and thereby preventing the enzyme from hydrolyzing ACh. In general, the physiological responses produced by these drugs are similar to direct-acting parasympathomimetic agents, and therefore are consistent with the physiological responses evoked by stimulation of postganglionic parasympathetic nerves.

Digestive tract: Physostigmine and neostigmine cause contraction of smooth muscle, thereby increasing motility and peristaltic movements of the gut. Frequency and strength of peristaltic waves are increased, and movement of intestinal contents is accelerated.

Eyes: Physostigmine causes pupillary constriction when applied locally to the eye or when injected for systemic effect.

Skeletal muscle: Besides its major action of inactivating AChE at the somatic myoneural junction, neostigmine is believed to directly stimulate nicotinic receptors of skeletal muscle fibers. The skeletal muscle effects of neostigmine are relatively more pronounced at low doses than the smooth muscle effects of this agent. Twitching of skeletal muscles may be observed when a large dose of physostigmine or neostigmine is injected.

Other effects: A therapeutic dose of physostigmine or neostigmine does not produce pronounced effects on cardiovascular function. Effects of higher doses are complicated by concurrent ganglionic stimulation and muscarinic effects on the heart and blood vessels. Usually, hypotension and a bradycardia are produced. Smooth muscle of the bladder is cholinergically innervated and therefore is contracted by cholinesterase inhibitors. Bronchiolar smooth muscle is also contracted by these agents.

Clinical Uses

Physostigmine, pyridostigmine, neostigmine, and edrophonium can be used to reverse the effects of nondepolarizing neuromuscular blocking drugs in voluntary muscles. AChE inhibitors are used in the therapy of dogs but rarely cats, with myasthenia gravis (MG). Additionally, intravenous edrophonium is sometimes used as an initial screening test for dogs with suspected MG. MG results from either a rare congenital absence of nicotinic receptors at the neuromuscular junction or as an acquired autoimmune diseases resulting in destruction and deficiency of these AChRs. The edrophonium chloride response test is used to make a presumptive diagnosis. Edrophonium is used because of its ultrashort action. A positive response is defined as a temporary increase in muscle strength after administration of the drug (Khorzad et al., 2011). This is not a definitive test and both false-positive and false-negative results are possible. A definitive diagnosis of MG is made by documentation of autoantibodies against muscle AChRs by immunoprecipitation radioimmunoassay. Oral AChE inhibitors are used in the therapy for MG.

Unlike humans, spontaneous remission of acquired MG in dogs is likely (Shelton and Linstrom, 2001) and treatment is aimed at improving muscle strength while titrating the dose to minimize other cholinergic side effects. Pyridostigmine bromide and neostigmine bromide are the most commonly used AChE inhibitors for MG. Pyridostigmine is preferred because of its longer duration of action and lower potential for adverse gastrointestinal effects. In dogs with MG, pyridostigmine bromide is administered at 0.5–3.0 mg/kg orally two or three times daily (Khorzad et al., 2011). Adverse effects are related to the muscarinic effects of excess ACh and include increased gastrointestinal motility, diarrhea, salivation, and bradycardia.

Toxicology

Large doses of physostigmine first stimulate and then depress the CNS; small to moderate doses have little effect, whereas massive doses can produce convulsions. Neostigmine does not cross the blood–brain barrier to an appreciable extent. Toxic doses of these agents produce marked skeletal muscle weakness, nausea, vomiting, colic, and diarrhea. The pupil is markedly constricted and fixed. Dyspnea is characteristically seen from constriction of the bronchiolar musculature. Bradycardia and lowered blood pressure are also characteristic signs. Respiratory paralysis caused by depolarization block of the neuromuscular junction and compounded by excess bronchiolar secretions is the usual cause of death. Atropine is the most effective pharmacological antagonist for physostigmine or neostigmine toxicity.

