11

The Autonomic Nervous System and Its Central Control

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What are the similarities and differences in the general organizations of the parasympathetic and sympathetic systems?
2. What are the respective actions of the parasympathetic and sympathetic innervation of the eye, and what symptoms arise when the parasympathetic or sympathetic innervation is lost?
3. What are the changes in the balance of parasympathetic and sympathetic activity to the bladder that occur during micturation?
4. What is meant by a "servomechanism"?
5. What are the specific feedback loops that regulate body temperature, feeding and body weight, and water intake?
6. What is the role of the hypothalamus in each of these feedback loops?

The main function of the **autonomic nervous system** is to assist the body in maintaining a stable internal environment **(homeostasis).** When internal stimuli signal that regulation of the body's environment is required, the central nervous system (CNS) and its autonomic outflow issue commands that lead to compensatory actions. For example, a sudden increase in systemic blood pressure activates the baroreceptors, which in turn modify the activity of the autonomic nervous system so that the blood pressure is lowered toward its previous level (see Chapter 17).

The autonomic nervous system has both sensory and motor divisions. The motor division is further divided into the **sympathetic** and **parasympathetic divisions.** Because much of the autonomic nervous system's actions relate to control of the viscera, it is sometimes called the **visceral nervous system**.

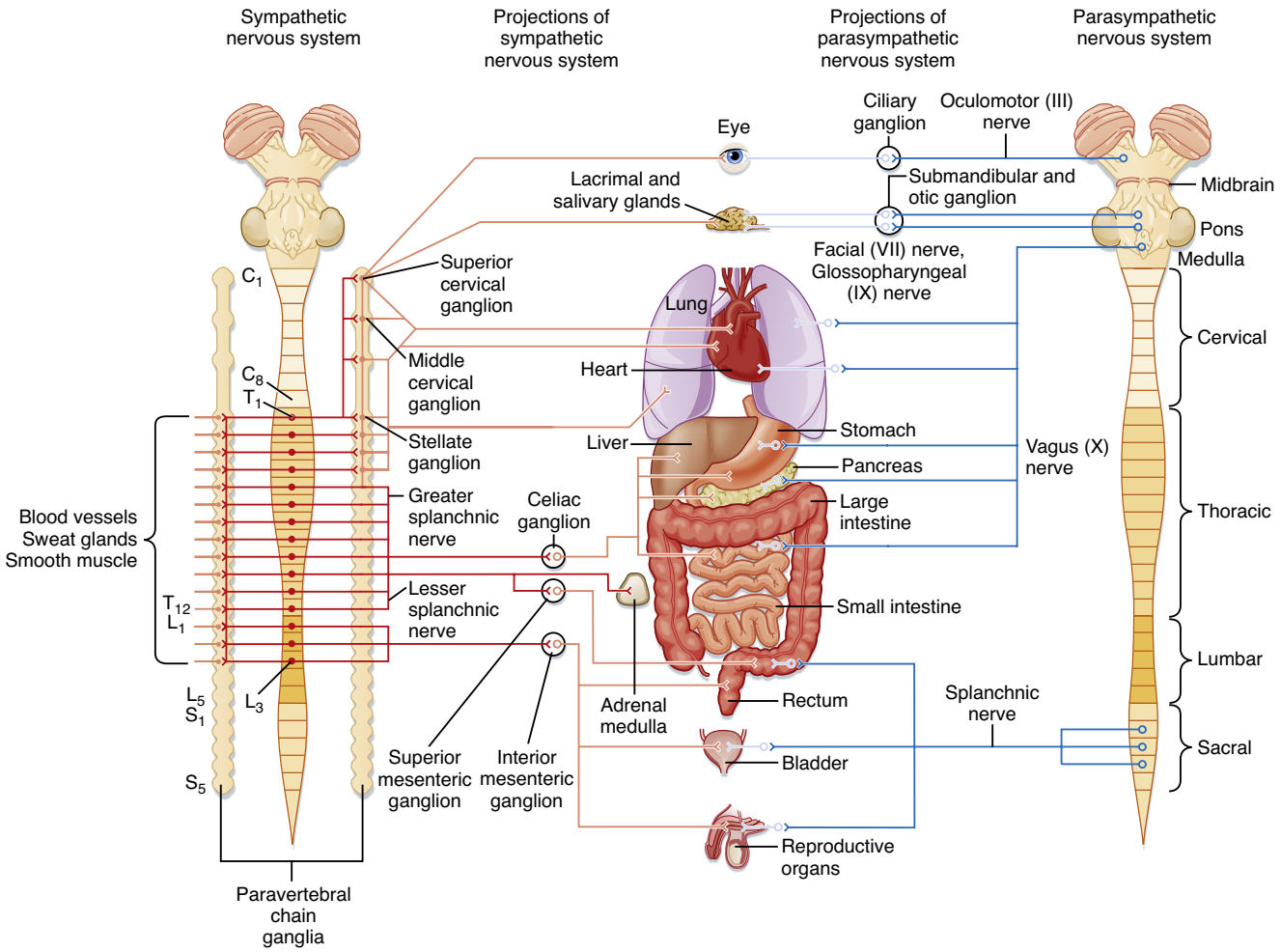
In service of its homeostatic function, the autonomic nervous system mediates visceral reflexes (e.g., the gastrocolic reflex, where stomach distention triggers peristalsis in the intestines) and provides sensory information to the CNS of the perception of the state of our viscera, a percept known to anyone who has eaten too much at a meal. More generally, activation of autonomic receptors can evoke a variety of sensory experiences such as pain, hunger, thirst, nausea, and a sense of visceral distention; these perceptions can then lead to compensatory voluntary behaviors that assist in maintaining homeostasis.

In addition to its central role in homeostasis, the autonomic nervous system also participates in appropriate and coordinated responses to external stimuli that are required for the optimal functioning of the somatic nervous system in performing voluntary behaviors. For example, the autonomic nervous system helps regulate pupil size in response to different intensities of ambient light, thus helping the visual system to operate over a large range of light intensity.

In this chapter, the **enteric nervous system** is also considered part of the autonomic nervous system, although it is sometimes considered a separate entity (see also Chapter 27). In addition, because the autonomic nervous system is under CNS control, the central components of the autonomic nervous system are discussed in this chapter. These central components include the hypothalamus and higher levels of the limbic system, which are associated with emotions (see Chapter 10) and with many visceral types of behavior (e.g., feeding, drinking, thermoregulation, reproduction, defense, and aggression) that have survival value.

Organization of the Autonomic Nervous System

The sensory autonomic neurons are located in the dorsal root ganglia and in the cranial nerve ganglia. Like the other neurons of the dorsal root ganglia, they are pseudounipolar cells with a peripheral axonal branch extended to one of the viscera and a central branch that enters the CNS. With regard to autonomic motor output, both the sympathetic and parasympathetic nervous systems use a two-neuron motor pathway, which consists of a preganglionic neuron, whose cell body is located in the CNS, and a postganglionic neuron, whose cell body is located in one of the autonomic ganglia (Figs. 11.1 and 11.2). The targets of this motor pathway are smooth muscle, cardiac muscle, and glands. The enteric nervous system includes the neurons and nerve



• **Fig. 11.1** Schematic illustration of the sympathetic and parasympathetic pathways. Sympathetic pathways are shown in *red* and parasympathetic pathways in *blue.* Preganglionic neurons are shown in *darker shades,* and postganglionic neurons, in *lighter shades.*

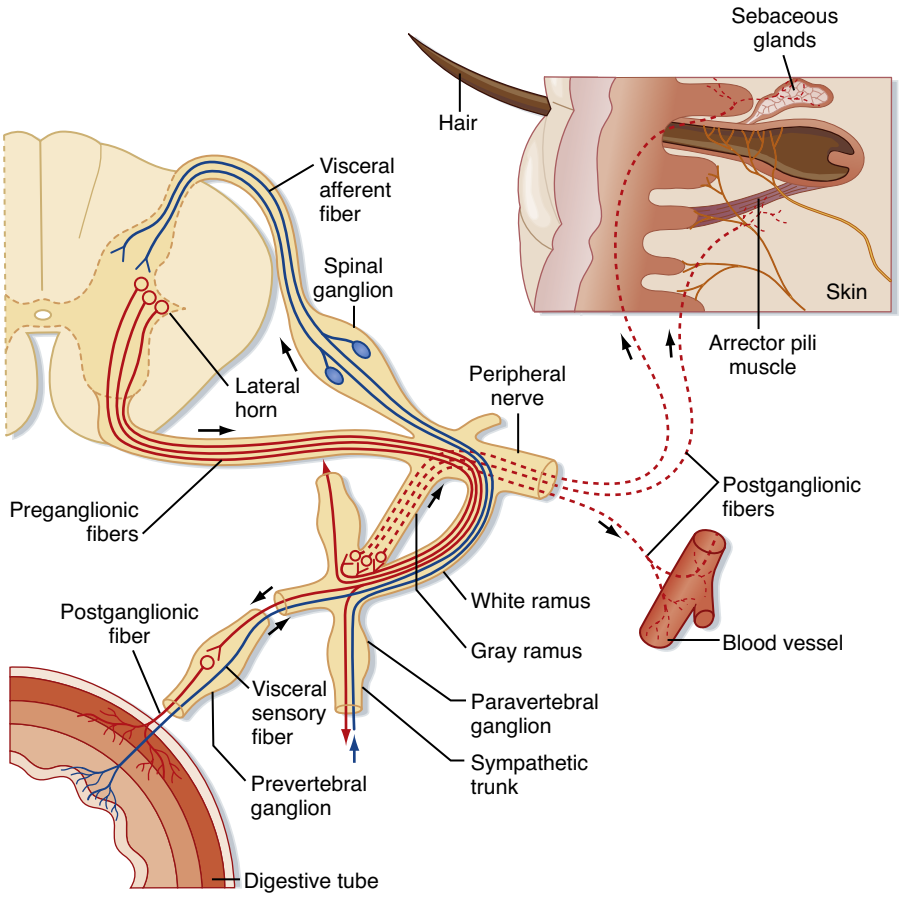
fibers in the myenteric and submucosal plexuses, which are located in the wall of the gastrointestinal tract.

