THE AUTONOMIC NERVOUS SYSTEM: BASIC ANATOMY AND PHYSIOLOGY

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ABSTRACT
The autonomic nervous system is the critical component of a central network involved in homeostasis and adaptation. It regulates arterial blood pressure and regional blood flow in response to metabolic demands in underlying tissues, thermoregulation, motility and secretion of the gastrointestinal and respiratory tracts, micturition, and sexual function. The autonomic system consists of three subdivisions: the sympathetic, parasympathetic, and enteric nervous systems. The sympathetic and parasympathetic systems each have a central preganglionic neuron in the brain stem or spinal cord and a peripheral neuron in the autonomic ganglia. The enteric nervous system consists of neurons located in ganglia within the walls of the gut. A major component of the autonomic control systems consists of visceral afferent pathways. These pathways convey signals from the periphery that trigger visceral reflexes, transmit visceral pain, and regulate visceral function via antidromic release of neurochemical signals. The central control of autonomic function depends on a neuronal network distributed throughout the neuraxis. These neurons receive numerous afferent inputs and integrate this information according to the type of stimulus and current behavioral state. After these converging inputs have been evaluated, a specific pattern of autonomic outflow is relayed to the periphery. The central autonomic network consists of neurons in the insular and anterior cingulate cortex, amygdala, hypothalamus, periaqueductal gray, parabrachial nucleus, nucleus of the solitary tract, ventrolateral reticular formation, and medullary raphe.

PERIPHERAL AUTONOMIC SYSTEM

Anatomical Organization and Functional Organization
The sympathetic and parasympathetic efferent pathways carry signals from the brain to the periphery. They are made up of two neurons. The first neuron is in the general visceral efferent column of the brain stem or spinal cord and is known as a preganglionic neuron. The second neuron runs from the autonomic ganglia to innervate a target structure and is known as a peripheral effector neuron (Figure 1-1) (Furness, 2006; Shields, 1993).

The preganglionic neurons send small myelinated axons to the peripheral autonomic ganglia and to the enteric nervous system. The neurons of the sympathetic or parasympathetic ganglia send unmyelinated axons (called “post-ganglionic” axons) that innervate the heart, smooth muscle, and exocrine glands. The peripheral parasympathetic
ganglia are located close to the target organs and send short axons to innervate these visceral effectors (Figure 1-1).

The Sympathetic System

The sympathetic preganglionic neurons are primarily located in the intermediolateral nucleus at the T1 to L2 levels of the spinal cord (Cabot, 1996) (Figure 1-2). These neurons are organized into clusters; however, the distribution of the preganglionic fibers does not follow the dermal pattern of somatic nerves. In the sympathetic system, spinal segments T1 to T3 innervate the head, T1 to T6 the upper extremities and thoracic viscera, T5 to T11 the abdominal viscera, and T11 to L2 the lower extremities and pelvic and perineal organs (Shields, 1993).

Preganglionic sympathetic axons exit through the ventral roots and pass via white rami communicantes on the corresponding spinal nerve to reach the paravertebral sympathetic chain. The majority of preganglionic fibers branch and run rostrally or caudally along the sympathetic chain and synapse on a large number of paravertebral ganglia. The remaining fibers pass through the paravertebral chain without synapsing and form the splanchnic nerves that innervate prevertebral ganglia or the adrenal medulla (Shields, 1993) (Figure 1-2).

The paravertebral sympathetic ganglia are primarily relay stations for preganglionic inputs. They innervate all tissues and organs except those in the abdomen, pelvis, and perineum. For example, the superior cervical ganglion
sends postganglionic axons that follow the branches of the carotid arteries to innervate the eye; facial sweat glands; salivary glands; blood vessels of the face and brain; and pineal, thyroid, and parathyroid glands. Outputs from the superior cervical ganglion elicit pupil dilatation, contraction of the Müller muscle of the eyelid, facial sweating, and vasoconstriction in facial and cerebral circulation and have complex effects on salivary and lacrimal secretions.

The stellate ganglion receives pre-ganglionic inputs from T2 to T6 segments. It sends postganglionic axons that join the peripheral nerve, via the gray rami communicantes, and follow the distribution of the corresponding somatic nerve to innervate blood vessels and sweat glands in the upper limbs and trunk. These outputs elicit either vasoconstriction or vasodilatation in the skin and muscle, sweating, or piloerection. The stellate ganglion, together with other cervical and thoracic ganglia, provides inputs to the esophageal, pulmonary, and cardiac plexuses. These sympathetic outputs elicit cardiac acceleration and bronchodilatation. The lumbar paravertebral ganglia innervate blood vessels and sweat glands in the lower limb.

The prevertebral ganglia are located anterior to the abdominal aorta, close to the origin of the celiac and mesenteric arteries. They innervate all abdominal, pelvic, and perineal organs. Preganglionic input from spinal segments T5 to L2 are carried by the splanchnic nerves to the celiac and superior mesenteric ganglia and provide postganglionic fibers to the celiac plexus that innervates all abdominal viscera, with the exception of the descending colon. Outputs from these prevertebral sympathetic ganglia produce vasoconstriction.

**KEY POINT:**
- Paravertebral sympathetic ganglia act as relay stations and innervate the skin, muscles, and all visceral organs except those in the abdomen, pelvis, and perineum.

**FIGURE 1-2** Organization of the sympathetic output.

ACh = acetylcholine; ENS = enteric nervous system; NE = norepinephrine; SCG = superior cervical ganglia.

