Autonomic Nervous System 4.9

Learning Objectives

- List the three components of the autonomic nervous system
- Compare the pathways of somatic motor neurons to sympathetic efferents
- Describe the sympathetic chain, identifying the cervical ganglia, celiac ganglion, and superior and inferior mesenteric ganglia
- Distinguish between paravertebral ganglia and prevertebral ganglia
- Distinguish between preganglionic and postganglionic sympathetic fibers
- Describe the anatomic location of the parasympathetic nervous system
- Compare preganglionic and postganglionic fibers in the sympathetic nervous system to those in the parasympathetic nervous system
- Identify the organs innervated by the parasympathetic nervous system through cranial nerves III, VII, IX, and X and the pelvic nerve

THE AUTONOMIC NERVOUS SYSTEM SERVES A HOMEOSTATIC FUNCTION AND AN ADAPTIVE FUNCTION

The autonomic nervous system (ANS) is divided into three divisions: the **sympathetic**, **parasympathetic**, and **enteric**. The sympathetic division regulates the use of metabolic resources and coordinating the emergency response of the body to potentially life-threatening situations (**"fight or flight"**). The parasympathetic division usually presides over the restoration of metabolic reserves and the elimination of wastes (**"rest and digest"**). The enteric nervous system is usually considered separately because of its restricted location to the intestines and related organs (see Figure 4.9.1).

The ANS controls the day-to-day operations of most of the internal organs including

- the cardiovascular system, including heart and blood vessels;
- digestive system;
- respiratory tract;
- kidney and urinary bladder.

Certain involuntary responses to external stimuli are also mediated by the ANS. These include

- constriction of the pupil in bright light and dilation of the pupil in dim light;
- vasodilation of the skin and sweating in response to high core temperature, and vasoconstriction, "goose bumps," and increased fat metabolism in response to low core temperature;
- the "flight or fight" response to threatening stimuli.

Most organs receive both parasympathetic and sympathetic efferents that often have opposite effects. For example, parasympathetic stimulation of the heart slows the heart rate and reduces the strength of contraction; sympathetic stimulation accelerates the heart rate and increases the strength of contraction. However, the **skin and blood vessels receive only sympathetic efferents**. Responses for these tissues occur by adjusting the level of stimulation above or below a tonic level. Most organs have some basal level of stimulation called parasympathetic tone, or sympathetic tone, that establish basal levels of function that can be changed either by increasing or decreasing the tonic frequency of firing of efferent fibers. Thus, removal of parasympathetic output to the heart removes part of its brake on heart rate, and the heart rate increases. The same response would occur if sympathetic output to the heart were increased.

AUTONOMIC REFLEXES ARE FAST

One of the advantages of neural control of organ function over hormonal control is its rapid action and equally rapid return to normal levels. Through nervous stimulation, the heart rate can double within 3–5 s. Goose bumps, sweating, or change of blood pressure can occur within seconds of stimulation. These rapid responses are **reflexes**, stereotypical responses in which specific groups of neurons respond to specific sensory inputs. Generally, these actions occur subconsciously and we are hardly aware of either the sensory information or the reflex responses to them. Some autonomic functions, such as defecation and urination, reach consciousness because they require contraction or relaxation of voluntary skeletal muscle.

THE EMOTIONAL STATE GREATLY AFFECTS AUTONOMIC EFFERENT FUNCTION

Emotions such as excitement, euphoria, fear, anxiety, or anger all influence the level of autonomic activity. These

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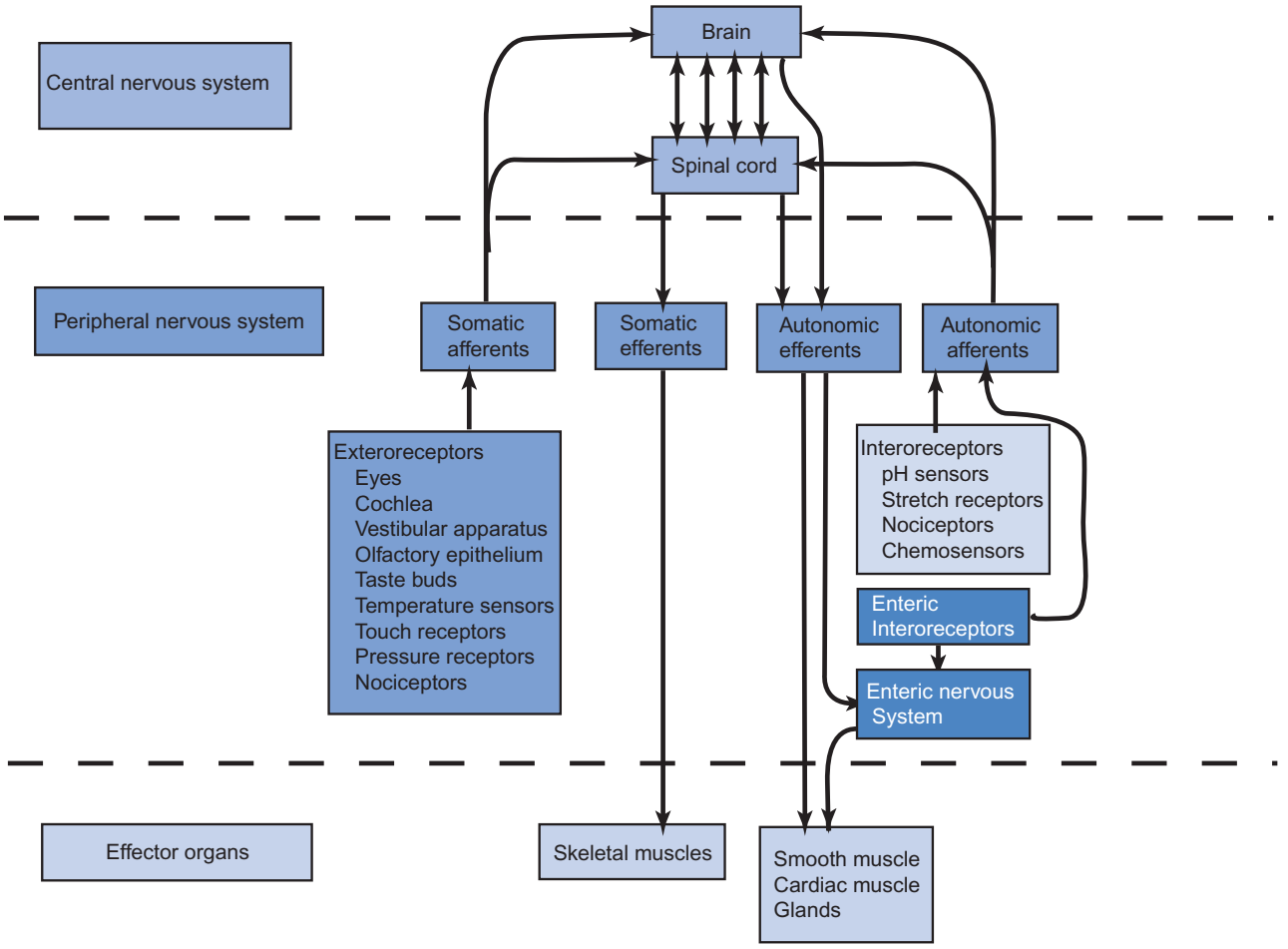


FIGURE 4.9.1 Role of the ANS in the organization of the nervous system. The autonomic efferent systems control the involuntary functions of the body, and they are driven by the integration of signals arriving from these organs along autonomic afferents and from information about the external world that enters the CNS through the exteroreceptors.

emotions stimulate the ANS to cause a variety of responses such as cold sweats, indigestion, excess stomach acid production, cardiac palpitations, high blood pressure, or low blood pressure. These responses are influenced by a variety of psychosocial factors and are conditioned by our previous experiences and individual variation. We live in a complex world of subtle social cues whose effect on us is filtered through the cerebral cortex and limbic system (the seat of the emotions), often subconsciously, into the autonomic system. Upheaval in our social world can literally make us sick, but only by our own permission. We in fact make ourselves sick by our reaction.

AUTONOMIC EFFERENT NERVES HAVE TWO NEURONS

As we saw in Chapter 4.4, motor nerves to skeletal muscles follow an uninterrupted path from the cell body located in the ventral horn of the spinal cord to the muscle. In the ANS the efferent path consists of two neurons: a **preganglionic neuron** and a **postganglionic neuron**. A comparison between the two systems is shown in Figure 4.9.2. Both the sympathetic and the parasympathetic system use these two-neuron paths to the effector cells, but their anatomic arrangement is different. Figure 4.9.2 illustrates the sympathetic division only.

PREGANGLIONIC NEURONS ARE IN THE CNS

The cell body of a preganglionic neuron lies in an appropriate nucleus of the brain or in the gray matter of the spinal cord **(intermediolateral column)**. Its axon is thin (2–4 μm) and myelinated. It usually terminates on a postganglionic neuron within a ganglion. A ganglion is a collection of nerve cell bodies outside of the CNS.