The sympathetic and parasympathetic nervous systems often regulate organ function through opposing actions. To highlight this contrast, the sympathetic and parasympathetic systems are sometimes referred to as the "fight or flight" and the "rest and digest" systems, respectively. Indeed, the fight-or-flight response to a threat to the organism reflects an intense activation of the sympathetic nervous system, which leads to a variety of responses, including increased heart rate and blood pressure, redistribution of blood to the muscles, decreased peristalsis and gastrointestinal secretions, pupil dilation, and sweating.

However, under most conditions, the two parts of the autonomic control system work in a coordinated manner—sometimes acting reciprocally and sometimes synergistically—to regulate visceral function. Furthermore, not all visceral structures are innervated by both systems. For example, the smooth muscles and glands in the skin and most of the blood vessels in the body receive sympathetic innervation exclusively; only a small fraction of the blood vessels have parasympathetic innervation. Indeed, the parasympathetic nervous system innervates not the body wall, but only structures in the head and in the thoracic, abdominal, and pelvic cavities.

The Sympathetic Nervous System

The sympathetic preganglionic neurons are located in the thoracic and upper lumbar segments of the spinal cord. For this reason, the sympathetic nervous system is sometimes referred to as the **thoracolumbar division** of the autonomic nervous system. Specifically, sympathetic preganglionic neurons are concentrated in the **intermediolateral cell column** (lateral horn) in the thoracic and upper lumbar segments of the spinal cord (see Fig. 11.2). Some neurons may also be found in the C8 segment. In addition to the intermediolateral cell column, groups of sympathetic preganglionic neurons are found in other locations, including the lateral funiculus, the intermediate gray matter, and the gray matter dorsal to the central canal. Sympathetic postganglionic neurons are generally found in the paravertebral or prevertebral ganglia. The paravertebral ganglia form two sets of ganglia, each lateral to one side of the vertebral column. The



• **Fig. 11.2** Details of the sympathetic pathway at a thoracic spinal segment. Autonomic sensory fibers are represented by *blue lines;* sympathetic fibers, by *red lines;* preganglionic axons, by *solid lines,* and postganglionic axons, by *dashed lines.* (Redrawn from Parent A, Carpenter MB. *Carpenter's Human Neuroanatomy.* 9th ed. Philadelphia: Williams & Wilkins; 1996:295.)

individual ganglia on each side are linked by longitudinally running axons that form a sympathetic trunk (see Figs. 11.1 and 11.2). Prevertebral ganglia are located in the abdominal cavity and include the celiac and superior and inferior mesenteric ganglia (see Fig. 11.1). Thus paravertebral and prevertebral ganglia are located at some distance from their target organs.

The axons of preganglionic neurons are often small, myelinated nerve fibers known as *B fibers* (see Table 5.1), although some are unmyelinated *C fibers.* They leave the spinal cord in the ventral root and enter the paravertebral ganglion at the same segmental level through a white communicating ramus. White rami are found only from the levels of T1 to L2. The preganglionic axon may synapse on postganglionic neurons in the ganglion at its level of entry; may travel rostrally or caudally within the sympathetic trunk and give off collaterals to the ganglia that it passes; or may pass through the ganglion, exit the sympathetic trunk, and enter a splanchnic nerve to travel to a prevertebral ganglion (see Figs. 11.1 and 11.2). Splanchnic nerves innervate the viscera; they contain both visceral afferents and autonomic motor fibers (sympathetic or parasympathetic).

Postganglionic neurons whose somata lie in paravertebral ganglia generally send their axons through a gray communicating ramus to enter a spinal nerve (see Fig. 11.2). Each of the 31 pairs of spinal nerves has a gray ramus. Postganglionic axons are distributed through the peripheral nerves to effectors, such as piloerector muscles, blood vessels, and sweat glands, located in the skin, muscle, and joints. Postganglionic axons are generally unmyelinated (C fibers), although some exceptions exist. The names white and gray rami reflect the relative contents of myelinated and unmyelinated axons in these rami.

Preganglionic axons in a splanchnic nerve often travel to a prevertebral ganglion and synapse, or they may pass through the ganglion and an autonomic plexus and end in a more distant ganglion. Some preganglionic axons pass through a splanchnic nerve and end directly on cells of the adrenal medulla, which are equivalent to postganglionic cells.

The organization of the sympathetic ganglion extending bilaterally from the cervical level to the coccygeal level forms a ganglionated chain and is often referred to as the sympathetic chain. This arrangement serves as a distribution system that enables preganglionic neurons, which are limited to the thoracic and upper lumbar segments, to activate postganglionic neurons that innervate all body segments. However, there are fewer paravertebral ganglia than there

are spinal segments because some of the segmental ganglia fuse during development. For example, the superior cervical sympathetic ganglion represents the fused ganglia of C1 through C4; the middle cervical sympathetic ganglion is the fused ganglia of C5 and C6; and the inferior cervical sympathetic ganglion is a combination of the ganglia at C7 and C8. The term **stellate ganglion** refers to fusion of the inferior cervical sympathetic ganglion with the ganglion of T1. The superior cervical sympathetic ganglion provides postganglionic innervation to the head and neck, and the middle cervical and stellate ganglia innervate the heart, lungs, and bronchi.

In general, the sympathetic preganglionic neurons are distributed to ipsilateral ganglia, and thus control autonomic function on the same side of the body. Important exceptions are the sympathetic innervation of the intestines and the pelvic viscera, which are both bilateral. As with motor neurons to skeletal muscle, sympathetic preganglionic neurons that control a particular organ are spread over several segments. For example, the sympathetic preganglionic neurons that control sympathetic functions in the head and neck region are distributed at levels C8 to T5. Similarly, those that control adrenal gland are distributed at levels T4 to T12.

The Parasympathetic Nervous System

The parasympathetic preganglionic neurons are found in several of the cranial nerve nuclei of brainstem and in the sacral spinal cord (S3-S4) gray matter (see Fig. 11.1). Hence, this part of the autonomic nervous system is sometimes called the **craniosacral division.** The cranial nerve nuclei that contain parasympathetic preganglionic neurons are the **Edinger-Westphal nucleus** (cranial nerve III), the **superior** (cranial nerve VII) and **inferior** (cranial nerve IX) **salivatory nuclei,** and the **dorsal motor nucleus of the vagus** and **nucleus ambiguus** (cranial nerve X). Postganglionic parasympathetic cells are located in cranial ganglia, including the **ciliary ganglion** (preganglionic input is from the Edinger-Westphal nucleus), the **pterygopalatine** and **submandibular ganglia** (input is from the superior salivatory nucleus), and the **otic ganglion** (input is from the inferior salivatory nucleus). The ciliary ganglion innervates the pupillary sphincter and ciliary muscles in the eye. The pterygopalatine ganglion supplies the lacrimal gland, as well as glands in the nasal and oral pharynx. The submandibular ganglion projects to the submandibular and sublingual salivary glands and to glands in the oral cavity. The otic ganglion innervates the parotid salivary gland and glands in the mouth.

Other parasympathetic postganglionic neurons are located near or in the walls of visceral organs in the thoracic, abdominal, and pelvic cavities. Neurons of the enteric plexus include cells that can also be considered parasympathetic postganglionic neurons. All of these cells receive input from the vagus or pelvic nerves. The vagus nerves innervate the heart, lungs, bronchi, liver, pancreas, and gastrointestinal tract from the esophagus to the splenic flexure of the colon. The remainder of the colon and rectum, as well as the urinary bladder and reproductive organs, is supplied by sacral parasympathetic preganglionic neurons that travel through the pelvic nerves to postganglionic neurons in the pelvic ganglia.