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and inhibition of gastrointestinal tract motility. Preganglionic axons from spinal segments L1 and L2 travel in the lumbar splanchnic nerves and synapse in the inferior mesenteric ganglion. They provide axons to the hypogastric plexus innervating the descending colon, rectum, bladder, and sexual organs. These sympathetic outputs elicit vasoconstriction, smooth muscle relaxation of the bladder and rectum, constriction of the internal sphincters of the bladder and rectum, and ejaculation. Unlike the paravertebral ganglia, which act primarily as relay stations of preganglionic inputs, the prevertebral ganglia integrate preganglionic with peripheral afferent inputs from the dorsal root ganglia and sensory neurons of the enteric nervous system and are therefore the site of ganglionic reflexes that are independent of the CNS.

The Parasympathetic System

Parasympathetic outputs arise from preganglionic neurons located in nuclei of the brain stem (cranial parasympathetic output) and sacral spinal cord (sacral parasympathetic output) (Shields, 1993). Preganglionic parasympathetic axons travel a long distance before eventually reaching their target ganglia, which are normally located close to, or even within, target end organs (Figure 1-1).

The cranial preganglionic parasympathetic nuclei project via cranial nerves III, VII, IX, and X. The Edinger-Westphal nucleus is a part of the oculomotor complex in the midbrain and sends preganglionic axons that occupy the peripheral portion of the oculomotor nerve and synapse on neurons of the ciliary ganglion in the orbit. These neurons innervate the iris and ciliary muscles, eliciting pupil constriction and accommodation of the lens. The superior salivatory nucleus, located in the pons, projects via the facial nerve to the sphenopalatine (or pterygopalatine) ganglion, which innervates the lacrimal gland (eliciting lacrimation) and the cranial and cerebral blood vessels (eliciting vasodilatation), and to the submandibular ganglion, which provides secretomotor and vasodilator inputs to the corresponding salivary glands (Shields, 1993). The inferior salivatory nucleus, located in the medulla, sends axons via the glossopharyngeal nerve, which synapse on the otic ganglion and stimulate parotid gland secretion.

Most preganglionic parasympathetic output from the brain stem is mediated by the vagus nerve. The vagus innervates the heart, respiratory tract, and the entire gastrointestinal tract with the exception of the descending colon and rectum (Figure 1-3). Most vagal preganglionic neurons are situated in the dorsal motor nucleus of the vagus, provide inputs to the gastrointestinal and respiratory tracts, and contribute to the innervation of the heart (Travagli et al, 2006). Vagal preganglionic output to the heart primarily arises from a subpopulation of neurons located in the ventrolateral portion of the nucleus ambiguus (Guyenet et al, 1996; Spyer, 1994). The vagus exerts cardioinhibitory, visceromotor, and secretomotor effects.

The sacral preganglionic output arises from neurons of the sacral preganglionic nucleus located in the lateral gray matter of spinal segments S2 and S3 (de Groat et al, 1996; Holstege, 2005). Their axons pass via the ventral roots to the pelvic splanchnic nerves, which join the inferior hypogastric plexus, and innervate the colon, bladder, and sexual organs. Parasympathetic outputs elicit contraction of the bladder detrusor muscle and circular smooth muscle of the rectum.

The sacral preganglionic parasympathetic neurons are involved in reciprocal inhibitory interactions via interneurons, with somatic motor neurons of the Onuf nucleus that innervate the external urethral and rectal sphincters and pelvic floor via the pudendal nerve.
The sacral parasympathetic output also elicits vasodilatation of the cavernous tissue of the penis, required for penile erection, whereas the sympathetic output controls ejaculation.

The Enteric Nervous System
The enteric nervous system includes several types of sensory neurons, interneurons, and motor neurons. These neurons are located within the walls of the gut in the myenteric plexus and submucosal plexus. They form local reflex circuits that mediate motility, secretion, and blood flow throughout the gut (Bornstein et al, 2004; Grundy et al, 2006). Although the control of the gut is largely carried out by these local and segmental reflexes, inputs from the vagus nerve and the prevertebral ganglia can modulate their activity.

VISCERAL AFFERENTS
Visceral afferents inform the CNS about mechanical and chemical events in the internal organs. This information is conveyed to produce conscious visceral sensation (including pain) and initiate visceral reflex responses (Grundy et al, 2006). Spinal visceral afferents innervate all peripheral organs. Their cell bodies are in the dorsal root ganglion and enter the spinal cord via the dorsal root. Brain stem visceral afferents are carried primarily by the glossopharyngeal and particularly the vagus nerves. Their cell bodies are in the petrosal and nodose ganglia, respectively. All brain stem visceral afferent nerves relay in the nucleus of the solitary tract (NTS) (Dampney et al, 2003; Saper, 2002; Spyer, 1994; Travagli et al, 2006).

The NTS is a major site of information integration for many bodily functions. The rostral portion of the NTS also receives taste afferents, primarily via the facial nerve (geniculate ganglion), but also from the glossopharyngeal and vagus nerves. The intermediate

KEY POINTS:
- The sacral parasympathetic output originates in the sacral parasympathetic nucleus at the S2-S3 levels of the spinal cord.
- The enteric nervous system consists of sensory neurons, interneurons, and motor neurons located in the myenteric and the submucosal plexus within the walls of the gut.
portion receives gastrointestinal afferents. The caudal portion of the NTS receives afferent information from the baroreceptors, cardiac receptors, chemoreceptors, and pulmonary receptors.

**Neurochemical Transmission**

The primary neurotransmitter of preganglionic sympathetic and parasympathetic neurons is acetylcholine (ACh) (Figure 1-4). ACh causes rapid excitation of the ganglion cells via ganglion-type nicotinic receptors. ACh is also the primary neurotransmitter of the parasympathetic ganglionic neurons and sympathetic neurons innervating the sweat glands and most enteric nervous system neurons. ACh is synthesized by choline acetyltransferase, and its synaptic effects are terminated by rapid hydrolysis with acetylcholinesterase. The effects of ACh are mediated by nicotinic and muscarinic receptors.