Organophosphorus Compounds

Organophosphates irreversibly phosphorylate the esteratic site of both AChE and the nonspecific or pseudocholinesterase throughout the body. Endogenous ACh is not inactivated, and the resulting effects are due to the excessive preservation and accumulation of endogenous ACh (Gutmann and Besser, 1990; Taylor, 1991, 2006a). Organophosphate poisoning produces diffuse cholinomimetic effects: profuse salivation, vomiting, defecation, hypermotility of the GI tract, urination, bradycardia, hypotension, severe bronchoconstriction, and excess bronchial secretions. These signs reflect excess activation of muscarinic receptors of postganglionic parasympathetic neuroeffector junctions with typical parasympathomimetic actions.

In addition to the muscarinic effects, organophosphates produce skeletal muscle fasciculations, twitching, and, subsequently, muscle paralysis occurs. These effects are due to persistent excessive stimulation of the nicotinic receptors of skeletal neuromuscular junctions, resulting in the depolarizing type of striated muscle paralysis (Gutmann and Besser, 1990). Convulsions and frequently death are seen in organophosphate poisoning, caused by penetration of the agent into the CNS and subsequent intensification of the activity of ACh at CNS sites (Gutmann and Besser, 1990).

Atropine is a competitive antagonist to ACh and therefore administration of this muscarinic receptor antagonist can reduce the severity of the parasympathomimetic effects produced by organophosphates, and can also increase the quantity of organophosphate required to produce death. An atropine test can be completed if signs of organophosphate poisoning are present (Wismer, 2012).

Although phosphorylation of the esteratic site of cholinesterase by organophosphates yields a normally irreversible complex, certain compounds cause a disassociation of the enzyme link. Pralidoxime (pyridine-2-aldoxime-methiodide, 2-PAM) was synthesized based on structural requirements postulated by Wilson (1958) to be necessary for a selective antidote to the organophosphate–cholinesterase interaction. This compound causes an effective removal of the phosphate group from the enzyme, so the enzyme is reactivated. This oxime compound is an adjunct to atropine therapy in treating organophosphate poisoning.

Animals previously exposed to toxic doses of organophosphates experience considerable improvement after treatment with 2-PAM. Since 2-PAM significantly reverses the combination of organophosphate with cholinesterase, the reactivated enzyme can then perform its normal function. The phosphorylated enzyme complex tends to age with time and to become resistant to reactivation by oximes.

Muscarinic Receptor Antagonists

Muscarinic receptor antagonists block the effects of ACh and related cholinergic receptor agonists from binding to and activating muscarinic receptors; therefore they are termed antimuscarinic agents or muscarinic receptor antagonists. Both naturally occurring antimuscarinic compounds and synthetic antimuscarinic compounds are available for use. Atropine, the prototypical muscarinic blocking agent, is an alkaloid extracted from *Atropa belladonna* (deadly nightshade) and *Datura stramonium* (jimsonweed), whereas scopolamine (hyoscine) is found in *Hyoscyamus niger* (henbane). There are numerous synthetic drugs with antimuscarinic effects, including propantheline, glycopyrrolate, tropicamide, and butylscopolamine. The following sections focus primarily on atropine because it is the prototype muscarinic receptor-blocking agent.

Mechanism of Action

Muscarinic receptor antagonists interact with muscarinic receptors of effector cells and, by occupying these sites, prevent ACh from binding to the receptor. Physiological responses to parasympathetic nerve impulses are thereby attenuated. Blockade of muscarinic receptors of smooth muscle, cardiac muscle, and glands by atropine-like drugs involves a competitive antagonism and large doses of ACh or other cholinomimetic drugs (e.g., carbachol, cholinesterase inhibitors) can overcome inhibitory effects of atropine at these sites.

Antimuscarinic drugs, such as atropine and scopolamine, are considered nonspecific for different muscarinic receptor subtypes; however, the physiological effects of the drugs are somewhat dose and drug dependent. For example, salivary and cholinergic sweat glands are quite susceptible to small doses of atropine, whereas somewhat larger doses are required for blocking the effect of the vagus nerve on the heart. GI and urinary tract smooth muscles are less sensitive to atropine, and even larger dosages are required to inhibit gastric secretion. Except for effects on salivation and cholinergic sweating, it is difficult to achieve a selective action on targeted structures without concurrently inducing side effects on other, more susceptible sites. Net pharmacological effects of antimuscarinic drugs in a particular organ are influenced by the relative dominance of parasympathetic or sympathetic tone in that structure.