POSTGANGLIONIC NEURON CELL BODIES ARE IN GANGLIA

The postganglionic neuron cell body lies in the ganglion, but its typically thin and unmyelinated axon (1.5 μm) leaves the ganglion to make contact with the target organ. Thus, the name "postganglionic" is used to describe its axon. It receives its input from preganglionic neurons that lie within the CNS.

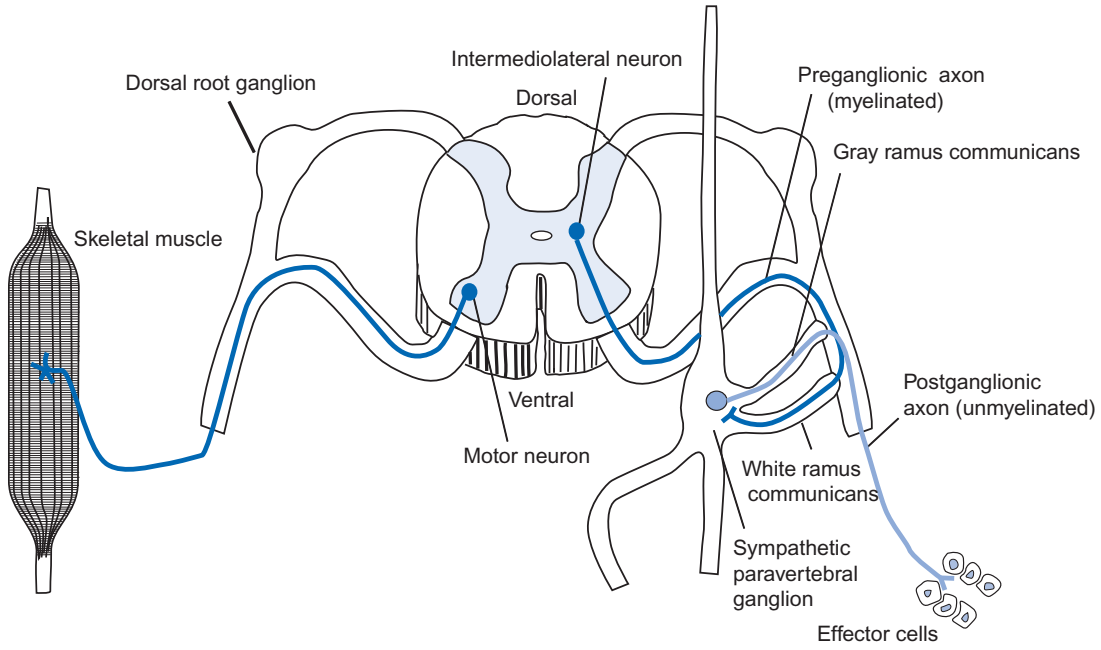


FIGURE 4.9.2 Schematic comparison of the two-neuron efferent pathway of the sympathetic nervous system with the single-neuron efferent pathway for the somatic motor system. The somatic motor system is driven by motor neurons with cell bodies in the ventral horn of the spinal cord, with direct connections to the muscle. The sympathetic neurons have cell bodies in the intermediate gray of the spinal cord and make a synapse on a ganglion cell, which then makes connections to effector cells.

THE SYMPATHETIC NERVOUS SYSTEM ORIGINATES IN THE *THORACOLUMBAR SPINAL CORD*

THE CELL BODIES OF PREGANGLIONIC SYMPATHETIC FIBERS LIE IN T1–T12 AND L1–L2

The preganglionic sympathetic fibers originate from cell bodies in the intermediolateral area of the gray matter of the spinal cord in thoracic segments T1–T12 and lumbar segments L1–L2. The axons leave the cord through the ventral roots and then leave the ventral roots through short branches called **white ramus communicans**. The axons in the white ramus enter a **paravertebral ganglion** at the same level of the cord.

THE PARAVERTEBRAL GANGLIA FORM A SYMPATHETIC CHAIN

Each spinal cord segment has two ventral roots that connect by a white ramus to a spinal sympathetic ganglion. These ganglia communicate with each other up and down the spinal cord, forming two sympathetic chains, one on each side of the vertebral column. Only those pairs of spinal sympathetic ganglia from T1 to L2 receive inputs via the white rami. Those above T1 receive inputs from fibers from the thoracic segments that climb the sympathetic chain. Those ganglia below L2 receive inputs from preganglionic fibers that descend the chain from the lower thoracic and lumbar ganglia (see Figure 4.9.3). Each pair of spinal sympathetic ganglia send out an efferent branch to effector organs. These fibers travel from the ganglia to the spinal nerve by a **gray ramus communicans**. It is gray because the axons it contains are unmyelinated postganglionic fibers. Thus, only some of the sympathetic ganglia have white rami, but all have gray rami.

PREVERTEBRAL GANGLIA *ARE UNPAIRED AND LIE IN THE ABDOMEN*

Postganglionic fibers that supply the visceral organs originate in three ganglia found within the abdominal cavity. These unpaired ganglia receive input from segments T5–L2 that travel through the sympathetic ganglia without making a synapse, to synapse on neurons within these ganglia. These ganglia are the:

- **celiac ganglion**
- **superior mesenteric ganglion**
- **inferior mesenteric ganglion.**

Fibers from these ganglia affect smooth muscles of the intestinal walls, smooth muscles of the blood vessels in the viscera, intestinal glands, and the enteric nervous system.

THE ADRENAL MEDULLA *IS A MODIFIED GANGLION*

Preganglionic fibers travel through the prevertebral ganglia and the celiac ganglion to synapse with **chromaffin cells** in the **adrenal medulla**. These cells derive their name from the colored reaction they produce in fixed tissue. These cells are modified postganglionic cells. They release their neurotransmitter, **epinephrine**, directly into the blood instead of at nerve terminals. They also release norepinephrine. Epinephrine is commonly known as **adrenaline**, and its circulating form prepares the body for emergency action. The adrenal medulla is discussed more thoroughly in Chapter 9.6.