The ganglion nicotinic ACh receptor is composed of $\alpha_3$ and $\beta_4$ subunits. It is a ligand-gated cation channel that mediates fast excitatory transmission in the autonomic ganglia, adrenal medulla, and enteric nervous system. Muscarinic receptors are G protein-coupled receptors that include several subtypes. The M$_1$-like receptors (including M$_1$, M$_3$, and M$_5$ receptors) elicit neuronal depolarization by inhibiting

**Cholinergic Transmission**

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**KEY POINTS:**
- Visceral afferents from the dorsal root ganglion terminate in the dorsal horn, whereas those carried primarily via the glossopharyngeal nerves terminate in the nucleus of the solitary tract in the medulla.
- Acetylcholine is the neurotransmitter of the preganglionic neurons and elicits fast excitation of sympathetic and parasympathetic ganglion neurons via ganglion-type ($\alpha_3/\beta_4$) nicotinic receptors.

**FIGURE 1-4** Primary neurotransmission in the sympathetic and parasympathetic systems.

- ACh = acetylcholine; $\alpha$ = $\alpha$-adrenoceptors; $\beta$ = $\beta$-adrenoceptors
- gnAChR = ganglion-type nicotinic acetylcholine receptors; M = muscarinic
- NE = norepinephrine

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K⁺ conductance and increasing the release of intracellular Ca²⁺. In contrast, M₂-like receptors (including M₂ and M₄ receptors) inhibit adenylyl cyclase, activate K⁺ channels, and inhibit presynaptic Ca²⁺ channels. In peripheral organs, M₂ receptors mediate most of the ACh-induced activation of visceral smooth muscle contraction and exocrine glan-
dular secretion and trigger endothelial nitric oxide (NO)-mediated vasodilata-
tion. The M₂-type receptors mediate the inhibitory effects of the vagus on cardiac automatism, excitability, and conduction. The M₂ receptors also elicit smooth muscle contraction in the bladder and gut via inhibition of adenylyl cyclase and cyclic adenosine mono-
phosphate production, thus antagonizing the smooth muscle relaxant effect of β-adrenoreceptor inputs to these organs (Case 1-1).

**Adrenergic Transmission**

With the exception of the sweat glands, NE is the primary neurotrans-
mittor in sympathetic ganglion neu-
rons (Figure 1-4). Epinephrine is released from chromaffin cells of the adrenal medulla and acts as a circulating hormone. These catecholamines, as well as their precursor dopamine, which may also be released from some sympathetic terminals, are syn-
thesized from l-tyrosine by the action of tyrosine hydroxylase, which cata-
lyzes the conversion of l-tyrosine into l-dihydroxyphenylalanine (l-DOPA). l-DOPA is decarboxylated to dopa-
mime by the nonspecific cytoplasmic enzyme dopa decarboxylase, and dopa-
mime is converted to NE by action of the dopamine-β-hydroxylase. NE is stored in synaptic vesicles by action of the vesicular monoamine transporters. Its release from sympathetic terminals is modulated by several presynaptic receptors. The main mechanism of in-
activation of NE is its reuptake at pre-
synaptic terminals by the NE trans-
porter. After its removal from the synaptic cleft, NE undergoes oxidative deamination by action of monoamine oxidase A.

NE and epinephrine act via three families of G protein–coupled receptors, α₁-, α₂- and β-receptors (Figure 1-4). The α₁ receptors elicit release of intra-
cellular Ca²⁺, resulting in contraction of smooth muscle in blood vessels, pupil dilator muscle, bladder neck, and vas deferens. The α₂ receptors inhibit adenylyl cyclase and Ca²⁺ currents and activate K⁺ currents. These receptors

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### Case 1-1

A 70-year-old man with a history of chronic pain, depression, and insomnia is evaluated for development of confusional state and hallucinations over the past 12 hours. In addition to impaired attention and psychomotor agitation, examination reveals tachycardia, hyperthermia, dilated pupils, dry mouth, dry skin, and urinary retention. The patient had been started on amitriptyline 25 mg to alleviate his pain and sleep disorder 2 days ago.

**Comment.** This patient has manifestations of impaired parasympathetic control of the heart, pupil, salivary glands, and bladder and sympathetic control of the sweat glands. These manifestations reflect blockade of peripheral muscarinic cholinergic receptors. Amitriptyline has a strong antimuscarinic effect that limits its clinical use for management of depression or pain. Blockade of central muscarinic receptors accounts for the patient’s confusional state because ACh, acting primarily via M₁ receptors, is critical for mechanisms of attention and sensory processing.

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KEY POINT:

- Acetylcholine is the primary parasympathetic neurotransmitter and acts via muscarinic receptors to elicit cardiac inhibition, smooth muscle contraction-dependent vasodilatation, and smooth muscle relaxation.
mediate presynaptic inhibition of NE release (autoreceptors) as well as other neurotransmitters. β-Adrenoceptors stimulate adenyl cyclase and cyclic adenosine monophosphate production. The β₁ receptors mediate the sympathetic stimulation of cardiac automatism, excitability, and contractility; β₂ receptors trigger smooth muscle relaxation in some blood vessels (such as the facial vein), bronchi, bladder, and gut; and β₃ receptors trigger lipolysis in the brown fat, which is important for thermogenesis.