The parasympathetic preganglionic neurons that project to the viscera of the thorax and part of the abdomen are located in the dorsal motor nucleus of the vagus (see Fig. 4.6*E*) and the nucleus ambiguus. The dorsal motor nucleus is largely **secretomotor** (it activates glands), whereas the nucleus ambiguus is **visceromotor** (it modifies the activity of cardiac muscle). The dorsal motor nucleus supplies visceral organs in the neck (pharynx, larynx), thoracic cavity (trachea, bronchi, lungs, heart, and esophagus), and abdominal cavity (including much of the gastrointestinal tract, liver, and pancreas). Electrical stimulation of the dorsal motor nucleus results in gastric acid secretion, as well as secretion of insulin and glucagon by the pancreas. Although projections to the heart have been described, their function is uncertain. The nucleus ambiguus contains two groups of neurons: (1) a dorsal group **(branchiomotor)** that activates striated muscle in the soft palate, pharynx, larynx, and esophagus; and (2) a ventrolateral group that innervates and slows the heart (see also Chapter 18).

Visceral Afferent Fibers

The visceral motor fibers in the autonomic nerves are accompanied by visceral afferent fibers. Most of these afferent fibers supply information that originates from sensory receptors in the viscera. The activity of these sensory receptors only rarely reaches the level of consciousness; however, these receptors initiate the afferent limb of reflex arcs. Both viscerovisceral and viscerosomatic reflexes are elicited by these afferent fibers. Even though these visceral reflexes generally operate at a subconscious level, they are very important for homeostatic regulation and adjustment to external stimuli.

The fast-acting neurotransmitters released by visceral afferent fibers are not well documented, although many of these neurons release the excitatory neurotransmitter, glutamate. Visceral afferent fibers also contain many neuropeptides or combinations of neuropeptides, including angiotensin II, arginine vasopressin, bombesin, calcitonin gene–related peptide, cholecystokinin, galanin, substance P, enkephalin, oxytocin, somatostatin, and vasoactive intestinal polypeptide.

Visceral afferent fibers that can mediate conscious sensation include nociceptors that travel in sympathetic nerves, such as the splanchnic nerves. Visceral pain is caused by excessive distention of hollow viscera, contraction against an obstruction, or ischemia. The origin of visceral pain is often difficult to localize because of the diffuse nature of the pain and its tendency to be referred to somatic structures (see Chapter 7). Visceral nociceptors in sympathetic nerves reach the spinal cord via the sympathetic chain, white rami,

and dorsal roots. The terminals of nociceptive afferent fibers project to the dorsal horn and to the region surrounding the central canal. They activate local interneurons, which participate in reflex arcs, and also projection cells, which include spinothalamic tract cells that signal pain to the brain.

A major visceral nociceptive pathway from the pelvis involves a relay in the gray matter of the lumbosacral spinal cord. These neurons send axons into the fasciculus gracilis that terminate in the nucleus gracilis; therefore, the dorsal columns not only contain primary afferents for fine touch, vibration, and proprioception sensation (their main component), but also second-order neurons of the visceral pain pathway (recall that second-order axons for somatic pain travel in the lateral funiculus as part of the spinothalamic tract). Visceral nociceptive signals are then transmitted to the ventral posterior lateral (VPL) nucleus of the thalamus, and presumably from the VPL to the cerebral cortex. Interruption of this pathway accounts for the beneficial effects of surgically induced lesions of the dorsal column at lower thoracic levels to relieve pain produced by cancer of the pelvic organs.

Other visceral afferent fibers travel in parasympathetic nerves. These fibers are generally involved in reflexes rather than sensation (except for taste afferent fibers; see Chapter 8). For example, the baroreceptor afferent fibers that innervate the carotid sinus are in the glossopharyngeal nerve. They enter the brainstem, pass through the solitary tract, and terminate in the nucleus of the solitary tract (see Fig. 4.6*E*). These neurons connect with interneurons in the brainstem reticular formation. The interneurons, in turn, project to the autonomic preganglionic neurons that control heart rate and blood pressure (see Chapter 18).

The nucleus of the solitary tract receives information from all visceral organs, except those in the pelvis. This nucleus is subdivided into several areas that receive information from specific visceral organs.

The Enteric Nervous System

The enteric nervous system, which is located in the wall of the gastrointestinal tract, contains about 100 million neurons. The enteric nervous system is subdivided into the myenteric plexus, which lies between the longitudinal and circular muscle layers of the gut, and the submucosal plexus, which lies in the submucosa of the gut. The neurons of the myenteric plexus primarily control gastrointestinal motility (see Chapter 27), whereas those in the submucosal plexus primarily regulate body fluid homeostasis (see Chapter 35).

The types of neurons found in the myenteric plexus include not only excitatory and inhibitory motor neurons (which can be considered parasympathetic postganglionic neurons) but also interneurons and primary afferent neurons. Afferent neurons supply mechanoreceptors within the wall of the gastrointestinal tract. These mechanoreceptors are the beginning of the afferent limb of reflex arcs within the enteric plexus. Local excitatory and inhibitory interneurons participate in these reflexes, and the output is sent through the motor neurons to smooth muscle cells. Excitatory motor neurons release acetylcholine and substance P; inhibitory motor neurons release dynorphin and vasoactive intestinal polypeptide. The circuitry of the enteric plexus is so extensive that it can coordinate the movements of an intestine that has been completely removed from the body. However, normal function requires innervation by the autonomic preganglionic neurons and regulation by the CNS.

Activity in the enteric nervous system is modulated by the sympathetic nervous system. Sympathetic postganglionic neurons that contain norepinephrine inhibit intestinal motility, those that contain norepinephrine and neuropeptide Y regulate blood flow, and those that contain norepinephrine and somatostatin control intestinal secretion. Feedback is provided by intestinofugal neurons that project back from the myenteric plexus to the sympathetic ganglia.

The submucosal plexus regulates ion and water transport across the intestinal epithelium and glandular secretion. It also communicates with the myenteric plexus to ensure coordination of the functions of the two components of the enteric nervous system. The neurons and neural circuits of the submucosal plexus are not as well understood as those of the myenteric plexus, but many of the neurons contain neuropeptides, and the neural networks are well organized.

Autonomic Ganglia

The main type of neuron in autonomic ganglia is the postganglionic neuron. These cells receive synaptic connections from preganglionic neurons, and they project to autonomic effector cells. However, many autonomic ganglia also contain interneurons. These interneurons process information within the autonomic ganglia; the enteric plexus can be regarded as an elaborate example of this kind of processing. One type of interneuron found in some autonomic ganglia contains a high concentration of catecholamines; hence, these interneurons have been called **small, intensely fluorescent (SIF) cells.** SIF cells are believed to be inhibitory.

Neurotransmitters

Neurotransmitters in Autonomic Ganglia

The classic neurotransmitter of autonomic ganglia, whether sympathetic or parasympathetic, is acetylcholine. The two classes of acetylcholine receptors in autonomic ganglia are **nicotinic** and **muscarinic receptors,** so named because of their responses to the plant alkaloids **nicotine** and **muscarine.** Nicotinic acetylcholine receptors can be blocked by such agents as **curare** or **hexamethonium,** and muscarinic receptors can be blocked by **atropine.** Nicotinic receptors in autonomic ganglia differ somewhat from those on skeletal muscle cells.

Nicotinic and muscarinic receptors both mediate excitatory postsynaptic potentials (EPSPs), but these potentials have different time courses. Stimulation of preganglionic neurons elicits a fast EPSP, followed by a slow EPSP. The

TABLE 11.1 Responses of Effector Organs to Autonomic Nerve Impulses

Effector Organs	Receptor Type	Adrenergic Impulses,[a] Responses[b]	Cholinergic Impulses,[a] Responses[b]
Eye			
Radial muscle, iris	α	Contraction (mydriasis) ++	—
Sphincter muscle, iris	α	—	Contraction (miosis) +++
Ciliary muscle	β	Relaxation for far vision +	Contraction for near vision +++
Heart			
Sinoatrial node	β_1	Increase in heart rate ++	Decrease in heart rate; vagal arrest +++
Atria	β_1	Increase in contractility and conduction velocity ++	Decrease in contractility and (usually) increase in conduction velocity ++
Atrioventricular (AV) node	β_1	Increase in automaticity and conduction velocity ++	Decrease in conduction velocity; AV block +++
His-Purkinje system	β_1	Increase in automaticity and conduction velocity +++	Little effect
Ventricles	β_1	Increase in contractility, conduction velocity, automaticity, and rate of idioventricular pacemakers +++	Slight decrease in contractility
Arterioles			
Coronary	α, β_2	Constriction +; dilation[c] ++	Dilation +
Skin and mucosa	α	Constriction +++	Dilation[d]
Skeletal muscle	α, β_2	Constriction ++; dilation[c,e] ++	Dilation[f] +
Cerebral	α	Constriction (slight)	Dilation[d]
Pulmonary	α, β_2	Constriction +; dilation[c]	Dilation[d]
Abdominal viscera, renal	α, β_2	Constriction +++; dilation[e] +	—
Salivary glands	α	Constriction +++	Dilation ++
Veins (Systemic)	α, β_2	Constriction ++; dilation ++	—
Lungs			
Bronchial muscle	β_2	Relaxation +	Contraction ++
Bronchial glands	?	Inhibition (?)	Stimulation +++
Stomach			
Motility and tone	α_2, β_2	Decrease (usually)[g] +	Increase +++
Sphincters	α	Contraction (usually) +	Relaxation (usually) +
Secretion		Inhibition (?)	Stimulation +++
Intestine			
Motility and tone	α_2, β_2	Decrease[g] +	Increase +++
Sphincters	α	Contraction (usually) +	Relaxation (usually) +
Secretion		Inhibition (?)	Stimulation +++
Gallbladder and Ducts		Relaxation +	Contraction +
Kidney	β_2	Renin secretion ++	—
Urinary Bladder			
Detrusor	β	Relaxation (usually) +	Contraction +++
Trigone and sphincter	α	Contraction +++	Relaxation ++
Ureter			
Motility and tone	α	Increase (usually)	Increase (?)
Uterus	α, β_2	Pregnant: contraction (α); nonpregnant: relaxation (β)	Variable[h]
Sex Organs, Male	α	Ejaculation +++	Erection +++
Skin			
Pilomotor muscles	α	Contraction ++	—
Sweat glands	α	Localized secretion[i] +	Generalized secretion +++