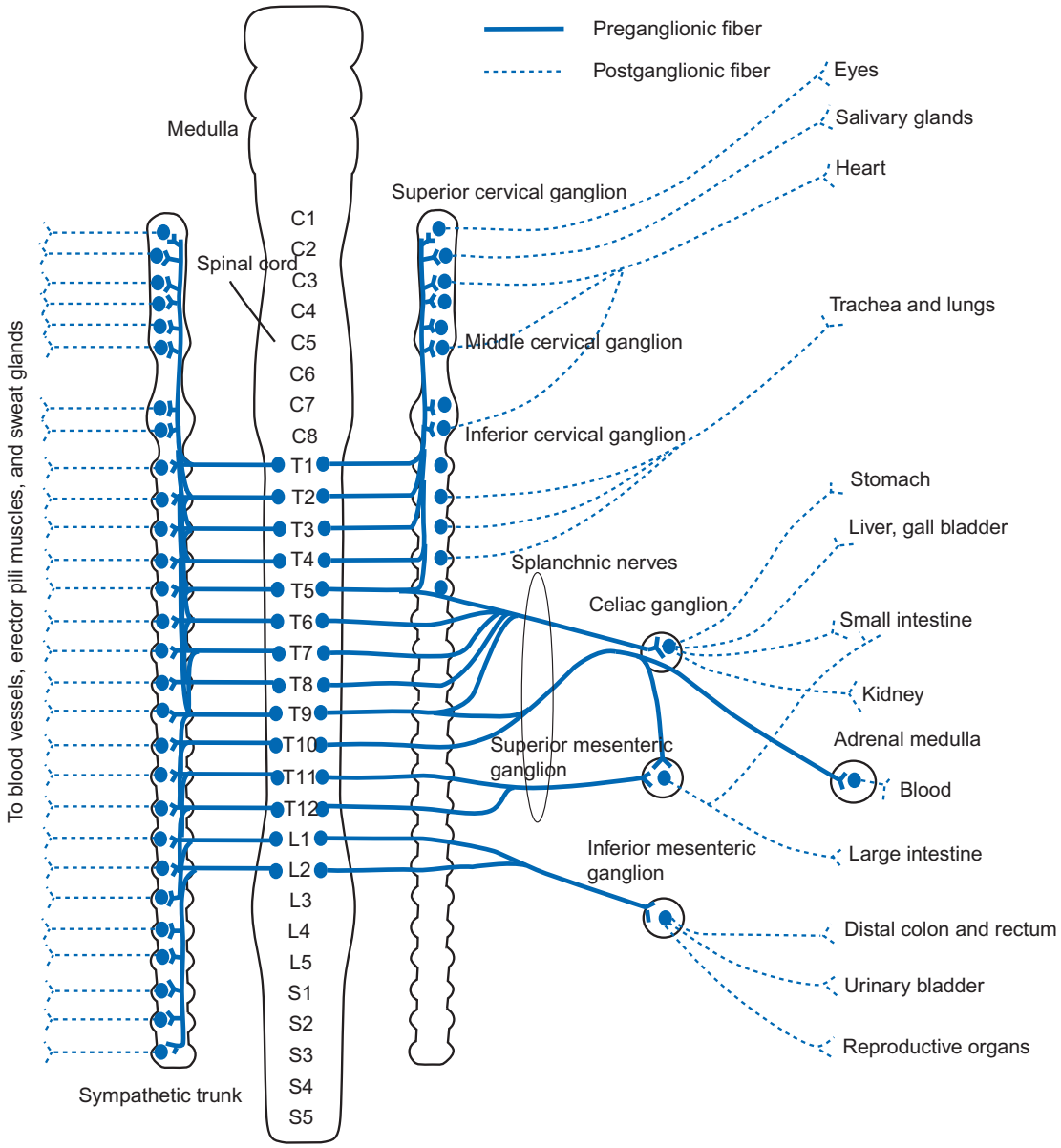


FIGURE 4.9.3 Schematic diagram of the connections of the sympathetic nervous system. Each segment of the spinal cord corresponds to a pair of sympathetic ganglia (paravertebral ganglia), one on each side of the column. These communicate up and down by interganglionic branches, so the set of ganglia resembles beads on a string and is called the sympathetic chain. The preganglionic cells originating in the cord synapse in the ganglia with postganglionic cells. These postganglionic cells send efferents to the skin, sweat glands, and blood vessels of the body, as shown at the left. The efferent output to the viscera, shown to the right, can occur via postganglionic cells in the paravertebral ganglia or via prevertebral ganglia. The prevertebral ganglia include the celiac, superior mesenteric, and inferior mesenteric ganglia. They receive inputs from preganglionic fibers that travel through the chain. All of the visceral organs receive sympathetic efferents as shown. Although the targets of efferent output are shown separately here, in reality both sympathetic chains give rise to both types of efferents. The adrenal medulla receives preganglionic input directly; it acts like a ganglion.

PREGANGLIONIC FIBERS HAVE THREE FATES

According to the description given above, preganglionic fibers with cell bodies in the interomedial column of the spinal cord have one of three fates (shown schematically in Figure 4.9.4):

- synapse on a postganglionic neuron within the paravertebral ganglion;
- travel through the paravertebral ganglion and synapse on a postganglionic cell in the prevertebral ganglia (celiac, superior mesenteric, inferior mesenteric, adrenal medulla);
- travel up or down the sympathetic trunk to synapse on a postganglionic cell in other segments.

CERVICAL GANGLIA *ARE FORMED FROM ASCENDING AXONS FROM T1 TO T5*

Preganglionic axons that inform the cervical ganglia arise from thoracic segments T1–T5. The three cervical ganglia are the **superior**, **middle,** and **inferior** cervical ganglia.

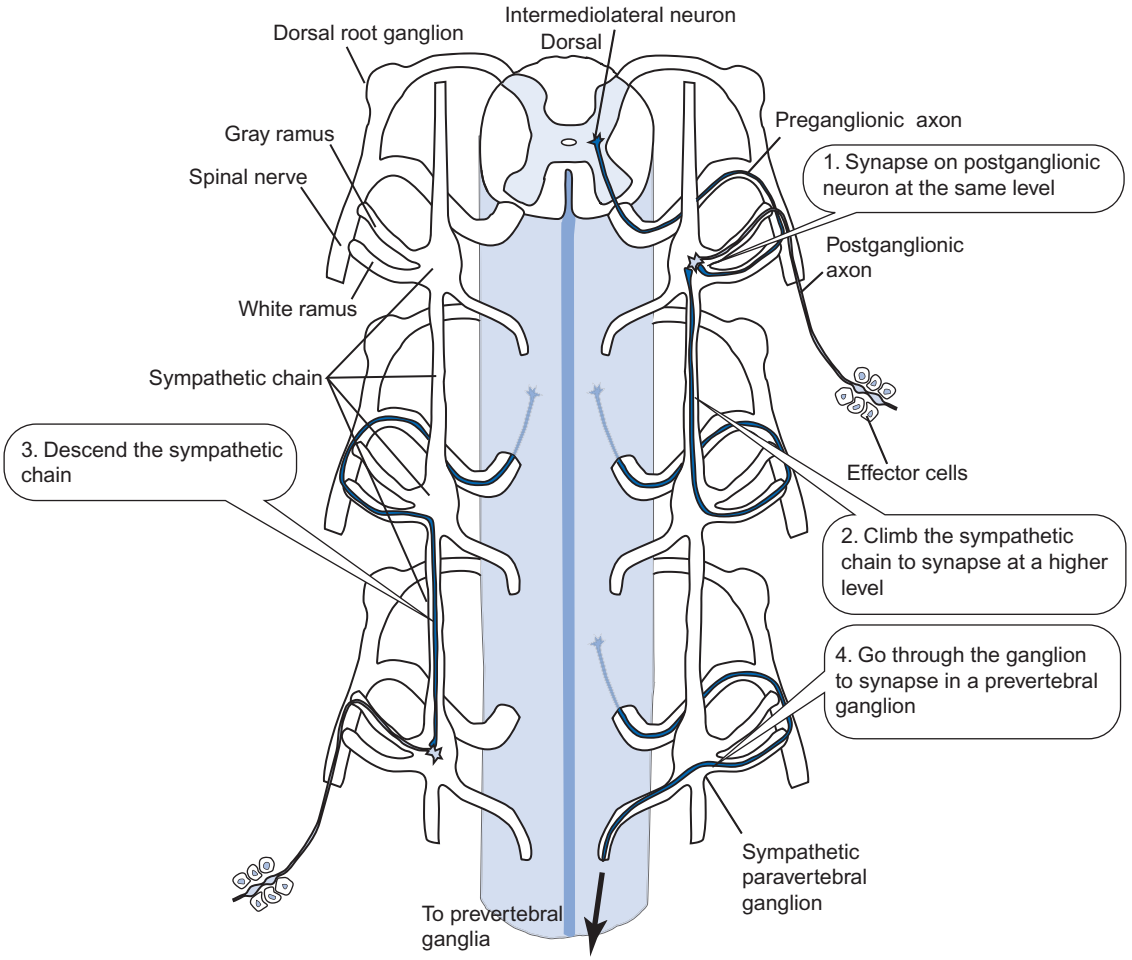


FIGURE 4.9.4 Schematic diagram of the wiring of the sympathetic chain. Preganglionic neurons with cell bodies in the interomedial column of the spinal cord exit the ventral root and their axons travel over the white ramus communicans to the sympathetic ganglia. There the axon can travel up (2) or down (3) the sympathetic chain to neighboring ganglia. Alternatively, the axon can make synapses with a neuron within the ganglia at the same level as the spinal nerve (1) or the axon can pass through the ganglia to make a synapse in a prevertebral ganglion located in the mesentery (4).

PREGANGLIONIC AXONS BRANCH TO ENABLE WIDESPREAD RESPONSES

The number of sympathetic postganglionic axons exceeds the number of preganglionic axons by a factor of about 100. Thus, each preganglionic axon branches many times and thereby spreads its influence over many postganglionic cells. This is an example of **divergence** (see Chapter 4.2). Divergence in the sympathetic nervous system allows widespread activation of many effectors when necessary. Preganglionic axons also **converge** on individual postganglionic neurons. The activity of the postganglionic neurons thereby reflects an integrated response of many preganglionic neurons.

THE PARASYMPATHETIC NERVOUS SYSTEM ORIGINATES IN CRANIAL AND SACRAL NERVES

Preganglionic parasympathetic nerve fibers originate in specific nuclei in the brain or in segments S2–S4 of the sacral spinal cord. These preganglionic axons (2–4 μm in diameter) are myelinated and make synapses with postganglionic cells that reside close to or within the effector organ. Thus, the parasympathetic nervous system has long preganglionic fibers and short postganglionic fibers. This is in stark contrast to the sympathetic nervous system in which the preganglionic fibers are short and the postganglionic fibers are long. In contrast to the sympathetic nervous system, the parasympathetic nervous system is more localized and less diffuse. The preganglionic fibers branch far less; the ratio of preganglionic neurons to postganglionic neurons is near 1:1 or 1:2 (Figure 4.9.5).

Parasympathetic efferents flow out through cranial nerves III, VII, IX, and X. **Cranial nerve III** is the **oculomotor nerve**, originating in the tectum of the midbrain where inputs from the optic nerve provide input for ocular reflexes. **Parasympathetic stimulation constricts the pupil and contracts the ciliary muscle**.