In response to loss of innervation by postganglionic sympathetic or parasympathetic axons, there is increased responsiveness of the visceral target organ to the neurotransmitter or an agonist that stimulates the adrenergic or muscarinic receptors, respectively. This phenomenon, known as denervation supersensitivity, reflects up-regulation of expression of membrane receptors as a consequence of the loss of the tonic neurotransmitter release from postsynaptic receptors in the target organs. Therefore, the presence of denervation supersensitivity indicates a peripheral (postganglionic) lesion. This phenomenon may lead to exaggerated pressor responses to small concentration of α₁-adrenergic agonists, similar to those present in over-the-counter decongestant preparations (Case 1-2).

**Other Peripheral Autonomic Neurotransmitters**

In addition to ACh and NE, many sympathetic and parasympathetic effects are mediated by neuropeptides, purines such as adenosine triphosphate (ATP) and NO (Lundberg, 1996). In most sympathetic terminals, neuropeptide Y coexists with NE and ATP. In parasympathetic terminals, vasoactive intestinal peptide (VIP) coexists with ACh and NO. In visceral afferents, substance P and calcitonin gene–related peptide (CGRP) coexist with glutamate and ATP. Neuropeptides exert potent effects on visceral structures; neuropeptide Y elicits a direct vasoconstrictor effect and presynaptically inhibits the release of NE and ACh. VIP and CGRP elicit vasodilatation, cardiac stimulation, and relaxation of visceral smooth muscle. Substance P elicits both endothelium-dependent vasodilatation and contraction of visceral smooth muscle.

ATP is a neurotransmitter in sympathetic, parasympathetic, and enteric

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**Case 1-2**

A 65-year-old man with a history of diabetes mellitus and laboratory evidence of autonomic neuropathy affecting cardiovagal and adrenergic functions is admitted to the emergency department for a severe headache. His blood pressure is 180/100 mm Hg, and heart rate is 90 beats per minute. The patient has no history of hypertension but had an upper respiratory infection and took an over-the-counter decongestant containing pseudoephedrine 1 hour prior to development of his symptoms.

**Comment.** This case illustrates the clinical relevance of denervation supersensitivity in patients with postganglionic lesions. This patient has diabetic autonomic neuropathy, affecting adrenergic vasomotor fibers, which leads to up-regulation of vascular α₁-adrenergic receptors. In these conditions, even minimal blood levels of an α₁-adrenergic agonist, such as pseudoephedrine, may lead to exaggerated pressor responses. This phenomenon has to be taken into account when these patients are started on midodrine for treatment of orthostatic hypotension.
nervous system neurons. It acts via two types of purinergic receptors. The P2X receptors are cation channels that mediate fast excitatory neurotransmission in nociceptive and visceral afferents and sympathetic terminals innervating smooth muscle. ATP is also released from peripheral structures, such as the bladder urothelium, where, via P2X receptors, it activates primary afferents to these organs. The P2Y receptors are G protein–coupled receptors, which trigger the release of NO and endothelium-mediated vasodilatation and relaxation of smooth muscle in the gut. NO is also released by some preganglionic, postganglionic, parasympathetic, and enteric neurons and is involved in endothelium-dependent vasodilation, penile erection, and smooth muscle relaxation in the gastrointestinal tract.

**PHYSIOLOGY**

**Sympathetic Outflow**

The sympathetic preganglionic neurons are organized into different functional units that control specific targets. They include muscle vasomotor, splanchnic vasomotor, skin vasoconstrictor, skin vasodilator, cardiomotor, sudomotor, and visceromotor preganglionic neurons (Jänig and Häbler, 2003). The different subsets of sympathetic preganglionic neurons are characterized by their reflex pattern of activation. Their activity is coordinated by descending inputs from distinct groups of neurons of the hypothalamus and brain stem. These supraspinal inputs provide tonic excitation of sympathetic preganglionic neurons, mediate reflex and adaptive influences on sympathetic activity, and allow a functionally selective pattern of sympathetic output according to the stimulus and required response (Morrison, 2001; Saper, 2002). Therefore, the concept of generalized sympathetic “tone” is no longer tenable.

The sympathetic system initiates coordinated responses that are necessary for the maintenance of blood pressure, thermoregulation, and integrated cardiovascular and metabolic responses to exercise, stress, and emotion. Sympathetic activity in muscle and skin nerves can be recorded in humans using microneurography (Vallbo et al, 2004). Sympathetically elicited vasoconstriction of skeletal muscle and splanchnic arteries and veins, mediated primarily by α1 receptors, is critical for maintenance of arterial blood pressure upon standing to prevent pooling of blood in the lower body and orthostatic hypotension (Smit et al, 1999).

Sympathetic outflow to the skin is critical for thermoregulation. Exposure to cold triggers skin vasoconstriction and piloerection via α1 receptors to preserve heat. Exposure to heat triggers sympathetically mediated sweating (via cholinergic M3 receptors) and skin vasodilatation to liberate heat. The mechanisms of sympathetically mediated skin vasodilatation are poorly understood, but may involve local release of NO (Charkoudian, 2003).

The sympathetic system, via α1 receptors, elicits pupil dilatation, contraction of the smooth muscle of the internal sphincters of the bladder and rectum, and contraction of the vas deferens necessary for ejaculation. In addition, it elicits constriction of some blood vessels via α2 receptors and presynaptically inhibits ACh release from presynaptic parasympathetic terminals in autonomic ganglia. Sympathetic inputs to the heart, mediated primarily by β1 receptors, are critical to increase cardiac output during exercise and other forms of stress. Activation of β2 receptors elicits bronchodilation and inhibits motility of the gut and bladder. Sympathetic output also mobilizes glucose and fatty acids in response to metabolic demands.