Continued

TABLE 11.1 Responses of Effector Organs to Autonomic Nerve Impulses—cont'd

Effector Organs	Receptor Type	Adrenergic Impulses,[a] Responses[b]	Cholinergic Impulses,[a] Responses[b]
Spleen Capsule	α, β_2	Contraction +++; relaxation +	—
Adrenal Medulla		—	Secretion of epinephrine and norepinephrine
Liver	α, β_2	Glycogenolysis, gluconeogenesis[j] +++	Glycogen synthesis +
Pancreas			
Acini	α	Decreased secretion +	Secretion ++
Islets (beta cells)	α	Decreased secretion +++	—
	β_2	Increased secretion +	—
Fat cells	α, β_1	Lipolysis[j] +++	—
Salivary glands	α	K^+ and water secretion +	K^+ and water secretion +++
	β	Amylase secretion +	—
Lacrimal glands		—	Secretion +++
Nasopharyngeal glands		—	Secretion +++
Pineal gland	β	Melatonin synthesis	—

[a]A long dash (—) signifies no known functional innervation.
[b]Responses are designated + to +++ to provide an approximate indication of the importance of adrenergic and cholinergic nerve activity in control of the various organs and functions listed.
[c]Dilation predominates in situ because of metabolic autoregulatory phenomena.
[d]Cholinergic vasodilation at these sites is of questionable physiological significance.
[e]Over the usual concentration range of physiologically released circulating epinephrine, a β receptor response (vasodilation) predominates in blood vessels of skeletal muscle and the liver, and an α receptor response (vasoconstriction) predominates in blood vessels of other abdominal viscera. The renal and mesenteric vessels also contain specific dopaminergic receptors, activation of which causes dilation, but their physiological significance has not been established.
[f]The sympathetic cholinergic system causes vasodilation in skeletal muscle, but this is not involved in most physiological responses.
[g]It has been proposed that adrenergic fibers terminate at inhibitory β receptors on smooth muscle fibers and at inhibitory α receptors on parasympathetic cholinergic (excitatory) ganglion cells of the Auerbach plexus.
[h]Depends on the stage of the menstrual cycle, the amount of circulating estrogen and progesterone, and other factors.
[i]Palms of the hands and some other sites ("adrenergic sweating").
[j]There is significant variation among species in the type of receptor that mediates certain metabolic responses.
From Goodman LS, Gilman A. *The Pharmacological Basis of Therapeutics.* 6th ed. New York: Macmillan; 1980.

fast EPSP results from activation of nicotinic receptors, which cause ion channels to open. The slow EPSP is mediated by muscarinic receptors (primarily the M_2 receptor; see Chapter 6) that inhibit the **M current,** a current produced by potassium conductance.

Neurons in autonomic ganglia also release neuropeptides that act as neuromodulators. Besides acetylcholine, sympathetic preganglionic neurons may release enkephalin, substance P, luteinizing hormone–releasing hormone, neurotensin, or somatostatin.

Catecholamines such as norepinephrine and dopamine serve as the neurotransmitters of SIF cells in autonomic ganglia.

Neurotransmitters Between Postganglionic Neurons and Autonomic Effectors

Sympathetic Postganglionic Neurons

Sympathetic postganglionic neurons typically release norepinephrine, which excites some effector cells, but inhibits others. The receptors on target cells may be either α- or β-adrenergic receptors. These receptors are further subdivided into α_1, α_2, β_1, β_2, and β_3 receptor types on the basis of pharmacological and genetic features. The distribution of these types of receptors and the actions that they mediate when activated by sympathetic postganglionic neurons are listed for various target organs in Table 11.1.

α_1 receptors are located postsynaptically, but α_2 receptors may be either presynaptic or postsynaptic. Receptors located presynaptically are generally called **autoreceptors;** they usually inhibit release of transmitter. The effects of agents that excite α_1 or α_2 receptors can be distinguished through the use of antagonists to block these receptors specifically. For example, prazosin is a selective α_1-adrenergic antagonist, and yohimbine is a selective α_2-adrenergic antagonist. The effects of α_1 receptors are mediated by activation of the inositol triphosphate (InsP3) and diacylglycerol (DAG) second messenger system (see Chapter 3; Table 3.1). In contrast, α_2 receptors decrease the rate of synthesis of cyclic adenosine monophosphate (cAMP) through action on a G protein.

β receptors were originally classified on the basis of the ability of antagonists to block them, but this has been supplemented by genetic studies. The β_1 and β_2 proteins have been much more extensively studied than has β_3, but it is thought that the proteins that make up all three types of β receptors are similar, with seven membrane-spanning regions connected by intracellular and extracellular domains (see Chapter 3). Agonist drugs that work on β receptors activate a G protein that stimulates adenylyl cyclase to increase

the cAMP concentration. This action is terminated by the buildup of guanosine diphosphate.

β receptor activity is controlled in a number of ways. It can be antagonized by the action of α_1 receptors. The β receptors can also be desensitized by phosphorylation with prolonged exposure to agonists. Regulation of β receptor numbers represents a third control mechanism. For example, β receptor numbers can be decreased by being internalized. Alternatively, β receptor numbers can be increased (upregulated) in certain circumstances: for example, after denervation. Note that the number of α receptors is likewise regulated.

In addition to releasing norepinephrine, sympathetic postganglionic neurons release neuropeptides such as somatostatin and neuropeptide Y. For example, cells that release both norepinephrine and somatostatin supply the mucosa of the gastrointestinal tract, and cells that release both norepinephrine and neuropeptide Y innervate blood vessels in the gut and the limb. Another chemical mediator in sympathetic postganglionic neurons is adenosine triphosphate (ATP).

The endocrine cells of the adrenal medulla are similar in many ways to sympathetic postganglionic neurons (see also Chapter 43). They receive input from sympathetic preganglionic neurons, are excited by acetylcholine, and release catecholamines. However, the cells of the adrenal medulla differ from sympathetic postganglionic neurons in that they release catecholamines into the circulation rather than into a synapse. Moreover, the main catecholamine released is epinephrine, not norepinephrine. In humans, 80% of the catecholamine released by the adrenal medulla is epinephrine, and 20% is norepinephrine.

Some sympathetic postganglionic neurons release acetylcholine rather than norepinephrine as their neurotransmitter. For example, sympathetic postganglionic neurons that innervate eccrine sweat glands are cholinergic. The acetylcholine receptors involved are muscarinic, and they are therefore blocked by atropine. Similarly, some blood vessels are innervated by cholinergic sympathetic postganglionic neurons. In addition to releasing acetylcholine, the postganglionic neurons that supply the sweat glands also release neuropeptides, including calcitonin gene–related peptide and vasoactive intestinal polypeptide.

Parasympathetic Postganglionic Neurons

The neurotransmitter released by parasympathetic postganglionic neurons is acetylcholine. The effects of these neurons on various target organs are listed in Table 11.1. Parasympathetic postganglionic actions are mediated by muscarinic receptors. Based on pharmacological binding studies, the action of selective antagonists, and molecular cloning, five types of muscarinic receptors have been identified (see Chapter 6). Activation of M_1 receptors enhances the secretion of gastric acid in the stomach. M_2 receptors are the most abundant receptor type in smooth muscle, including smooth muscle in the intestines, uterus, trachea, and bladder. In addition, they are present in autonomic ganglia and in the heart, where they exert negative chronotropic and inotropic actions (see Chapter 18). M_3 receptors are also present in the smooth muscle of a variety of organs, and although they are less abundant than M_2 receptors, normal contractile patterns appear to require an interaction between the two types of receptors. M_4 receptors, like M_2 receptors, are present in autonomic ganglia and thus play a role in synaptic transmission at these sites. M_5 receptors are present in the sphincter muscle of the pupil, in the esophagus, and in the parotid gland, as well as in cerebral blood vessels.