Parasympathetic output of the **facial nerve**, **cranial nerve VII**, originates in the superior salivary nucleus in the rostral medulla. Some fibers synapse on postganglionic neurons in the pterygopalatine ganglion, which innervates the **lachrymal glands** and the nasal and palatine mucosa. Parasympathetic stimulation enhances secretion of tears. Other fibers in the facial nerve travel in

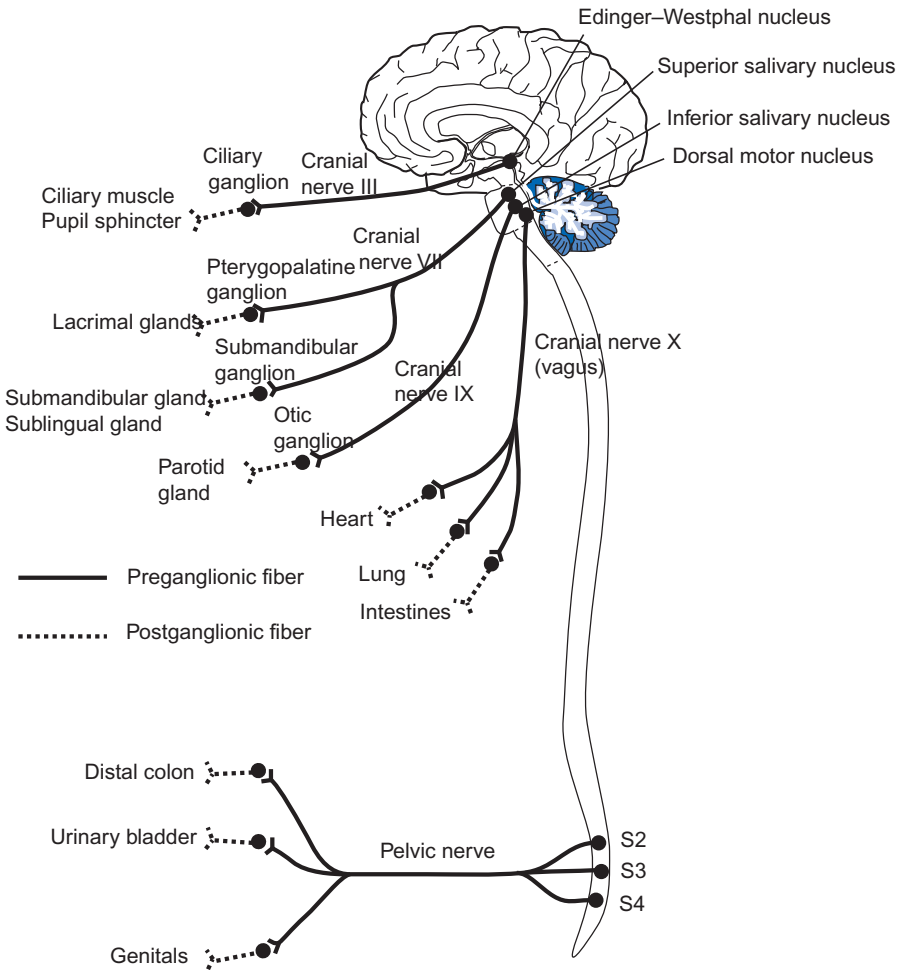


FIGURE 4.9.5 Connections of the parasympathetic nervous system. This system originates from cranial and sacral centers and is characterized by long preganglionic fibers that synapse in ganglia near or in the organ being regulated.

the chorda tympani, a division of the facial nerve, to synapse with cells in the submandibular ganglion. These innervate the submandibular and sublingual glands; **parasympathetic stimulation increases salivary secretion of fluid.**

Preganglionic parasympathetic neurons reside in the inferior salivary nucleus in the medulla and travel over the **glossopharyngeal nerve**, or cranial nerve IX. These synapse on cells in the **otic ganglion**, where the postganglionic fibers join cranial nerve V to travel to the parotid gland. **Parasympathetic stimulation of the parotid gland increases its rate of saliva secretion**. The glossopharyngeal nerve also brings sensory information into the medulla. The carotid bodies sense the arterial P_{O_2} and P_{CO_2} and relay this information to the respiratory centers of the medulla. Baroreceptors in the carotid sinus sense arterial blood pressure and relay that information to the **tractus solitarius** in the medulla.

The **vagus nerve**, **cranial nerve X**, is the major parasympathetic nerve. The **nucleus ambiguus** and the **dorsal motor nuclei** in the **medulla** provide efferent output to the vagus nerve that supplies a variety of internal organs including the heart, lungs, kidney, liver, spleen, pancreas, and the gastrointestinal tract. Long preganglionic fibers travel over the vagus nerves to ganglia located in the target tissues. The right vagus nerve supplies the **sinoatrial node** (SA node) of the heart whereas the left vagus nerve supplies the **atrioventricular node** (AV node) (see Chapter 5.5). **Vagal stimulation of the heart slows its rate and reduces its strength of contraction**. Vagal efferents to the lung control the caliber of the bronchioles through control of the smooth muscles in the bronchiole walls. **Vagal stimulation constricts the bronchioles and also regulates secretory activity.** Vagal inputs to the esophagus and stomach make synapses with enteric ganglia. Innervation by the vagus regulates gastrointestinal motility and secretion.

Preganglionic parasympathetic nerves originate in the interomedial gray of segments S2, S3, and S4 of the spinal cord. Their long presynaptic axons reach enteric ganglia in the lower portion of the gastrointestinal tract (the descending colon, sigmoid colon, rectum, and internal anal sphincter), the urinary bladder, and the genitalia. **Parasympathetic stimulation causes urination, defecation, and erection**, but not simultaneously.

AUTONOMIC REFLEXES LINK SENSORY INPUT TO MOTOR EFFERENTS

Traditionally, the ANS is viewed as an efferent system. However, efferent activity is brought about in response to sensory input, which travels over the same nerves as the efferents. The vagus nerve, for example, carries 10 times

as many afferent fibers as efferent fibers: the afferents are a necessary part of the ANS as much as the cutaneous and muscle sensors are necessary to the somatic motor system. Sensory information from the visceral organs, blood vessels, and skin forms the afferent limb of the autonomic reflex arc. This sensory input modulates the activity of the sympathetic neurons in the interomedial lateral column of the spinal cord from T1 to L2, or of parasympathetic neurons in the parasympathetic nuclei of the medulla or in the sacral cord. The sensory input that drives autonomic reflexes may or may not reach consciousness. Thus some of the inputs climb the cord to reach higher centers. Sensations perceived from the viscera may be vaguely localized or may be felt in a somatic structure other than the organ. Thus, damage to the heart can be referred to the left arm. This is called **referred pain**.

Just as sensory input from the internal organs can reach higher centers to produce a conscious perception, output from higher centers can influence autonomic function. Thus, the traffic of information up the cord is accompanied by modulatory inputs from higher centers down the cord. These "higher centers" are autonomic ganglia in the brain stem that receive input from the amygdala and the hypothalamus, but have no direct input from the somatic motor cortex. Thus there is no conscious control of autonomic function. A schematic of these events is shown in Figure 4.9.6 for sympathetic reflexes.

THE MAJOR AUTONOMIC NEUROTRANSMITTERS ARE *ACETYLCHOLINE* AND *NOREPINEPHRINE*

Both sympathetic and parasympathetic preganglionic neurons release acetylcholine at their terminals. The postsynaptic membrane on the postganglionic cell has nicotinic receptors for acetylcholine, so named because nicotine is an agonist. This receptor is similar to the nicotinic receptor at the neuromuscular junction, but the two receptors are not identical. Unlike the nicotinic receptor at the neuromuscular junction, the ANS receptor is not blocked by **curare**, but it is blocked by **hexamethonium**. The nicotinic receptor is ionotropic and binding of acetylcholine opens a channel for cations that causes a depolarization of the postsynaptic cell membrane. Similar to the neuromuscular junction, acetylcholine is rapidly degraded by acetylcholinesterase, which shuts off the signal.

Postganglionic fibers of the sympathetic division mainly release norepinephrine whereas postganglionic parasympathetic fibers release acetylcholine. An exception to this rule is the postganglionic sympathetic fibers to sweat glands, which release acetylcholine. Figure 4.9.7 shows the neurotransmitters released by preganglionic and postganglionic fibers in both the sympathetic and parasympathetic divisions of the ANS.

PARASYMPATHETIC RELEASE OF ACETYLCHOLINE WORKS ON *MUSCARINIC* RECEPTORS

Postganglionic neurons in parasympathetic the division generally are located within the target tissue and have short postganglionic axons. They release acetylcholine onto **muscarinic receptors** located on the target cells, so named because the plant alkaloid **muscarine** is an agonist for these receptors. The muscarinic receptors are all metabotropic. There are multiple isoforms of the muscarinic receptors designated **M1, M2, M3, M4,** and **M5**. Muscarinic receptors are blocked by **atropine**.