Pharmacological Effects

Cardiovascular system: An increase in heart rate and intranodal conduction velocity are the predominant effects of therapeutic doses of atropine. However, a dose-dependent decrease of heart rate and development of a second-degree atrioventricular block after treatment of bradycardia with atropine can occur. The effect of atropine on heart rate and the potential for subsequent tachycardia is dependent in part upon the degree of vagal tone. Because atropine blocks transmission of vagal impulses to the heart, animals with a preexisting high vagal tone would show a relatively greater tachycardia than those with low vagal tone.

Cardiac output may increase with atropine secondary to the increase in heart rate. Arterial blood pressure either remains unchanged or increases slightly as a result of the increased cardiac output. In animals exposed to exogenous ACh or other cholinomimetics (e.g., cholinesterase inhibitors), atropine can cause a relative increase in blood pressure, because muscarinic effects of the agonists will be blocked. Because atropine blocks the cardiac vagus, it markedly reduces or abolishes cardiac inhibitory effects of drugs acting through a vagal mechanism and will attenuate vagal-mediated reflex responses. Accordingly, the pressor effects of epinephrine and norepinephrine are accentuated in atropinized animals by blockade of the cardiac limb of vagal–baroreceptor reflexes.

Gastrointestinal system: Atropine causes relaxation of GI smooth muscle by inhibiting contractile effects of cholinergic nerve impulses. Thus, atropine and related drugs can be helpful in treatment of intestinal spasm and hypermotility. Inhibition of smooth muscle motility extends from stomach to colon, although the degree of blockade may not be uniform. Secretions of the GI tract are also blocked by atropine. Salivation is reduced quite markedly. Similarly, secretions of intestinal mucosa are inhibited; however, gastric secretions are reduced only with exceedingly high doses that also block virtually all other muscarinic sites.

Bronchioles: Cholinergic innervation to the bronchioles modulates secretion of mucus and contraction of bronchiolar smooth muscle via activation of muscarinic receptors. Atropine and other drugs of the belladonna group block effects of cholinergic impulses and thereby decrease secretions and increase luminal diameter of the bronchioles. The dilator action of atropine is valuable in counteracting constriction of bronchioles following overdosage of a parasympathomimetic drug.

Ocular effects: Atropine blocks the cholinergically innervated sphincter muscle of the iris and the ciliary muscle, resulting in mydriasis and cycloplegia after topical or systemic administration. Because atropine blocks cholinergic effects, adrenergic nerve impulses dominate and the pupil actively dilates. Atropine is contraindicated in the presence of increased intraocular pressure from glaucoma because the drainage system of the anterior chamber of the eye is impeded during mydriasis.

Urinary tract: Atropine relaxes smooth muscle of the urinary tract. The spasmolytic effect on the ureters may be of some benefit in treatment of renal colic. Atropine tends to cause urine retention because it inhibits smooth muscle tone.

Sweat glands: Atropine has a definite anhydrotic action in species such as humans, who have a cholinergic mechanism in control of sweat secretion, and a large dose may cause a hyperpyrexic response. Atropine does not directly affect sweating in species that have adrenergic mechanisms in control of sweating (e.g., equines) and has minimal effect in species that do not use cholinergic sweating as an important component of thermoregulation.

Central nervous system: Therapeutic doses of atropine produce minimal effects on the CNS (Fisher et al., 2004). Excessive doses may cause hallucinations and disorientation in humans and mania and excitement in domestic animals. Excessive motor activity followed by depression and coma is the usual sequence of events. Scopolamine has a slight sedative effect; when combined with morphine it produces analgesia and amnesia (referred to as "twilight sleep") in human patients. These effects of scopolamine usually are not detectable in domestic animals.