**KEY POINTS:**

- Neuropeptides, adenosine triphosphate, and nitric oxide may act as cotransmitters in sympathetic and parasympathetic terminals and the enteric nervous system.
- Preganglionic sympathetic neurons form functionally distinct subunits that are selectively activated by supraspinal inputs.
- Sympathetically induced vasoconstriction of skeletal muscle and splanchnic vessels is critical to avoid orthostatic hypotension.
- Sympathetic outflow to the skin blood vessels and sweat glands is critical for thermoregulation.
Parasympathetic Outflow

The main brain stem parasympathetic outflow is mediated by the vagus nerve (Figure 1-3). The vagus nerve exerts cardioinhibitory effects and provides a beat-to-beat control of heart rate (Eckberg et al, 1985; Spyer, 1994). Vagal modulation of the heart involves a relay in cholinergic ganglion neurons of the cardiac plexus, which, via M\(_2\) receptors, inhibits the automatism of the sinoatrial node and atrioventricular conduction. Vagal outputs, via the pulmonary plexus, elicit constriction of the bronchial smooth muscle and stimulate bronchial gland secretion.

In the gastrointestinal tract, the vagus nerve exerts complex effects. The vagal influence from the dorsal vagal nucleus is critical for control of esophageal and gastric motility but only has a modulatory facilitatory role on the motility of the intestine, which depends primarily on the enteric nervous system (Travagli et al, 2006). The vagus stimulates esophageal motility; gastric relaxation (to receive a meal) and evacuation; coordinated peristalsis along the gut; and secretion of electrolytes and digestive enzymes in the stomach, intestine, and pancreas. The stimulating effects of the vagus on smooth muscle contraction and exocrine secretion are mediated by M\(_3\) receptors, but M\(_1\) receptors activate secretion in the stomach. The relaxing effects of vagus nerve activity on the esophagus and stomach may be mediated by VIP, NO, or both.

The sacral parasympathetic output is critical for micturition, defecation, and penile erection (de Groat et al, 1996; Holstege, 2005). ACh activates the smooth muscle of the bladder (detrusor) and rectum both directly via M\(_3\) receptors and indirectly via M\(_2\) receptors, which antagonize \(\beta\)-adrenergic-mediated relaxation. Penile erection depends primarily on NO, which relaxes the cavernous tissue, with a possible contribution from VIP and ACh (Lundberg, 1996).

Most visceral organs have a dual sympathetic and parasympathetic control. The interactions between the sympathetic and parasympathetic systems may be antagonistic or functionally complementary and may occur at the level of the neuroeffector junction or at the target organ (Case 1-3). The effects of the sympathetic system and the neurochemical mechanisms are summarized in Table 1-1.

Sensorimotor Nerves

Nociceptive and visceral afferents release substance P, tachykinin A, and CGRP at the peripheral site of stimulation. This antidromic release of substance P induces endothelium-mediated vasodilatation and stimulates smooth muscle, whereas CGRP directly dilates vascular and other smooth muscles and stimulates the heart. In the skin, these substances elicit vasodilatation and increase vascular permeability (neurogenic inflammation) (Lundberg, 1996).

Enteric Nervous System

The enteric nervous system includes several types of sensory neurons, interneurons, and motor neurons, which form integrative local reflex circuits that control motility, secretion, and blood flow throughout the gut (Bornstein et al, 2004; Grundy et al, 2006). The activity of the enteric nervous system is largely independent of extrinsic innervation but is modulated both by vagal inputs from the dorsal vagal nucleus (Travagli et al, 2006) and sympathetic inputs from the prevertebral ganglia.

Mechanical distension or distortion of the mucosa, or change in intraluminal chemistry can elicit polarized reflex responses in the gut, leading to propulsion of its contents. At short distances motility is regulated by monosynaptic reflexes and at longer
Case 1-3
A 55-year-old man with insulin-dependent diabetes mellitus is evaluated for lightheadedness upon standing, particularly in the early morning and after a meal. He also experiences nausea after eating and has a 3-year history of constipation and erectile dysfunction.

On neurologic examination, his pupils fail to dilate when examined under a dim light. There is weakness in foot dorsiflexors, absent ankle jerks, and loss of sensation to all modalities below the midcalf. His feet are dry. He has a 30-mm Hg fall of systolic pressure upon standing accompanied by symptoms of lightheadedness. Supine heart rate is 94 beats per minute with no change upon standing. Autonomic laboratory testing reveals impaired sudomotor axon reflex responses to local iontophoresis of ACh, marked reduced variation of the heart rate in response to deep breathing, reduced Valsalva ratio, abnormal blood pressure profile during the Valsalva maneuver, and orthostatic hypotension. Gastrointestinal motility study shows delayed gastric emptying. Ultrasound reveals a postvoid residual of 250 cc. Administration of 5 mg of midodrine orally in the office results in a 40-mm Hg increase of systolic and 20-mm Hg increase in diastolic arterial pressure.

Comment. This case shows the clinical and laboratory consequences of loss of sympathetic and parasympathetic axons due to diabetic autonomic neuropathy. In this patient, sympathetic failure is manifested by orthostatic hypotension, impaired sweating, oculosympathetic impairment, and abnormal blood pressure profile during the Valsalva maneuver. Vagal impairment is reflected by delayed gastric emptying, constipation, and reduced variability of the heart rate in response to orthostatic stress, respiration, and Valsalva maneuver. Sacral parasympathetic failure is manifested by urinary retention and erectile dysfunction. This syndrome of generalized autonomic failure may also be a manifestation of central neurodegenerative disorders, such as multiple system atrophy or Lewy body disease. However, in this patient, the impaired sudomotor axon reflex responses and the exaggerated pressor response to a peripheral $\alpha_1$-receptor agonist (midodrine) are more consistent with a postganglionic (peripheral) than a central disorder. Central disorders, such as multiple system atrophy, however, may also be associated with exaggerated pressor responses to adrenergic agonists due to impairment of the baroreflex.

distances by polysynaptic pathways involving chains of interneurons. The same types of stimuli that elicit the peristaltic reflex also cause concomitant secretory and vasomotor changes.