As described in Chapter 4.2, M1, M3, and M5 receptors are linked to **G_q-coupled receptors**. Recall that these heterotrimeric G-proteins consist of α, β, and γ subunit

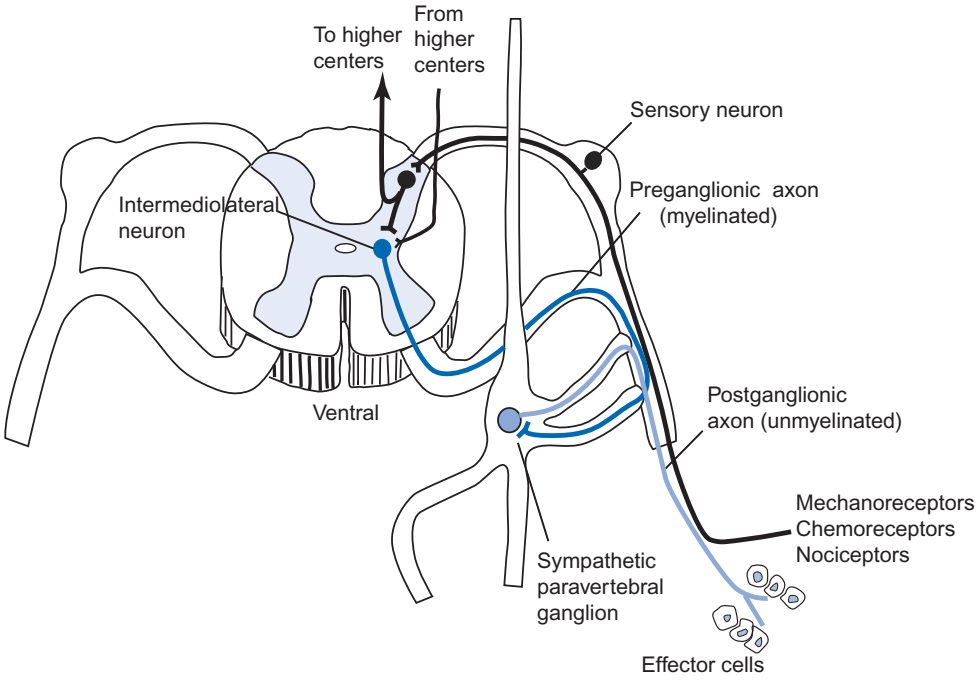


FIGURE 4.9.6 Hypothetical example of an autonomic reflex. Sensory information due to mechanoreceptors, chemoreceptors, or nociceptors enters the spinal cord along the dorsal root. This information is conveyed to an interneuron that conveys it to autonomic preganglionic neurons located in the intermediolateral column of the spinal cord. Some of these sensory fibers send sensory information up the cord to the brain stem, enabling conscious perception of visceral events. Higher centers return input to the intermediolateral neurons, thereby providing a mechanism for the influence of autonomic function by the emotional state. Most of these reflex activities occur subconsciously, but visceral pain can quickly draw one's attention.

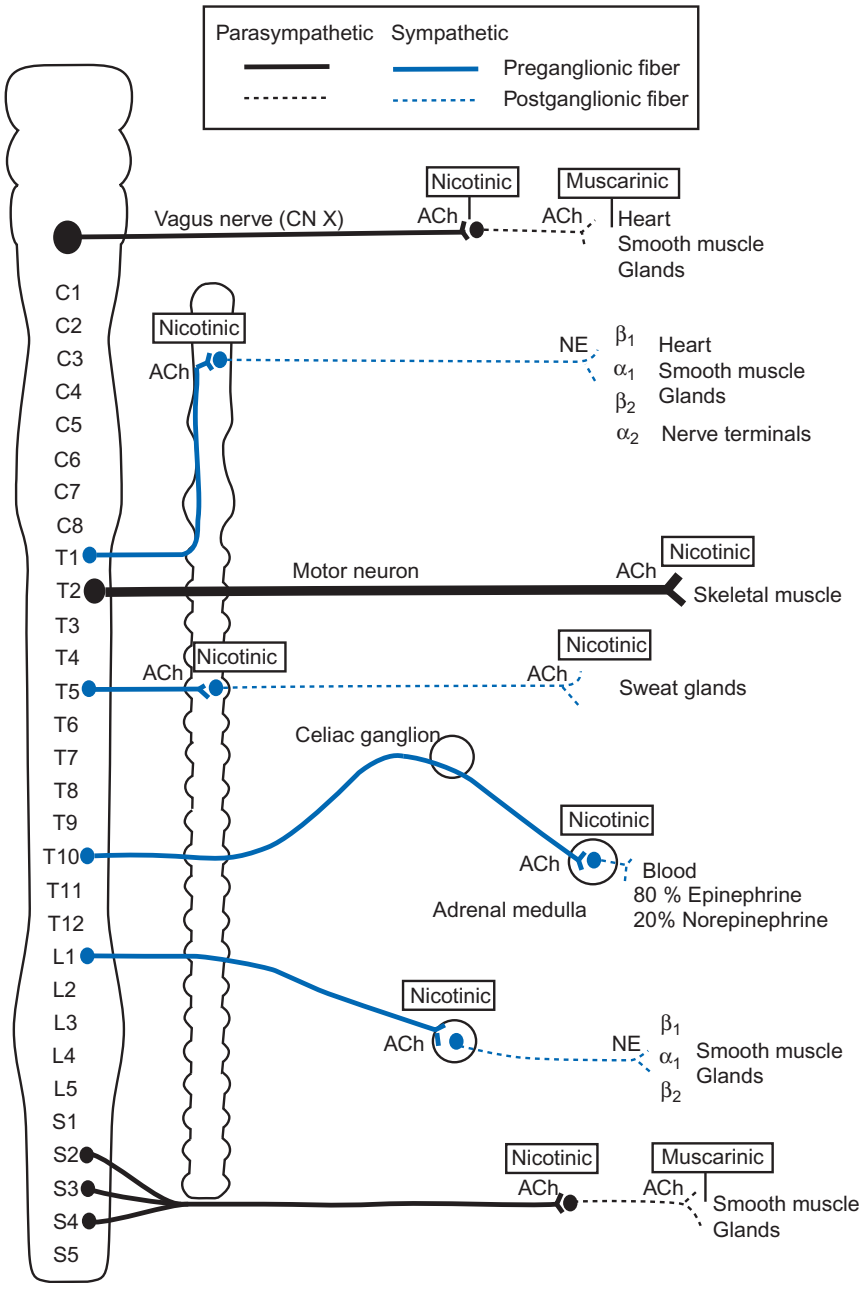


FIGURE 4.9.7 Neurotransmitters used by the parasympathetic and sympathetic nervous systems. Preganglionic sympathetic and parasympathetic fibers both use acetylcholine as neurotransmitter and the postganglionic cells have nicotinic cholinergic receptors. The postganglionic parasympathetic nerves also release acetylcholine, and the postsynaptic target cells have muscarinic cholinergic receptors. In contrast, postganglionic sympathetic fibers release norepinephrine onto cells that have α_1-, α_2-, β_1-, or β_2-receptors. An exception to this rule is postganglionic fibers that release acetylcholine onto muscrinic receptors in the sweat glands. For comparison, a somatic α-motor neuron that controls skeletal muscle is also shown. Preganglionic fibers are solid lines; postganglionic fibers are dashed lines. Red color signifies sympathetic nervous system; black indicates parasympathetic connections.

exchanges GTP for GDP upon ligand binding and dissociates from the $\beta\gamma$ subunits. The α subunit for M1, M3, and M5 receptors activates **phospholipase C** to release **inositol tris phosphate (IP3)** and **diacylglycerol (DAG)** from phosphatidylinositol 4,5-bisphosphate. The released IP3 releases Ca^{2+} from intracellular stores, and this activates **CAM kinase,** a protein kinase that phosphorylates target proteins within the cell. The DAG activates **protein kinase C (PKC)** of which there are multiple subtypes. This phosphorylation brings about the final response to the neurotransmitter.

The M4 receptor is coupled to a **G_i receptor**: binding of acetylcholine to these receptors inhibits the enzyme **adenylyl cyclase**, which produces **3′,5′-cyclic AMP** from ATP. Cyclic AMP stimulates **protein kinase A (PKA)**, which phosphorylates its target proteins. Thus, binding of acetylcholine to cells with M2 and M4 receptors results in less phosphorylation of target proteins. The M2 receptor is also coupled to a G_i mechanism, but the $\beta\gamma$ subunit also directly activates a K^+ channel, which typically causes a hyperpolarization in target cells.

NOREPINEPHRINE RELEASED BY POSTGANGLIONIC SYMPATHETIC NEURONS ACTS THROUGH α- AND β-RECEPTORS

Epinephrine is a hormone released from the adrenal medulla in response to stress through activation of sympathetic preganglionic efferents. "Epinephrine" derives its name from "epi," meaning "above" and "nephros,"

for kidney, because the adrenal gland is located on top of the kidney. Its other name "adrenaline" derives from "renal," another root for kidney. Receptors for both norepinephrine and epinephrine are called **adrenergic receptors**. There are four main types of these receptors, which were first described by their different responses to pharmacological agents. The β-receptors respond to much lower concentrations of epinephrine or norepinephrine than do the α-receptors. β_1-receptors respond to epinephrine and norepinephrine about equally whereas β_2-receptors are much more sensitive to epinephrine than to norepinephrine. These receptors were described previously in Chapter 4.2.