Muscarinic receptors, like adrenergic receptors, have diverse actions. Some of their effects are mediated by specific second messenger systems. For example, cardiac M_2 muscarinic receptors may act by way of the IP3 system, and they may also inhibit adenylyl cyclase and thus cAMP synthesis. Muscarinic receptors also open or close ion channels, particularly K^+ or Ca^{++} channels. This action on ion channels is likely to occur through activation of G proteins. A third action of muscarinic receptors is to relax vascular smooth muscle by an effect on endothelial cells, which produce endothelium-derived relaxing factor (EDRF). EDRF is actually nitric oxide, a gas released when arginine is converted to citrulline by nitric oxide synthase (see Chapter 18). Nitric oxide relaxes vascular smooth muscle by stimulating guanylate cyclase and thereby increasing levels of cyclic guanosine monophosphate (cGMP), which in turn activates a cGMP-dependent protein kinase (see Chapter 3). The number of muscarinic receptors is regulated, and exposure to muscarinic agonists decreases the number of receptors by internalization of the receptors.

IN THE CLINIC

Chagas disease is the result of infection by the parasite *Trypanosoma cruzi*. About 18 million people are infected worldwide, and approximately 50,000 die each year as a result of complications from the disease. The most serious forms involve enlargement of the esophagus, colon, and heart. Loss of parasympathetic control is a significant component of the initial stages of the disease; shortly after the initial infection, the parasympathetic neurons innervating the heart, esophagus, and colon are destroyed, which leads to arrhythmias (and potentially, sudden death) and aperistalsis. Chronic cardiomyopathy (malfunction of the heart muscle) that can lead to death occurs in approximately 30% of those infected. Although the pathogenesis of the cardiomyopathy is not fully understood, one leading idea involves autoimmunity. Antibodies against the parasitic antigens have been found to bind to the β-adrenergic and M_2 acetylcholine receptors in the heart. These antibodies not only trigger autoimmune responses that destroy heart muscle but also act as agonists at these receptors and cause inappropriate responses of the cardiovascular system to changing external demands.

Central Control of Autonomic Function

The discharges of autonomic preganglionic neurons are controlled by pathways that synapse on autonomic preganglionic

neurons. The pathways that influence autonomic activity include spinal cord and brainstem reflex pathways, as well as descending control systems originating at higher levels of the nervous system, such as the hypothalamus.

Examples of Autonomic Control of Particular Organs

Pupil

The dilator and constrictor muscles of the iris, which are under the control of sympathetic and parasympathetic fibers, respectively, determine the size of the pupil. Activation of sympathetic innervation of the eye, via thoracic white rami and sympathetic trunk ganglia, dilates the pupil, which occurs during emotional excitement and also in response to painful stimulation. The neurotransmitter at the sympathetic postganglionic synapses is norepinephrine, and it acts at α receptors.

The parasympathetic nervous system exerts an action on pupillary size opposite to that of the sympathetic nervous system. Whereas the sympathetic system elicits pupillary dilation, the parasympathetic system constricts the pupil. The preganglionic parasympathetic nerves that innervate the pupillary constrictor are in the Edinger-Westphal nucleus, which is in the midbrain, and travel in cranial nerve III, and so damage to this nerve can lead to a dilated pupil (mydriasis).

IN THE CLINIC

Sympathetic control of the pupil is sometimes affected by disease. For example, interruption of the sympathetic innervation of the head and neck results in **Horner's syndrome.** This syndrome is characterized by the triad of miosis (abnormal pupillary constriction), ptosis (slight droop to eyelid caused by loss of the superior tarsal muscle function; also called Müller's muscle), and anhydrosis (loss of sweating) on the face. Horner's syndrome can result from damage to different areas of the sympathetic circuit: (1) disruption of first-order neurons in the CNS, including the hypothalamus, which sends descending fibers through the brainstem to the spinal cord to influence sympathetic function; (2) disruption of second-order sympathetic preganglionic fibers that exit the spinal cord at T1 and enter the cervical sympathetic chain; or (3) disruption of third-order postganglionic fibers that innervate Müller's muscle, the sweat glands of the face, and the iris dilator muscle. In the first case, damage to fibers in the brainstem would result in many other symptoms, depending on which brainstem nuclei were also damaged.

Pupil size is reduced by the **pupillary light reflex** and during accommodation for near vision. In the pupillary light reflex, light that strikes the retina is processed by retinal circuits that excite W-type retinal ganglion cells (see Chapter 8). These cells respond to diffuse illumination. The axons of some of the W-type cells project through the optic nerve and tract to the pretectal area, where they synapse in the olivary pretectal nucleus. This nucleus contains neurons that also respond to diffuse illumination. Activity of neurons of the olivary pretectal nucleus causes pupillary constriction by means of bilateral connections with parasympathetic preganglionic neurons in the Edinger-Westphal nuclei. The reflex results in contraction of the pupillary sphincter muscles in both eyes, even when light is shone into only one eye.

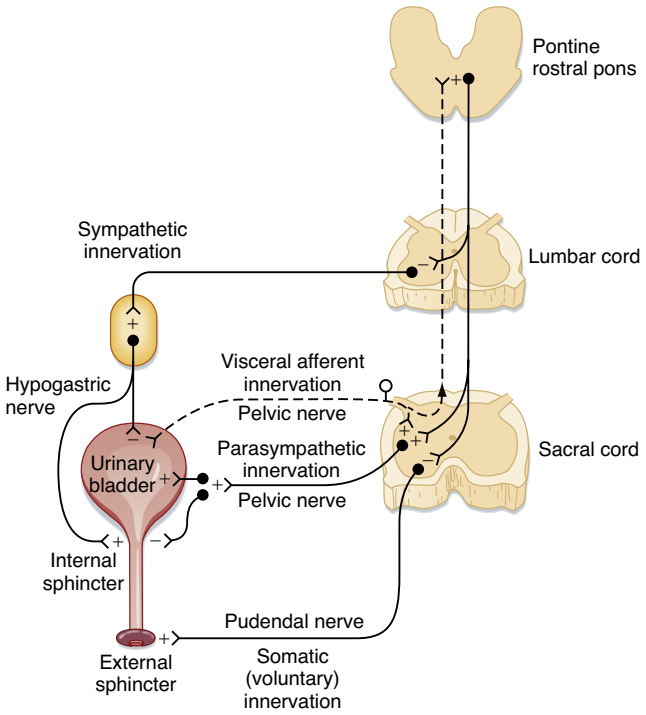
The **accommodation response,** which is important for focusing on near objects, involves pupillary constriction, increasing the curvature of the lens, and convergence of the eyes. This response is triggered by information from M cells of the retina that is transmitted to the striate cortex through the geniculostriate visual pathway (see Chapter 8). The specific stimuli that trigger accommodation are thought to be a blurred retinal image and disparity of the image between the two eyes. After the information is processed in the visual cortex, signals are transmitted directly or indirectly to the middle temporal cortex, where they activate neurons in a visual area known as MT. Area MT neurons transmit signals to the midbrain that activate parasympathetic preganglionic neurons in the Edinger-Westphal nuclei, which results in pupillary constriction. At the same time, signals are transmitted to the ciliary muscle that cause it to contract. The ciliary muscle contraction allows the lens to round up and increase its refractile power. (Convergence is a somatic response mediated by neurons in the oculomotor [cranial nerve III] nucleus of the midbrain.)

IN THE CLINIC

The pupillary light reflex is sometimes absent in patients with tertiary (advanced) syphilis, which affects the CNS (i.e., in the form of tabes dorsalis). Although the pupil fails to respond to light, it has a normal accommodation response. This condition is known as the **Argyll Robertson pupil.** The exact mechanism is controversial. One explanation rests on the fact that some optic tract fibers project to the pretectal area in the midbrain. These fibers can be damaged in syphilitic meningitis, possibly by the presence of spirochetes in the subarachnoid space. Note that the pretectal area projects to the Edinger-Westphal nucleus, also in the midbrain, whose cells originate the parasympathetic innervation of the eye, which controls the pupillary sphincter muscle. Although input to the olivary pretectal nucleus is interrupted, the optic tract fibers projecting to the lateral geniculate nucleus are not destroyed, and thus vision is maintained, as is pupillary constriction during accommodation.

Urinary Bladder

The urinary bladder is controlled by reflex pathways in the spinal cord and also by a supraspinal center (Fig. 11.3). The sympathetic innervation originates from preganglionic sympathetic neurons in the upper lumbar segments of the spinal cord. Postganglionic sympathetic axons act to inhibit the smooth muscle **(detrusor muscle)** throughout the body of the bladder, and they also act to excite the smooth muscle of the trigone region and the internal urethral sphincter. The detrusor muscle is tonically inhibited during filling of



• **Fig. 11.3** Illustration of descending and efferent pathways for reflexes that control the urinary bladder. For clarity, only some of the major involved pathways are shown. (Redrawn from de Groat WC, Booth AM. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. *Peripheral Neuropathy.* 2nd ed. Philadelphia: WB Saunders; 1984.)

the bladder, and such inhibition prevents urine from being voided. Inhibition of the detrusor muscle is mediated by the action of norepinephrine on β receptors, whereas excitation of the trigone and internal urethral sphincter is elicited by the action of norepinephrine on α receptors.