Clinical Uses

Muscarinic receptor antagonists can be used as antispasmodics or spasmolytics to control smooth muscle spasm. Antispasmodics can be used to decrease or abolish GI hypermotility and depress hypertonicity of the uterus, urinary bladder, ureter, bile duct, and bronchioles. Antimuscarinic drugs are not as effective as epinephrine or other adrenergic amines in dilating the bronchioles, but atropine is effective in antagonizing excessive cholinergic stimulation at these sites.

Systemically administered atropine is used predominantly to treat bradyarrhythmias that are associated with significant effects on cardiac output and/or systemic blood pressure. Given that the duration of effect on heart rate is approximately 30–60 minutes, this limits the use of atropine to initial or emergency treatment of bradyarrhythmias, or, more frequently, as a treatment for bradycardia that is induced by other drugs such as mu agonist opioids or acetylcholinesterase inhibitors. The routine use of anticholingergic drugs as anesthetic premedicants is no longer recommended, and treatment of bradycardia associated with drugs that markedly increase vascular resistance, such as dexmedetomidine may be contraindicated. Atropine may be administered as a diagnostic test to determine the responsiveness of a bradyarrhythmia to an anticholinergic drug.

Atropine is used to facilitate ophthalmoscopic examination of internal ocular structures and also for treatment of various ocular disorders. Atropine sulfate is available as a 1% ophthalmic solution and ointment and is a potent mydriatic and cycloplegic. Atropine is used commonly in the treatment of iridocyclitis in veterinary medicine because of its long duration of action. In dogs, the peak onset of mydriasis after application of 1% atropine solution is within 1 hour, and the mydriasis lasts for 96–120 hours (Rubin and Wolfes, 1962). Patients with dark irides may have a delayed onset and longer duration of atropine due to binding of atropine by the melanin in the irides, where it is slowly released from the pigment onto the muscarinic receptors (Salazar and Patil, 1976). A common side effect associated with the use of topical atropine is excessive salivation and vomiting, which is most likely due the bitter taste of the drug. After topical application, a portion of the solution will enter the nasolacrimal duct and may be ingested. This side effect is more likely to occur with use of the solution compared to the ointment formulation. Atropine can cause an increase in intraocular pressure and can decrease tear production, therefore it should be avoided in patients with glaucoma or keratoconjunctivitis sicca.

Diagnostic ophthalmoscopy is more frequently facilitated by topical tropicamide. Tropicamide is available as a 0.5% and 1% solution. The rapid onset and short duration of action make it an ideal drug for diagnostic ophthalmoscopy. Tropicamide has less cycloplegic effects than atropine, and is not commonly used to treat iridocyclitis.

Glycopyrrolate

The antimuscarinic effects of this synthetic muscarinic receptor antagonist are similar to atropine. It is often considered that glycopyrrolate may be associated with a lower risk of marked tachyarrhymias when compared to atropine. While clinical experience would suggest this is the case in veterinary patients, there is little research data to support this (Lemke, 2001). In dogs this compound effectively diminishes the volume and acidity of gastric secretions and reduces intestinal motility; it also reduces and controls excessive secretions of the respiratory tract. Similar control of respiratory secretions by glycopyrrolate has been reported in cats, and its duration of action exceeds that of atropine. Also, because of its more polar nitrogen moiety, glycopyrrolate penetrates the blood–brain barrier less effectively than atropine, with less propensity for unwanted CNS side effects.

N-butylscopolamine bromide

N-butylscopolamine bromide (NBB) is a quaternary ammonium that serves as a peripherally acting antimuscarinic, anticholinergic agent similar in action to atropine, and is approved in the United States for use in horses that demonstrate colic signs resulting from gas, spasms, or mild impactions. The efficacy of NBB for the treatment of spasmodic colic was based on a multicentered field study of naturally occurring simple colic in horses (Roelvink et al., 1991).

The elimination half-life of NBB in plasma is approximately 6 hours. The pharmacological effects produced by NBB are consistent with those of other anticholinergic drugs. In a study of the hemodynamic parameters, NBB decreased right atrial pressure, while cardiac output was maintained. The hemodynamic changes were similar to those reported following the administration of low doses of other anticholinergic agents such as atropine.