CENTRAL CONTROL OF AUTONOMIC FUNCTION

Components of the Central Autonomic Network
The central autonomic network includes telencephalic structures (insula cortex, anterior cingulate cortex, and amygdala), diencephalic structures (hypothalamus and thalamic visceral relay nuclei), and brain stem structures (periaqueductal gray, parabrachial nucleus, NTS, ventrolateral medullary (VLM) reticular formation, and medullary raphe (Benarroch, 1993; Saper, 2002) (Figure 1-5).

Telencephalic Components
The insular cortex, the anterior cingulate cortex, adjacent orbitofrontal cortex, and amygdala are intimately connected with
one another and with the hypothalamus and brain stem areas controlling autonomic function. These communication links play a critical role in integration of bodily sensation, emotion, and decision making.

The insula is the primary viscerosensory cortex and has a viscerotropic organization. Functional neuroimaging studies show that the insula is activated in response to visceral, as well as nociceptive stimuli, in humans (Craig, 2003; Saper, 2002). The insula is also a visceromotor area, controlling both the sympathetic and parasympathetic outputs, primarily via a relay in the lateral hypothalamic area.

The anterior cingulate cortex initiates autonomic responses related to motivation and goal-directed behaviors. Its ventral or subcallosal region has extensive connections with the prefrontal

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**TABLE 1-1** Effects of the Sympathetic and Parasympathetic Systems on Different Targets and the Neurotransmitter Receptor Involved

| Target                          | Sympathetic (Receptor) | Parasympathetic (Receptor) |
|--------------------------------|------------------------|-----------------------------|
| Pupil                          | Dilatation (α₁)        | Constriction (M₃)           |
| Ciliary muscle                 | ...                    | Accommodation (M₃)          |
| Salivary and lacrimal glands   | Inhibition (presynaptic [α₂?]) | Stimulation (M₃)             |
| Heart                          | Stimulation (β₁)       | Inhibition (M₂)             |
| Bronchi                        | Dilatation (β₂)        | Constriction (M₃)           |
| Muscle vessels                 | Constriction (α₁), (α₂) |                             |
|                                | Dilatation (β₂)        |                             |
| Skin vessels                   | Constriction (α₁)      |                             |
|                                | Dilatation (NO?)       |                             |
| Visceral vessels               | Constriction (α₁)      | Dilatation (M₃ via NO; VIP) |
| Sweat glands                   | Stimulation (M₃)       |                             |
| Gastrointestinal motility      | Inhibition (β₂)        | Contraction (M₃)             |
| Gastrointestinal secretion     | Inhibition (α₂)        | Gastric stimulation (M₄)    |
| Bladder detrusor               | Inhibition (β₂)        | Gut and glands (M₃, VIP)    |
| Bladder neck                   | Stimulation (α₁)       | Inhibition?                 |
| Rectal smooth muscle           | Inhibition (β₂)        | Stimulation (M₃)             |
| Erectile tissue                | Constriction (α₁)      | Dilatation (NO)             |
| Vas deferens                   | Contraction (α₁)       |                             |
| Endocrine secretion            | Stimulation of epinephrine, glucagon, renin, and thyroxine (β₂) | Stimulation of insulin, gastrin, secretin, cholecystokinin, and pancreatic polypeptide (M₃?) |
| Glycogenolysis                 | Stimulation (β₂)       |                             |
| Lipolysis                      | Stimulation (β₃)       |                             |

**Note:** ATP = adenosine triphosphate; NO = nitric oxide; VIP = vasoactive intestinal neuropeptide.

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cortex, amygdala, hypothalamus, and brain stem. It is involved in the modulation of autonomic output in response to pain and other emotionally or behaviorally significantly stimuli (Critchley et al, 2003).

The amygdala gives emotional significance to sensory stimuli and is involved in the mechanisms of conditioned fear responses (LeDoux, 2000). Its effector structure is the central nucleus. The amygdala has connections with the bed nucleus of the stria terminalis, hypothalamus, and brain stem. It initiates autonomic and endocrine responses and motor activation that is critical for expression of emotional responses.

**Hypothalamus**

The hypothalamus has a central role in integrating autonomic and endocrine responses. It plays a critical role in adaptation to internal or external stimuli, while maintaining homeostasis. The hypothalamus is subdivided into three functional zones (Toni et al, 2004). (1) The *paraventricular zone* is involved in neuroendocrine control via connections to the pituitary. (2) The *medial zone* has a central role in coordinating homeostatic mechanisms, such as thermoregulation, osmoregulation, food intake, response to stress, and reproduction. (3) The *lateral zone* regulates arousal and behavior, including sleep-wake cycles, feeding, and reward responses. The outputs from the hypothalamus arise from the paraventricular nucleus and lateral hypothalamic zone and project to autonomic nuclei in the brain stem and spinal cord. The dorsomedial and arcuate nucleus also contribute inputs to autonomic nuclei of the medulla and spinal cord (Benarroch, 1993; Saper, 2002).
Brain Stem Components

The periaqueductal gray is involved in the integration of autonomic, somatic, and antinociceptive responses to external stress. It is subdivided into different longitudinal columns with specific inputs and outputs. The periaqueductal gray coordinates the cardiovascular, respiratory, thermoregulatory, urinary, reproductive, and pain control systems (Misslin, 2003).