The external sphincter of the urethra also helps control voiding. This sphincter is a striated muscle, and it is innervated by motor axons in the pudendal nerves, which are somatic nerves. The motor neurons are located in the **Onuf nucleus,** in the ventral horn of the sacral spinal cord.

The parasympathetic preganglionic neurons that control the bladder are located in the sacral spinal cord (the S2 and S3 or S3 and S4 segments). These cholinergic neurons project through the pelvic nerves and are distributed to ganglia in the pelvic plexus and the bladder wall. Postganglionic parasympathetic neurons in the bladder wall innervate the detrusor muscle, as well as the trigone and sphincter. The parasympathetic activity contracts the detrusor muscle and relaxes the trigone and internal sphincter. These actions result in **micturition,** or urination. Some of the postganglionic neurons are cholinergic and others are purinergic (they release ATP).

Micturition is normally controlled by the **micturition reflex** (see Fig. 11.3). Mechanoreceptors in the bladder wall are excited by both stretch and contraction of the muscles in the bladder wall. As urine accumulates and distends the bladder the mechanoreceptor afferents begin to discharge. The pressure in the urinary bladder is low during filling (5 to 10 cm H_2O), but it increases abruptly when micturition begins. Micturition can be triggered either reflexively or voluntarily. In reflex micturition, bladder afferent fibers excite neurons that project to the brainstem and activate the micturition center in the rostral pons **(Barrington's nucleus).** The descending projections also inhibit sympathetic preganglionic neurons that prevent voiding. When a sufficient level of activity occurs in this ascending pathway, micturition is triggered by the micturition center. Commands reach the sacral spinal cord through a reticulospinal pathway. Activity in the sympathetic projection to the bladder is inhibited, and the parasympathetic projections to the bladder are activated. Contraction of muscle in the wall of the bladder causes a vigorous discharge of the mechanoreceptors that supply the bladder wall and thereby further activates the supraspinal loop. The result is complete emptying of the bladder.

A spinal reflex pathway also exists for micturition. This pathway is operational in newborn infants. However, with maturation, the supraspinal control pathways take on a dominant role in triggering micturition. After spinal cord injury, human adults lose bladder control during the period of spinal shock (urinary incontinence). As the spinal cord recovers from spinal shock, some degree of bladder function is recovered because of enhancement of the spinal cord micturition reflex. However, the bladder has increased muscle tone and fails to empty completely. These circumstances frequently lead to urinary infections.

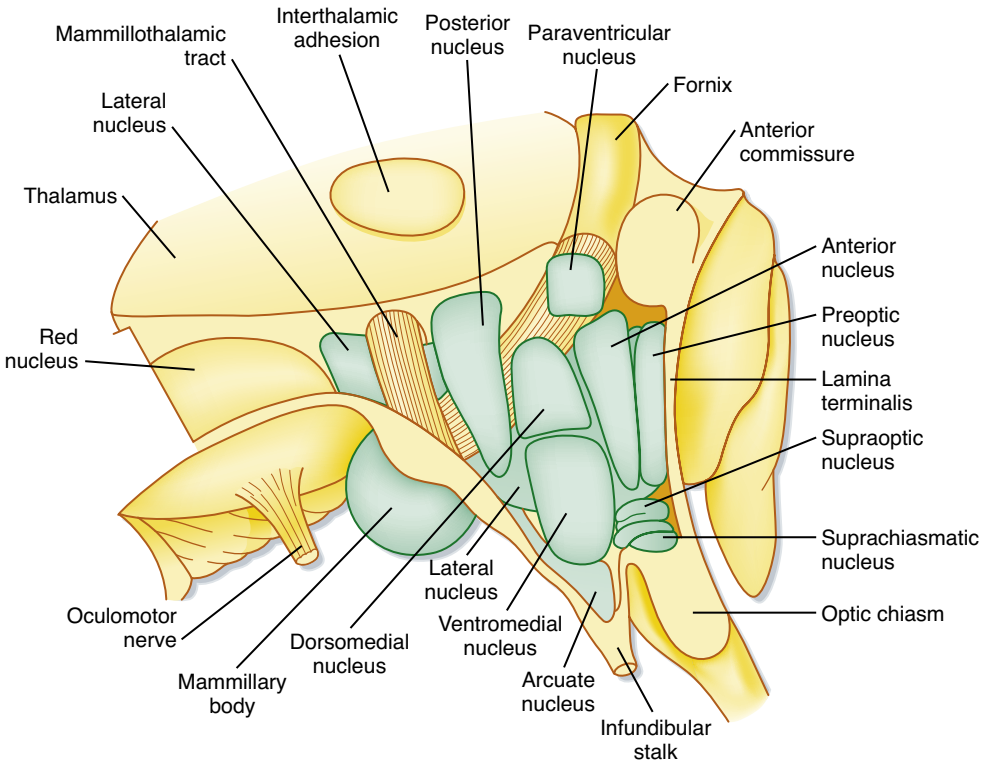
Autonomic Centers in the Brain

Influence over autonomic output is maintained by autonomic centers, which consist of local networks of neurons, in a variety of brain regions. The micturition center in the pons, which was just discussed, is one example. Many other autonomic centers with diverse functions exist. Vasomotor and vasodilator centers are in the medulla, and respiratory centers are in the medulla and pons. Perhaps the greatest concentration of autonomic centers is found in the hypothalamus.

The Hypothalamus and Preoptic Area

The hypothalamus is part of the diencephalon. Some of the nuclei of the hypothalamus are shown in Fig. 11.4. Located anteriorly from the hypothalamus are telencephalic structures: the preoptic region and septum, both of which help regulate autonomic function. Important fiber tracts that course through the hypothalamus are the **fornix,** the **medial forebrain bundle,** and the **mammillothalamic tract.** The fornix is used as a landmark to divide the hypothalamus into medial and lateral zones.

The hypothalamus has many functions; see Chapter 41 for a discussion of hypothalamic control of endocrine function. Its control of autonomic function is emphasized here. In its control of autonomic function, the hypothalamus functions much like a control system that is termed, in engineering, a



• **Fig. 11.4** Illustration of main nuclei of the hypothalamus, viewed from the third ventricle. Anterior is to the right. (Redrawn from Nauta WJH, Haymaker W. *The Hypothalamus.* Springfield, IL: Charles C Thomas; 1969.)

servomechanism: that is, a system in which a particular physiological parameter is controlled through the use of negative feedback loops to maintain the parameter at a particular set point or value. The following examples illustrate this principle for body temperature, body weight and adiposity, and water intake.

Temperature Regulation

Homeothermic animals maintain a relatively constant core body temperature in situations of fluctuating environmental temperatures and differing levels of bodily activity that cause endogenous heat production. This ability rests on information from three main groups of thermoreceptors located in the skin, CNS, and viscera.

Information about the external temperature is provided by thermoreceptors in the skin. Core body temperature is monitored by central thermoreceptive neurons in the preoptic area (and possibly the spinal cord), which monitor the temperature of local blood. Thermoreceptors in the viscera monitor the temperature in these organs. All of these receptors provide temperature information to the preoptic area (pathways described later), along with parts of the hypothalamus, in which this information is used to keep core body temperature constant. Thus, the preoptic area and hypothalamus act together as a servomechanism with a set point at the normal body temperature.

Although the signals from each of these sources are integrated, their relative importance may shift, depending on the various conditions. Changes in environmental temperature evoke more rapid and much larger changes in the temperature of the skin than in the body core, and so cutaneous receptors are probably the initial and most often used mechanism for compensating for external changes in temperature. Central thermoreceptors are more important for situations with internal causes of temperature change, such as during exercise, or in which external changes temperature are so severe or prolonged that core body temperature starts to change despite the signals from peripheral thermoreceptors. Last, alteration of body temperature by ingestion of hot or cold food or liquids is detected by the visceral thermoreceptors.

Error signals (i.e., cooling and warming of the body), which represent a deviation from the set point of the servomechanism, evoke responses that tend to restore body temperature toward the set point. These responses are mediated by the autonomic, somatic, and endocrine systems.

Situations involving cooling, for example, trigger a variety of responses that increase heat production (thermogenesis) and minimize heat loss. Heat production is increased by mechanisms that include **shivering thermogenesis** (asynchronous contractions of skeletal muscle that increases heat production) and **brown adipose tissue (BAT) thermogenesis** (in BAT thermogenesis, oxidative phosphorylation is uncoupled from ATP synthesis, which allows the energy released by the reaction to be dissipated as heat instead), and increased thyroid hormone levels lead to increased

metabolism. Heat loss is reduced by cutaneous vasoconstriction and by piloerection. Piloerection is effective in animals with fur but not in humans; in the latter, the result is only goose bumps. In addition, tachycardia occurs, which may help provide metabolites to be used in thermogenesis to the thermogenic tissues (fat and muscle) and help distribute the heat generated throughout the body. Finally, the perception of being cold influences the decision to initiate voluntary behaviors; in this case, possibly putting on a jacket.