Both β_1- and β_2-receptors couple to a G_s protein that increases [cAMP] and activates PKA to phosphorylate target proteins. The β-receptors are blocked by **propranolol**. The α_1-receptors are coupled to G_q proteins that activate phospholipase C to increase cytosolic concentrations of DAG and IP3 as detailed above for the M1, M3, and M5 receptors. The α_2-receptors are linked to a G_i protein that inhibits adenylyl cyclase, decreasing [cAMP]. The α-receptors are blocked by **phenoxybenzamine**.

Norepinephrine is typically released by postganglionic sympathetic fibers, but those that innervate the general sweat glands of the skin release acetylcholine. However,

TABLE 4.9.1 Effect of Parasympathetic and Sympathetic Stimulation on Target Tissues

Target Tissue	Parasympathetic Stimulation	Sympathetic Stimulation
Eye		
Pupil	Contraction (miosis)	Dilation (α_1)—mydriasis
Ciliary muscle	Contraction	Relaxation (β_2)
Mueller's muscle	–	Contraction (α_1)
Lachrymal glands	Increased secretion	–
Salivary glands	Increased secretion (M3)	Increased protein secretion (β_1)
Nasal glands	Increased secretion	Decreased secretion (α_1)
Skin		
Sweat glands	–	Increased secretion (M)
Palms	–	Emotional sweating (α_1) contraction(α_1)
Erector pili	–	
Heart		
Rate	Decreased (M2)	Increased (β_1)
Contractility	Decreased (M2)	Increased (β_1)
Lungs		
Bronchioles	Constriction	Dilation (β_2)
Secretion	Increased secretion	–
Blood vessels		
Skin	–	Constriction (α_1)
Skeletal muscle	–	Dilation (β_2) constriction (α_1)
Viscera	–	Constriction (α_1)
Gastrointestinal tract		
Motility	Increased	Decreased (α_2, β_2)
Sphincters	Relaxation	Contraction (α_1)
Glands	Increased secretion (M3 in pancreas)	Decreased secretion
Gall bladder	Contraction	Relaxation
Liver	–	Glycogenolysis and gluconeogenesis (β_2, α_1)
Urinary system		
Detrusor muscle	Contraction	Relaxation (β_2)
Ureter	Relaxation	Contraction (α_1)
Sphincter	Relaxation	Contraction (α_1)
Fat tissue	–	Lipolysis (β)

fibers to sweat glands of the palms of the hands release norepinephrine.

AUTONOMIC NERVE TERMINALS ALSO RELEASE OTHER NEUROTRANSMITTERS

Sympathetic nerves that cause vasoconstriction release both norepinephrine and **neuropeptide Y**. **Vasoactive intestinal peptide (VIP)** is released along with acetylcholine by sympathetic nerves to the sweat glands and also by parasympathetic nerves to the enteric nervous system. Some postganglionic parasympathetic neurons release **nitric oxide (NO)**. These neurons are important in the intestine and in erectile function and are the basis of action of Viagra. These neurons are called nonadrenergic noncholinergic (NANC).

EFFECTS OF AUTONOMIC STIMULATION DEPEND ON THE RECEPTOR ON THE TARGET CELL

The specificity of autonomic effects derives from the use of a variety of neurotransmitters from the presynaptic cell and the use of a variety of receptors on the postsynaptic cell. Postganglionic parasympathetic fibers releasing acetylcholine will have no effect on target cells that have only α- or β-adrenergic receptors. These same fibers will have different effects on target cells expressing M1 on their surface compared to those expressing M4. Typically cells with M1, M3, and M5 receptors are activated by parasympathetic stimulation, whereas those with M2 and M4 are inhibited. Table 4.9.1 shows the effects of parasympathetic or sympathetic stimulation on a variety of target tissues.

THE PUPILLARY LIGHT REFLEX REGULATES LIGHT INTENSITY FALLING ON THE RETINA: A PARASYMPATHETIC REFLEX

The size of the pupil is determined by two thin layers of muscle within the **iris**, as described in Chapter 4.8. Muscle fibers in the **dilator** muscle orient radially and are controlled by sympathetic nerves (α_1-receptors). Sympathetic stimulation dilates the pupils, but only in unusually stressful situations. The fibers in the **sphincter** muscle orient circumferentially, as shown in Figure 4.9.8. Parasympathetic nerves contract this muscle and constrict the pupil. The **direct pupillary reflex** refers to the constriction of the pupil upon exposure to bright light. The sphincter muscle receives tonic parasympathetic stimulation, so dilation of the pupil in dim light normally results from reduction in parasympathetic tone rather than from sympathetic stimulation of the dilator muscle. Special retinal ganglion cells (RGCs) containing a photodetector called **melanopsin** detect the level of illumination without contributing to image formation. These RGCs project fibers to the midbrain on the ipsilateral side. These areas of the midbrain project to the **Edinger–Westphal nucleus** near the midline of the medulla, which then sends efferent motor fibers to the ciliary ganglia and from there to the pupil sphincter muscle and the **ciliary body**, which controls tension on the lens. The effect is to constrict the pupil and release tension on the lens, causing it to increase its refractory power. Simultaneously, information about the bright illumination passes over to the other side of the brain through the posterior commissure, and project to the Edinger–Westphal nucleus on the contralateral side. This causes constriction of the pupil in the other

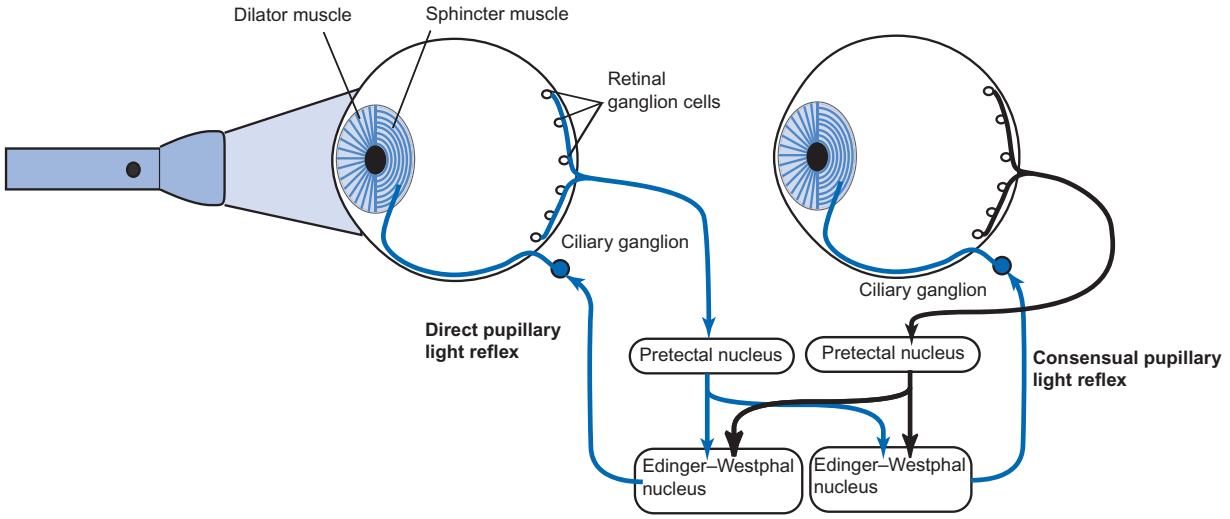


FIGURE 4.9.8 Direct and consensual pupillary reflex. Special retinal ganglion cells that contain melanopsin, now called "intrinsically photosensitive retinal ganglion cells," or ipRGCs, begin a four-neuron reflex pathway. The first neurons, the ipRGCs, project to the ipsilateral pretectal nucleus at the level of the superior colliculus. A second cell there projects to each Edinger–Westphal nucleus. A third cell in the Edinger–Westphal nucleus connects to the ciliary ganglion, where the final postganglionic parasympathetic fiber innervates the sphincter muscle. In the direct pupillary reflex, exposing one eye to light causes constriction of the pupil in that eye. This is accomplished by the reflex in the figure. Activated axons are shown in blue, whereas quiescent fibers are in black. Because the pretectal fibers project to both Edinger–Westphal nuclei, light incident on one eye also causes pupil constriction in the other eye, even when it is kept dark. Light exposure causing constriction of the pupil in the contralateral eye is the consensual pupillary light reflex. Constriction of the pupils to a pin point is called **miosis**. A separate sympathetic innervation of the dilator muscle occurs through the sympathetic system from nerve cells in the superior cervical ganglion. Widening of the pupil is called **mydriasis**. Dilation of the pupils in dim light is normally due to removal of parasympathetic tone.

eye, even though that eye is not exposed to bright light. This is the **consensual pupillary light reflex**. These reflexes have the effect of limiting light exposure to the retina so that good visual discrimination is maintained over wide ranges of illumination.