Recent work has focused on the potential utility of NBB administration for the treatment of marked airway

obstruction that may occur with conditions of airway inflammation such as recurrent airway obstruction or heaves. Current evidence provides support for the use of NBB as an immediate bronchodilator (Couetil et al., 2012). Although tachycardia and reduced gastrointestinal motility are valid considerations, based on the short duration of activity and evidence to support improved ventilator function it is considered an appropriate therapeutic option when managing equine patients with severe airway obstruction. Additional evidence to support the use of NBB in horses suffering from airway obstruction is supported by a cross-over investigation in recurrent airway obstruction affected horses where atropine and NBB provided similar bronchodilatory effects, yet the systemic effects such as pupillary dilation and one horse developing colic signs were only observed following atropine administration (de Lagarde et al., 2014). From this study it was concluded that NBB bromide was associated with fewer systemic side effects and is therefore a preferred treatment for reversible airway obstruction in horses. See Chapter 48 for further discussion.

Methantheline, Propantheline, and Methylatropine

These drugs are quaternary amines used primarily as smooth muscle relaxants. Because of the charged quaternary group, these compounds do not cross the blood–brain barrier to an appreciable extent. Accordingly, they are considerably less effective than atropine as antagonists to organophosphates, since the CNS effects of the latter agents would not be blocked. In addition to muscarinic blocking effects, these drugs act as autonomic ganglionic blockers, which most likely contributes to their antispasmodic effect on GI smooth muscle. Propantheline has been used in dogs with myasthenia gravis that develop significant muscarinic side effects in response to the administration of pyridostigmine.

Autonomic Ganglionic Blocking Drugs

Following Langley's investigations in 1889, it was known that small doses of nicotine stimulate autonomic ganglion cells, and larger doses block the transmitter function of ACh at these same sites. Therefore, the cholinergic receptors located at autonomic ganglia, primarily on postganglionic neurons, have been classified as nicotinic. The nicotinic receptor represents the primary ganglionic transmission pathway present in all autonomic ganglia, although muscarinic receptors on postganglionic neurons can modulate ganglionic impulse transmission.

Nicotine is not used clinically in animals or humans as a ganglionic blocker; however, several drugs have been discovered that preferentially block autonomic ganglia by a competitive mechanism. These compounds interact with nicotinic neural receptors and block impulse transmission across the ganglionic synapse. Members of this group of ganglionic blocking agents include hexamethonium, pentamethonium, and chlorisondamine.

Because of the blockade of impulse transmission at the ganglia, ganglionic blocking drugs affect physiological responses at targets innervated by postganglionic fibers of the SNS and the PSNS. The overall effects of these agents on various functions are dependent upon the predominance of sympathetic or parasympathetic tone at a particular target, as indicated in Table 8.3 (Taylor, 2006b). Because the GI system functions predominantly under parasympathetic tone, ganglionic blockade often results in decreased motility and reduced secretions. Similarly, because heart rate is under dominant vagal tone, a relative tachycardia may result following ganglionic blockade. Because the smooth muscle tone of peripheral blood vessels is dominated by the SNS, vasodilation and hypotension occur after ganglionic block, and the output of catecholamines from the adrenal medulla is reduced.

Table 8.3 Usual predominance of sympathetic or parasympathetic tone in various tissues and consequent effects of autonomic ganglionic blockade

Structures	Predominant tone	Effects of ganglionic blockade
Eye		
Iris	Parasympathetic	Mydriasis
Ciliary muscle	Parasympathetic	Cycloplegia
Sweat glands	Sympathetic	Anhidrosis
Salivary glands	Parasympathetic	Dry mouth
Cardiovascular		
Arterioles	Sympathetic	Vasodilation: ↑ peripheral blood flow; hypotension
Veins	Sympathetic	Vasodilation: pooling of blood; ↓ venous return
Heart	Parasympathetic	Tachycardia
Gastrointestinal	Parasympathetic	↓ Tone and motility; constipation
Urinary bladder	Parasympathetic	Urinary retention