Warming the body generally causes changes in the opposite direction. The activity of the thyroid gland diminishes, which leads to reduced metabolic activity and less heat production. Heat loss is increased by sweating, salivation (in some animals but not humans), and cutaneous vasodilation (because of decreased sympathetic activity). However, again tachycardia occurs, this time presumably to allow optimal perfusion of the cutaneous circulation for heat dissipation.

Early studies identified the preoptic region and anterior hypothalamus as a heat loss center and the posterior hypothalamus as a heat conservation center. For example, lesions in the preoptic region prevent sweating and cutaneous vasodilation, and if an individual with a lesion in this region is placed in a warm environment, **hyperthermia** occurs. Conversely, electrical stimulation of the heat loss center causes cutaneous vasodilation and inhibits shivering. In contrast, lesions in the area dorsolateral to the mammillary body interfere with heat production and conservation and can cause **hypothermia** when the person is in a cold environment. Electrical stimulation in this region of the brain evokes shivering.

Many details of the circuitry and physiologic processes underlying the temperature regulation responses are now known, and they indicate that the preoptic area and **dorsal medial hypothalamic nucleus** are key components in the regulation of body temperature. The preoptic area in particular appears to be the target of the various sources of sensory information. Cutaneous temperature information is conveyed by thermosensitive primary afferents that synapse in the dorsal horn of the spinal cord onto neurons that project up to and excite the **parabrachial nucleus** in the caudal midbrain. Information from visceral afferents is relayed by the solitary nucleus to the parabrachial nucleus as well. The parabrachial neurons in turn excite neurons within a specific part of the preoptic area, the **median nucleus** (of the preoptic area). Many median nucleus neurons are also sensitive to local changes in blood temperature and contain prostaglandin E2 (PGE2) receptor 3 (EP3), which mediates fever responses (see the following "In the Clinic" box).

Thus, the median preoptic nucleus is a key component of the thermoregulatory control system in which information from the various types of thermoreceptors is integrated. Output from this nucleus is directed to the neighboring medial preoptic area, which projects to regions of the rostral medulla, both directly and via the dorsal medial hypothalamic nucleus. The rostral medulla has neurons that project to the lateral horn of the spinal cord, where the preganglionic sympathetic neurons are located, and the activity of these neurons regulates BAT thermogenesis and modulates cutaneous vasomotor tone. The rostral medulla also projects to the ventral horn of the spinal cord, which contains the somatic motor neurons that contract skeletal muscle and thus mediate the shivering response.

IN THE CLINIC

Fever, which accompanies some infections, can be thought of as an elevation of the set point for body temperature. This elevation can be caused by the release of **pyrogens** by microorganisms or by cells mediating the inflammatory response. The pyrogen's effect to raise the set point is mediated primarily by the action of prostaglandin PGE2's binding to EP3 receptors on neurons in the preoptic area. PGE2 is released by peripheral tissues and by blood vessels supplying the preoptic area. The binding of PGE2 to EP3 receptors causes a reduction in the activity of preoptic neurons. This reduction in neuronal activity leads to increased heat production through shivering and BAT thermogenesis, and to heat conservation by cutaneous vasoconstriction, the combined effect of which is to raise body temperature. Evidence of this mechanism of fever production includes studies in which injection of PGE2 into the preoptic area induced fever and others in which selective deletion of the EP3 receptor from preoptic neurons abolished the ability of PGE2 injections to induce fever.

Regulation of Feeding and Body Weight

Energy homeostasis is crucial for the survival of the animal. The challenge is that most cells need a continuous supply of nutrients to function, but most animals do not constantly eat; instead, they have periodic meals. Thus, to achieve energy homeostasis, feeding behavior is controlled by many factors, which operate both on a short-term basis to control ingestion and on a long-term basis to control body weight in order to ensure sufficient energy stores. Both hedonic (in this context, pleasure derived from eating) and homeostatic factors are involved; however, in this chapter, the focus is on the latter because of the central role that the hypothalamus plays in energy homeostasis.

In the short run, eating is controlled by a number of mechanisms. First, the stomach wall has stretch receptors that signal distention as food fills the stomach. These signals are conveyed by the afferents of the vagus nerve to the solitary nucleus in the medulla. From there the information is relayed to several brain areas, including the hypothalamus, either directly or via a relay in the parabrachial nucleus, to organize autonomic responses to the ingested material, and the thalamus and cortex, for conscious awareness of the fullness of the stomach. In the hypothalamus, the paraventricular, dorsomedial, and arcuate nuclei and the lateral hypothalamus are the major targets of these signals.

Sensory afferents also sense the concentrations of glucose and lipids in the intestines and the hepatic portal circulation and send this information to the solitary nucleus and,

from there, to the hypothalamus, in a manner similar to that described for the stretch receptors. In addition, the stomach and gut release a number of hormones in response to feeding, including cholecystokinin, peptide YY, glucagon-like peptide-1 (GLP-1), and ghrelin. Hypothalamic cells have receptors for many of these hormones and can be influenced directly by them. In addition, cells in other brain areas have receptors for these hormones and thus may provide an indirect pathway to the hypothalamus. One such region is the **area postrema,** which is just dorsal to the solitary nucleus and projects to it. The area postrema, at the base of the fourth ventricle, is not protected by the blood-brain barrier (it is one of the circumventricular organs), and its neurons respond to cholecystokinin and GLP-1, which leads to decreased food intake (area postrema also responds to chemotoxins by eliciting a vomiting response).

Control of body weight over the long run is influenced by many factors and involves the interaction of the nervous and endocrine systems. In this section, the focus is on the role of hypothalamus and its control of the autonomic nervous system, which provides another example of how the hypothalamus is part of a servomechanism. In this case, adiposity is the controlled parameter. For further details on the endocrine system's role, see Chapters 38 and 39.

Early studies in which researchers used lesions and electrical stimulation provided evidence that the ventromedial and ventrolateral hypothalamus are involved in energy homeostasis. A lesion in the ventromedial region causes an increase in food intake (hyperphagia) that results in obesity, whereas electrical stimulation of the same region decreases feeding behavior. These lesions were also shown to alter autonomic activity, increasing parasympathetic and decreasing sympathetic tone, both of which lead to high blood insulin levels, which in turn promote energy conservation and storage (see Chapter 39). These observations led to the idea that the ventromedial hypothalamus contains a satiety center. However, an alternative interpretation is that the primary controlled variable may not be simply eating behavior, per se, but rather body weight, and more specifically, body fat levels (i.e., adiposity). Thus, modulation of feeding behavior may be just one of several actions used to defend a body weight set point. Consistent with this complexity is the observation that lesions can cause an initial period of dynamic weight gain in which hyperphagia is present, followed by a static period in which the higher weight is maintained without hyperphagia. Moreover, animals with a lesion in the ventromedial hypothalamus that are fed a fixed (normal) amount of food to prevent hyperphagia nonetheless become obese, which implies changes in the regulation of other metabolic processes. Last, lesions of the ventromedial hypothalamus have been shown to alter levels of energy expenditure.

In contrast to lesions of the ventromedial hypothalamus, those of the lateral hypothalamus suppress food intake (hypophagia) and lead to a decrease in body weight; indeed, animals can starve to death after such lesions. Conversely, electrical stimulation of the medial forebrain bundle in the lateral hypothalamus evokes exploratory behavior and eating, if food is present. This stimulation also provides a dopamine-dependent reward that mediates the incentive effects of natural rewards (food, sex) as well as the rewarding effects of most drugs of abuse. These observations led to the view that the lateral hypothalamus contains a feeding center. This interpretation, however, is complicated by the fact that the dopaminergic axons of substantia nigra neurons pass just lateral to the lateral hypothalamus on their way to the striatum, and so loss or stimulation of these fibers could account for the effects produced in these experiments. However, lateral hypothalamic neurons have been found to synthesize peptides, such as orexin, that affect feeding behavior, and so the lateral hypothalamus probably does play a role in energy homeostasis.

In newer studies, investigators have identified a number of hormones and neuropeptides involved in feeding and control of body weight, and many of the interactions between the endocrine and nervous systems that underlie energy homeostasis have been clarified.

In normal individuals, blood **insulin** levels are correlated with adiposity (in addition to varying acutely with blood levels of glucose and other substances). Similarly, the level of the protein **leptin**, a hormone released by adipocytes (primarily those forming white adipose tissue), is correlated with adiposity. High levels of leptin inhibit food intake and stimulate catabolic processes, including loss of fat tissue, whereas low leptin levels trigger the reverse actions. Similarly, high insulin levels promote energy storage processes.

The ability of leptin and insulin to regulate body weight has been linked to their actions on the hypothalamus, particularly the arcuate nucleus, whose neurons express receptors for both hormones (see also Chapter 39). Two major classes of arcuate nucleus neurons that respond to leptin and insulin have been identified. Neurons that express proopiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) are stimulated by leptin and insulin, and their activity leads to increased catabolism. In contrast, the activity of a second group of neurons, those expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP), triggers anabolic processes, but is inhibited by leptin and insulin. Thus increased body fat levels lead to high leptin and insulin levels, which in turn both (1) increase the activity of POMC- and CART-expressing neurons, leading to increased catabolism, and (2) decrease the activity of NPY- and AgRP-expressing neurons, leading to decreased anabolism; both of which act to return body fat levels to their set point. Lowering body fat levels would result in a sequence of events opposite to that just described to increase body fat levels to their original level or set point.