MICTURITION INVOLVES AUTONOMIC REFLEXES AND VOLITIONAL NERVOUS ACTIVITY

The urinary bladder is a muscular sac that stores between 150 and 250 mL of urine produced by the kidneys until it can be voided. The ability to hold urine in the bladder is called **continence** and emptying the bladder is called **micturition**. Micturition can occur automatically by a spinal reflex, but it can be overridden by higher control. Reflex contraction of the **detrusor muscle** in the bladder is controlled by afferent stretch receptors in the walls of the bladder that travel over the **pelvic nerve** to the sacral spinal cord (S2–S4) where they engage efferent fibers. Information from these stretch receptors ascends the cord to make us consciously aware of the need to urinate. Simultaneously, parasympathetic efferents relax the internal sphincter muscle on the urethra.

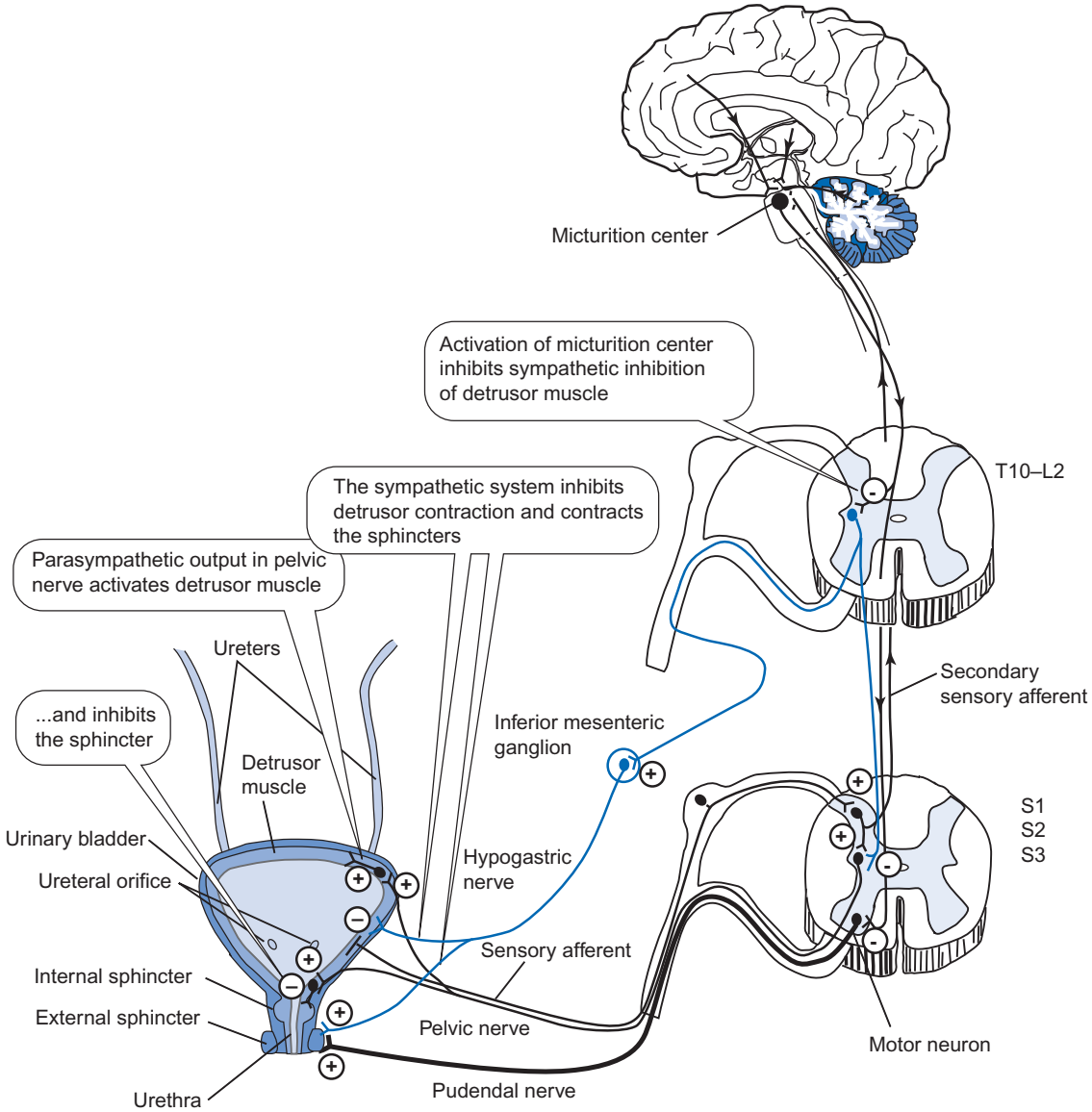


FIGURE 4.9.9 Parasympathetic and sympathetic control of micturition. Stretch receptors in the wall of the bladder activate a parasympathetic urination reflex in the sacral spinal cord. The parasympathetic afferents and efferents both travel over the pelvic nerve. The efferent parasympathetics contract the detrusor muscle that empties the bladder and relaxes the internal sphincter. Sympathetic efferents originate in the intermediolateral gray column of T10–L2 and travel to the inferior mesenteric ganglion. The hypogastric nerve carries the sympathetic efferents to the bladder where they promote relaxation of the detrusor and contraction of the internal sphincter. An intraspinal tract from the intermediolateral sympathetics also inhibits the sacral micturition reflex. Micturition can be overridden by conscious control of somatic α-motor neurons in the ventral horn of the sacral spinal cord. Efferent signals from the motor neuron travel over the pudendal nerve to contract the external sphincter. The micturition center located in the rostral pons receives inputs from the cerebrum, cerebellum, and other superpontine centers. It coordinates the parasympathetic, sympathetic, and somatic motor control of micturition. The sympathetic fibers are shown in blue; parasympathetics are in black; somatic motor neuron in thick black. The effects shown are for promotion of micturition; a positive sign indicates excitation, a negative sign indicates inhibition. The overall effect of any pathway can be determined by multiplying the signs. Thus the parasympathetic micturition reflex is stretch receptor (+) $\times$ interneuron (+) $\times$ preganglionic fiber (+) $\times$ postganglionic fiber on detrusor (+) = detrusor contraction (+).

Sympathetic fibers originating in the intermediolateral horn in the distal thoracic and lumbar spinal cord travel to the inferior mesenteric ganglion where they synapse on postganglionic sympathetic fibers. These fibers travel in the hypogastric nerve to the bladder where they inhibit the detrusor muscle through β_2-receptors and contract the internal sphincter muscle through α_1-receptors. The sympathetic fibers also inhibit the stretch reflex through intraspinal connections. The sympathetic system inhibits bladder emptying whereas the parasympathetic system promotes it.

Nearly everyone has at one time or another found themselves with a full bladder with no socially acceptable way of relieving themselves. The only recourse is to "hold it" until a proper place is found. This is the function of the **external sphincter** muscles that are controlled by somatic α motor neurons in the sacral spinal cord that reach the external sphincter muscle over the **pudendal nerve**. These motor neurons are under conscious control through higher centers and through spinal tracts.

A **micturition center** in the rostral pons receives input from the cortex, cerebellum, and other centers above the pons and controls micturition through the **reticulospinal tract**. This center can be either activated, to void the bladder, or suppressed to inhibit micturition. Figure 4.9.9 shows the effects of nervous activity that promotes micturition. To promote micturition, the micturition center inhibits sympathetic output to remove inhibition of detrusor contraction and contraction of the internal sphincter. Simultaneously, it strengthens the spinal stretch reflex and inhibits somatic motor neuron contraction of the external sphincter. All of these actions result in contraction of the detrusor muscle and relaxation of the sphincters.

The control of defecation follows the same basic principles as the control of micturition.

Clinical Applications: Nerve Gases

Nerve gases bind to and inhibit acetylcholinesterase. As a result, all cholinergic synapses are chronically stimulated because the neurotransmitter, acetylcholine, is not properly hydrolyzed following excitation. The resulting symptoms depend somewhat on the dose of poison. All cholinergic parasympathetic effects are activated: salivation, lacrimation, urination, defecation, emesis, (SLUDE), bronchial secretion, bronchioconstriction, and bradycardia. Other cholinergic synapses are also activated, producing sweating, muscle spasm, and effective paralysis. The agents affect both the respiratory center and the respiratory muscles so that death typically occurs by suffocation. At high doses, victims may lose consciousness and convulse, and death may occur so quickly that the parasympathetic effects may not have time to develop. Thus, these nerve gases kill by jamming the off switch to cholinergic neurotransmission.

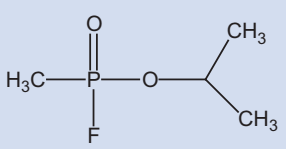
The most important nerve gases are **Sarin** and **VX**, whose chemical structures are shown below. Sarin was first produced by the Germans in 1938 and named for the four scientists who discovered it: **S**chrader, **A**mbros, **R**udinger, and L**in**de. By the end of the war the German military had 30 tons of it. Allied military planners assumed the gas would be used, and Britain had stockpiled 30 million gas masks in preparation for the event. Fortunately, Germany never used Sarin during World War II, probably in fear of like retaliation and because its dispersal is not easily controlled. Its only known use was by the Japanese cult Aum Shinrikyo, who dropped plastic bags wrapped in newspaper on five separate subway trains in Tokyo on March 20, 1995. The bags were punctured by sharpened umbrella tips in a coordinated attack. The liquid leaked out and vaporized, poisoning several thousand commuters and killing 12.