The parabrachial nucleus receives converging inputs from visceral receptors, nociceptors, and thermal receptors and relays this information to the hypothalamus, amygdala, and thalamus (Saper, 2002). The parabrachial nucleus receives these inputs both via the NTS and spinobulbar pathways. The parabrachial nucleus also contains several subnuclei involved in taste, salivation, gastrointestinal activity, cardiovascular activity, respiration, osmoregulation, and thermoregulation (Saper, 2002).

The NTS is the first relay station for taste and visceral afferent information carried in cranial nerves VII, IX, and X. It has a viscerotopic organization; its rostral one third receives taste afferents; the intermediate one third receives esophageal, gastric, and intestinal afferents; and the caudal one third receives cardiovascular and respiratory afferents (Saper, 2002; Travagli et al, 2006). The NTS also receives nociceptive information from the dorsal horn and trigeminal nucleus caudalis. Different subnuclei of the NTS relay this information, either directly or via the parabrachial nucleus, to the periaqueductal gray, hypothalamus, thalamus (and then to the insular cortex), and amygdala (Saper, 2002). The NTS is also the first central relay station for all medullary cardiovascular (Dampney et al, 2003; Spyer, 1994), respiratory (Feldman et al, 2003), and gastrointestinal (Travagli et al, 2006) reflexes.

The VLM contains the neurons that control vasomotor tone (Dampney et al, 2003; Guyenet et al, 1996; Morrison, 2001), cardiac function (Guyenet et al, 1996; Spyer, 1994), and respiration (Feldman et al, 2003). Neurons of the rostral VLM include C1 epinephrine-synthesizing neurons and glutamatergic neurons that provide the major tonic excitatory input to sympathetic preganglionic neurons innervating resistance vessels of the muscle and visceral organs. Their activity generates vasomotor output that is essential for the maintenance of arterial blood pressure. Neurons in the caudal VLM include γ-aminobutyric acid (GABA)-ergic neurons and A1 noradrenergic neurons. The GABAergic neurons mediate several cardiovascular reflexes, and the A1 noradrenergic neurons control hypothalamic function. The medullary raphe contains neurons that project to sympathetic preganglionic neurons that provide sympathetic vasomotor outputs to the skin, which are critical for thermoregulation and emotional responses (Morrison, 2001).

CENTRAL MECHANISMS OF AUTONOMIC CONTROL

Selective Activation of Sympathetic Preganglionic Units

Sympathetic preganglionic neurons are highly organized into functionally separate units. These units innervate selective subpopulations of ganglionic neurons, which in turn control specific organs (Cabot, 1996; Jänig and Häbler, 2003). Each specialized functional sympathetic pathway receives selective segmental and descending inputs and generates distinct reflex patterns (Jänig and Häbler, 2003). Descending pathways from the hypothalamus and brain stem also modulate sympathetic preganglionic outflow. These pathways primarily arise from neurons in the paraventricular nucleus, lateral hypothalamus (including
hypocretin/orexin neurons), arcuate nucleus, A5 noradrenergic neurons of the pons, rostral VLM (including glutamatergic and C1 adrenergic neurons), and medullary raphe (Benarroch, 1993; Morrison, 2001; Saper, 2002).

The individual sympathetic preganglionic units are incorporated into pattern-generator modules. Each module is capable of influencing separate spinal effector pathways, which are controlled by different inputs. These complex interconnecting pathways allow the integration of information from various regions (Morrison, 2001; Saper, 2002). An example of this is in the rostral VLM. The rostral VLM generates a pattern of activity in the vasoconstrictor neurons that innervate the muscular and splanchnic vasculature, which are essential in the maintenance of arterial blood pressure. These neurons are under inhibitory influence from the baroreflex; thus, when blood pressure rises and the baroreflex is activated, sympathetic output can be withdrawn to induce vasodilatation. Another example is the neurons in the rostral medullary raphe that control skin vasoconstriction and sympathetic outflow to brown fat. They receive input from the hypothalamus, which relates to thermoregulation (Morrison, 2001).

When the descending pathways innervating the sympathetic preganglionic neurons are injured, for example with spinal cord lesions above the T5 level, autonomic regulation can be severely impaired and autonomic dysreflexia can occur. The most serious consequence of autonomic dysreflexia is severe hypertension in response to bladder distension or other peripheral inputs. These segmental inputs lead to massive, nonpatterned sympathoexcitation, which cannot be buffered by the baroreflex.

**Medullary Reflexes**

The medullary cardiovascular and respiratory reflexes have several features in common. Afferent nerves carrying information from baroreceptors, cardiac receptors, chemoreceptors, and pulmonary mechanoreceptors travel to the medulla and synapse at specific subdivisions within the NTS. Modality-selective NTS neurons are capable of communicating with one another via direct and indirect propriobulbar connections to integrate the excitatory inputs from multiple peripheral sensors. Once this information is evaluated, it is relayed to several efferent neurons to activate or inhibit efferent reflex outflow.