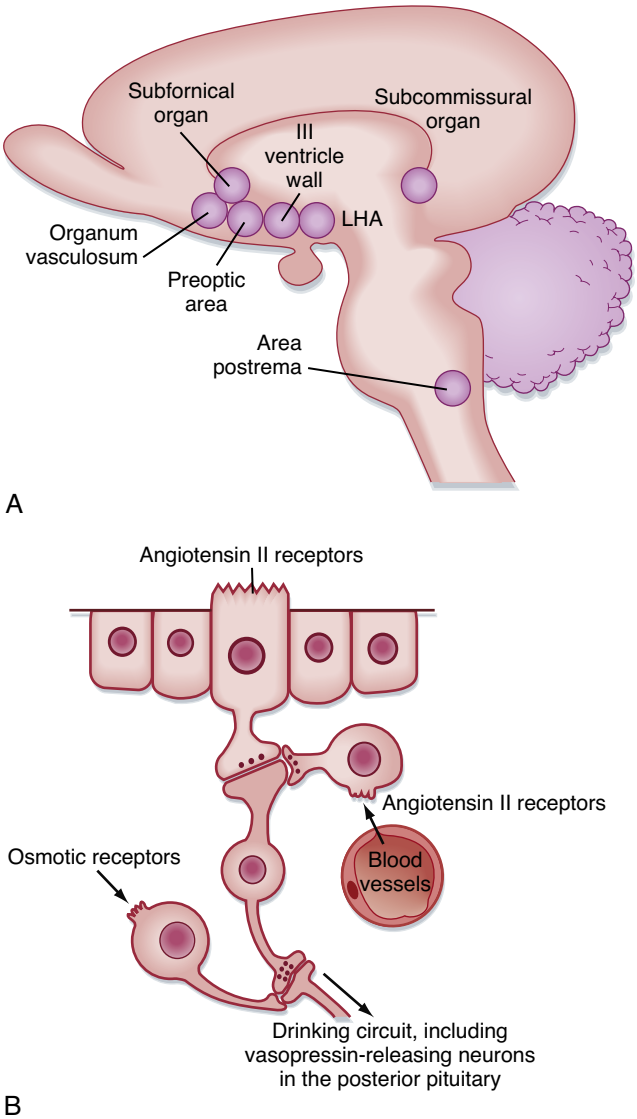
The efferent limb that mediates the actions of these sets of arcuate neurons is not fully worked out. However, the arcuate nucleus projection to the **paraventricular nucleus (PVN) of the hypothalamus** appears to be an important step in the pathway. Paraventricular neurons contain oxytocin. Many of them project to the posterior pituitary gland and are involved in lactation and uterine contractions during labor (see Chapter 44). However, the PVN

neurons involved in body weight regulation are a distinct subset of neurons that project to the brainstem and spinal cord, where they probably synapse with autonomic and preautonomic nuclei that control parasympathetic vagal fibers to the pancreas, which act to stimulate insulin release, and sympathetic fibers, which act to inhibit its release.

Regulation of Water Intake

Water intake also depends on a servomechanism. Fluid intake is influenced by blood osmolality and volume (Fig. 11.5).

With water deprivation, the extracellular fluid becomes hyperosmotic, which in turn causes the intracellular fluid to become hyperosmotic. The brain contains neurons that serve as osmoreceptors for detection of increases in the osmotic pressure of extracellular fluid (see also Chapter 35). The osmoreceptors appear to be located in the organum vasculosum of the lamina terminalis, which is a circumventricular organ. Circumventricular organs surround the cerebral ventricles and lack a blood-brain barrier. The subfornical organ and the organum vasculosum are involved in thirst.



• **Fig. 11.5** **A,** Structures thought to play a role in the regulation of water intake in rats. *LHA*, Lateral hypothalamic area. **B,** Neural circuits that signal changes in blood osmolality and volume. (**A,** Redrawn from Shepherd GM. *Neurobiology.* New York: Oxford University Press; 1983.)

Water deprivation also causes a decrease in blood volume, which is sensed by receptors in the low-pressure side of the vasculature, including the right atrium of the heart (see also Chapter 17). In addition, decreased blood volume triggers the release of renin by the kidneys. Renin breaks down angiotensinogen into angiotensin I, which is then hydrolyzed to angiotensin II (see Chapter 34). This peptide stimulates drinking by an action on angiotensin II receptors in another of the circumventricular organs, the subfornical organ. Angiotensin II also causes vasoconstriction and release of aldosterone and antidiuretic hormone (ADH).

Insufficient water intake is usually a greater problem than excessive water intake. However, when more water is taken in than required, it is easily eliminated by inhibition of the release of ADH from neurons in the supraoptic nucleus at their terminals in the posterior pituitary gland (see Chapter 41). As mentioned previously, signals that inhibit release of ADH include increased blood volume and decreased osmolality of extracellular fluid. Other areas of the hypothalamus, particularly the preoptic region and lateral hypothalamus, help regulate water intake, as do several structures outside the hypothalamus.

Other Autonomic Control Structures

Several regions of the forebrain other than the hypothalamus also play a role in autonomic control. These regions include the central nucleus of the amygdala and the bed nucleus of the stria terminalis, as well as a number of areas of the cerebral cortex. Information reaches these higher autonomic centers from viscera through an ascending system that involves the nucleus of the solitary tract, the parabrachial nucleus, the periaqueductal gray matter, and the hypothalamus. Descending pathways that help control autonomic activity originate in such structures as the PVN of the hypothalamus, noradrenergic cell group A5, the rostral ventrolateral medulla, and the raphe nuclei and adjacent structures of the ventromedial medulla.

Neural Influences on the Immune System

Environmental stress can cause immunosuppression, in which the number of helper T cells and the activity of natural killer cells are reduced. Immunosuppression can even be the result of classical conditioning. One mechanism for such an effect involves the release of corticotropin-releasing factor from the hypothalamus. Corticotropin-releasing factor causes the release of adrenocorticotropic hormone (ACTH) from the pituitary gland; release of ACTH stimulates the secretion of adrenal corticosteroids, which cause immunosuppression (see Chapter 43). Other mechanisms include direct neural actions on lymphoid tissue. The immune system may also influence neural activity.

Key Points

1. The autonomic nervous system controls smooth muscle, cardiac muscle, and glands. It helps maintain homeostasis and coordinates responses to external stimuli. It has sensory and motor components, and the motor component consists of sympathetic and parasympathetic divisions. The enteric nervous system is often considered as part of the autonomic nervous system but is concerned specifically with control of the gastrointestinal tract.
2. Autonomic motor pathways have preganglionic and postganglionic neurons. Preganglionic neurons reside in the CNS, whereas postganglionic neurons lie in peripheral ganglia. Sympathetic preganglionic neurons are located in the thoracolumbar region of the spinal cord, and sympathetic postganglionic neurons are located in paravertebral and prevertebral ganglia. Parasympathetic preganglionic neurons are located in cranial nerve nuclei or in the sacral portion of the spinal cord. Parasympathetic postganglionic neurons reside in ganglia located in or near the target organs.
3. Autonomic afferent fibers innervate sensory receptors in the viscera. Most function to activate reflexes; for some, activation also leads to sensations that are experienced consciously.
4. The enteric nervous system includes the myenteric and submucosal plexuses in the wall of the gastrointestinal tract. The myenteric plexus regulates motility, and the submucosal plexus regulates ion and water transport and secretion.
5. Neurotransmitters at the synapses of preganglionic neurons in autonomic ganglia include acetylcholine (acting at both nicotinic and muscarinic receptors) and a number of neuropeptides. Interneurons in the ganglia release catecholamines. Norepinephrine (acting on adrenergic receptors) is the neurotransmitter generally released by sympathetic postganglionic neurons; neuropeptides are also released. Sympathetic postganglionic neurons that supply sweat glands release acetylcholine. Parasympathetic postganglionic neurons release acetylcholine (acting on muscarinic receptors).
6. The pupil is controlled reciprocally by the sympathetic and parasympathetic nervous systems. Sympathetic activity causes pupillary dilation (mydriasis); parasympathetic activity causes pupillary constriction (meiosis).
7. Emptying of the urinary bladder depends on parasympathetic outflow during the micturition reflex. Sympathetic constriction of the internal sphincter of the urethra prevents voiding. The micturition reflex is triggered by stretch receptors, and it is controlled in normal adults by a micturition center in the pons.
8. The hypothalamus contains many nuclei that have a variety of functions related to regulation of basic bodily functions, including body temperature, body weight, and fluid intake.
9. The goal of hypothalamic function is to maintain homeostasis of critical physiological parameters by acting as a servomechanism. The hypothalamus receives information about specific physiological parameters and uses this information to maintain each of these parameters at a specific set point. It does so via multiple mechanisms. This chapter illustrates how it maintains homeostasis via its control of the autonomic system.