A typical example of a medullary reflex is the baroreceptor reflex (Figure 1-6). The baroreflex is a powerful moment-to-moment negative feedback loop that regulates arterial blood pressure. It minimizes fluctuations of arterial pressure, for example during standing, exercise, or emotion (Dampney, 2003; Guyenet et al, 1996; Spyer, 1994). The baroreflex “starts” in the periphery, where mechanosensitive baroreceptor terminals, sitting in the walls of the carotid sinus and aortic arch, sense distension of the vessel wall when blood pressure rises. Afferent information travels from the carotid baroreceptors in the glossopharyngeal nerve and from the aortic arch baroreceptors in the vagus nerve to the NTS. These baroreceptive afferents excite baroreceptive neurons within the NTS. Three baroreceptive neuronal pathways lead from the NTS. The first involves projections to cardiac vagal neurons of the nucleus ambiguus that elicit a decrease in heart rate. The second is mediated by neurons in the caudal VLM that inhibit sympathetic outflow from the rostral VLM to decrease peripheral vasomotor tone. The third consists of ascending projections to the supraoptic and paraventricular nuclei to inhibit vasopressin release. The combination of bradycardia and peripheral vasodilatation restores blood pressure.
Upon standing, gravity causes blood to pool in the lower limbs, which reduces venous return and cardiac output, and this unloads the baroreceptors. Reduced afferent activity causes vagal withdrawal, sympathetic excitation, and the release of vasopressin. Baroreflex-mediated sympathetic vasoconstriction of muscle and splanchnic blood vessels is essential in preventing orthostatic hypotension (Smit et al, 1999).

The medullary respiratory and cardiovascular reflexes are able to interact with one another. One typical example of this is respiratory sinus arrhythmia, the rhythmical fluctuation in blood pressure and heart rate over the breathing cycle, generated by the activity of cardiovagal and sympathetic premotor neurons (Eckberg et al, 1985). During inspiration, phasic inhibition of cardiovagal neurons in the nucleus ambiguus produces tachycardia, and during expiration, this inhibition is withdrawn and cardiac vagal activation produces bradycardia. These heart rate changes, occurring at the respiratory frequency, can be detected by power spectrum analysis (Case 1-4).

**Micturition Reflex**

The micturition reflex involves a spino-bulbospinal pathway activated by high-frequency discharge of bladder afferents (de Groat et al, 1996; Holstege, 2005). The afferent limb of the micturition reflex activates neurons in the periaqueductal gray that project to a pontine micturition center in the dorsolateral pontine tegmentum. The pontine micturition center contains neurons that project to the sacral spinal cord. Via a monosynaptic connection the pontine micturition center activates the parasympathetic neurons that innervate the bladder detrusor muscle. In addition, this pathway also activates...
**Case 1-4**

A 59-year-old man is evaluated for episodes of paroxysmal hypertension associated with headache and sensation of facial flushing. Examination reveals bilateral palate weakness and loss of sensation to pinprick in the face and tongue. In the supine position, his blood pressure is 120/80 mm Hg and heart rate is 88 beats per minute. During emotional stress elicited by mental arithmetic exercises, his blood pressure increases to 200/110 mm Hg, and his heart rate remains at 88 beats per minute. An MRI of the head reveals syringobulbia with bilateral involvement of the NTS and relative sparing of the VLM.

**Comment.** Episodes of paroxysmal hypertension are the typical manifestation of baroreflex failure. This disorder results from damage to the arterial baroreceptors, baroreceptor afferents, or the NTS where these afferents terminate. Baroreflex failure may occur in patients with Guillain-Barré syndrome, porphyria, extensive neck surgery, radiation therapy for cancers of the neck, or bilateral carotid tumor resections. The episodes are commonly triggered by psychological stress, physical exercise, or pain.

Baroreflex failure may also occur as a manifestation of bilateral lesions involving the NTS, for example with syringobulbia, as long as the lesions spare the sympathoexcitatory neurons of the rostral VLM. One important differential diagnosis is pheochromocytoma. Clonidine, a centrally acting drug that inhibits the sympathoexcitatory neurons of the rostral VLM, profoundly reduces arterial pressure and plasma NE levels in patients with baroreflex failure, whereas it has no effect in patients with pheochromocytoma.

**Thermoregulation**

Thermoregulation is one important example of the integrative function of the hypothalamus. It involves autonomic, endocrine, and behavioral responses that are intimately related to other hypothalamic functions, including regulation of circadian rhythms, sleep-wake cycle, fluid regulation, and food intake. The medial preoptic area of the hypothalamus acts as a thermostat (Boulant, 2000). It contains warm-sensitive neurons that initiate skin vasodilatation and sweating to dissipate heat and cold-sensitive neurons that trigger shivering, brown fat metabolism, and skin vasoconstriction to generate and conserve heat. Thermoregulatory signals from the hypothalamus relay in the periaqueductal gray before being transmitted to the medullary sympathetic control centers. The responses to cold are initiated by neurons in the caudal periaqueductal gray that communicate with the rostral medullary raphe to modulate skin vasoconstrictor...
activity and increase sympathetic outflow to the brown fat tissue (Morrison, 2001). In contrast, the pathways mediating heat responses, particularly sweating, are less well understood.

Emotion and Responses to Stress

The autonomic responses to emotion and stress involve the anterior cingulate gyrus, ventromedial prefrontal cortex, amygdala, hypothalamus, and periaqueductal gray. The amygdala is essential in providing affective value to incoming sensory information. It initiates visceral, endocrine, and motor responses during emotional states, particularly fear (LeDoux, 2000). Acute, transient stressful stimuli produce a short-term response known as the “defense reaction.” The key element of the defense reaction is to redistribute blood flow to the limbs and prepare the body for “fight or flight.” This blood redistribution is achieved by sympathetic and adrenomedullary activation that overrides normal baroreflex blood pressure control. The defense reaction resembles the response to physical exercise. It is brought about by selectively modulating regional sympathetic activity that originates in the rostral VLM, and involves the lateral hypothalamus and periaqueductal gray. When the stress exceeds a certain threshold, the sympathoadrenal and adrenocortical systems become activated and vasopressin is released. Reciprocal interactions between the central nucleus in the amygdala, paraventricular nucleus, and noradrenergic neurons in the locus ceruleus have a critical role the activation of all these systems (Benarroch, 2005).

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