British chemists made VX in 1952 at the Porton Down Weapons Research Center in Wiltshire. They traded information about its methods to the United States in return for secrets on thermonuclear weapons. This nasty chemical has the advantage of being stable and so can contaminate areas for longer times. The British abandoned nerve agents in favor of thermonuclear weapons. The LD_{50} (the dose that kills 50% of those exposed) for VX is 10 mg.

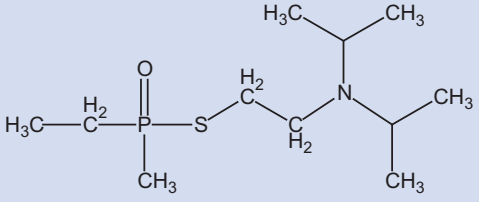
The term "nerve gas" is something of a misnomer because the agents are liquids at ambient temperatures and pressures. However, they can be dispersed as gas or aerosols, and the liquid form is readily absorbed through the skin.

One antidote for these nerve agents is **atropine**. This does not reverse the effect of the agents, but blocks the effects of excess acetylcholine neurotransmitters. The dose is about 1 mg. A second agent, pralidoxime chloride, is part of the Mark I Kit issued to the U.S. military and contains 600 mg. Pralidoxime rescues the acetylcholinesterase from nerve agent inhibition.

Who has nerve agents, in what quantities, and with what delivery capabilities, is a question for Intelligence Agencies. The United States and Russia have admitted to having stockpiles of VX, and both are committed to destroying them. Although there is no proof, some claim that Iraq used nerve agents in attacks on the Kurds in Halabja in Northern Iraq in 1988.



Sarin



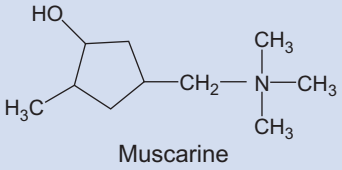
VX

Clinical Applications: Muscarine Poisoning

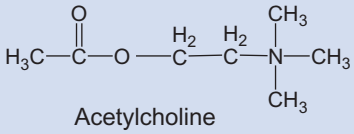
Eating mushrooms can be a tricky business because some are poisonous. The mushroom *Amanita muscaris* makes an alkaloid poison called **muscarine**, whose structure is shown below. Note that it has some structural similarities to acetylcholine, shown next to it. Because of its structural similarity to acetylcholine, muscarine can bind to the acetylcholine receptor and activate it. Thus, muscarine is a cholinergic **agonist**. Muscarine acts on the muscarinic receptors, but not on the nicotinic receptors. The chemical structure of nicotine is shown for comparison. However, muscarine does not have the acetyl ester group that is hydrolyzed by acetylcholinesterase, so its stimulation cannot be shut off by hydrolysis. Instead, muscarine is slowly cleared from the body by urinary excretion.

Muscarine poisoning causes a chronic stimulation of the muscarinic receptors. These are largely on target cells of parasympathetic stimulation. Their effects include stimulation of glandular secretions including tearing, salivation, sweating, and nasal and bronchial secretions. Smooth muscle of the intestinal tract is stimulated, causing both defecation and emesis. The urinary bladder contracts and the sphincter relaxes, causing urination. Constriction of the bronchioles makes it difficult to breathe, and the heart rate slows (bradycardia). It is altogether a nasty business.

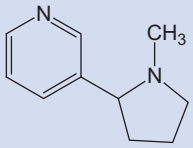
Fortunately, there is help. Another plant, the deadly nightshade, *Atropa belladona*, produces another poison called **atropine**, whose chemical structure is shown above. This chemical is a **muscarinic receptor antagonist**, and it blocks the effects of muscarine. One effect of parasympathetic stimulation is constriction of the pupillary sphincter muscle, which constricts the pupil. Ordinarily, this occurs in response to bright light to limit the light intensity on the retina. Blocking this effect with atropine therefore dilates the pupils. Ladies in Europe discovered this effect and administered it to themselves to appear more attractive. Hence the plant was named "belladona," meaning "beautiful lady." Although atropine can block the effects of muscarine, it is a poison in its own right.



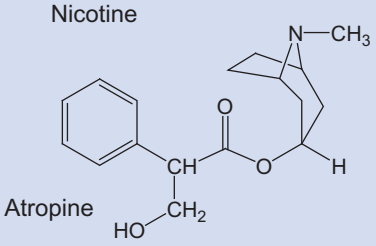
Muscarine



Acetylcholine



Nicotine



Atropine

SUMMARY

The sympathetic nervous system consists of nuclei in the brain stem that connect to preganglionic neurons in the interomedial gray in the spinal cord. The preganglionic fibers exiting the cord through the ventral root reach the paravertebral ganglia over the white rami communicans. The paravertebral ganglia form a sympathetic chain on each side of the cord. Preganglionic fibers synapse with neurons in the paravertebral ganglion at the same level of the cord, ascend the chain to make synapses above, descend the chain to make synapses below, or travel through the ganglion to prevertebral ganglia: the celiac ganglion, superior mesenteric ganglion, the inferior mesenteric ganglion, or the adrenal gland. The cervical part of the sympathetic chain form the inferior, middle, and superior cervical ganglia. Sympathetic preganglionic fibers originate in T1–L2 and are relatively short. The postganglionic fibers are long. The preganglionic synapse uses acetylcholine and the postganglionic synapse uses norepinephrine, but sympathetic postganglionic fibers use acetylcholine on sweat glands. The sympathetic nervous system prepares the body for action. It increases heart rate and cardiac contractility, dilates bronchioles, redistributes blood flow to the muscles, inhibits gastrointestinal motility and secretion, and mobilizes metabolic fuels.

The targets of sympathetic stimulation respond through two major classes of surface receptors: the α- and β-receptors. The α_1-receptors act through a G_q mechanism which raises intracellular $[Ca^{2+}]$ by IP3-induced release of Ca^{2+} stores; the α_2-receptors act through G_i which inhibits adenylyl cyclase and reduces phosphorylation of target proteins within the cell. Both β_1- and β_2-receptors activate a G_s that stimulates adenylyl cyclase and increases phosphorylation of target proteins. Activation of β-receptors on smooth muscle relaxes them; activation of α_1-receptors causes constriction.

The parasympathetic nervous system originates in the cranium and sacral cord, has long preganglionic fibers and short postganglionic ones, and uses acetylcholine at both preganglionic and postganglionic synapses.

It diverges less than the sympathetic nervous system. It constricts the pupil and controls accommodation through the oculomotor nerve, cranial nerve III. Parasympathetic innervation also controls lacrimation (cranial nerve VII) and salivation (cranial nerve VII and IX). The heart, lungs, and intestines are all controlled through the vagus nerve, cranial nerve X. The shutting off of the parasympathetic stimulation requires destruction of acetylcholine by acetylcholinesterase. Inhibition of acetylcholinesterase by nerve gas causes SLUDE: salivation, lacrimation, urination, defecation, and emesis. Other effects include bradycardia, bronchoconstriction, and bronchial secretion.

The receptors at the preganglionic parasympathetic synapse are nicotinic; those at the postganglionic synapse are muscarinic. The muscarinic receptor subtypes M1, M3, and M5 use a G_q mechanism (activation of phospholipase C, releasing IP3 and diacylglycerol (DAG); IP3 releases intracellular stores of Ca^{2+} while DAG activates PKC); M2 and M4 receptors use a G_i mechanism, but M2 receptors also modulate a K^+ channel through the $\beta\gamma$ subunit of the G protein.

The pupillary light reflex involves special retinal cells that sense light but do not contribute to image formation. These intrinsically photosensitive retinal ganglion cells use a different chromophore, melanopsin, to detect light. Their output is to the pretectal nucleus, which then connects to cells in the Edinger–Westphal nucleus in the medulla. These cells then project to a fourth neuron in the ciliary ganglion, which in turn innervates the sphincter muscle in the iris that constricts the pupil.

REVIEW QUESTIONS

1. In general, what does the sympathetic nervous system do? What does the parasympathetic nervous system do?
2. Where are the preganglionic sympathetic neurons? Where do their axons go? Are these myelinated? Where are the ganglionic sympathetic neurons? What is a paravertebral ganglion? What is meant by "sympathetic chain"? Where do the postganglionic fibers go? Are they myelinated? What is the white rami communicans? Why is it white? What is the gray rami communicans? Why is it gray?
3. Are sympathetic preganglionic fibers long or short? Are sympathetic postganglionic fibers long or short?
4. What neurotransmitters are used at the preganglionic sympathetic nerve terminal? Postganglionic? What is the exception to this generality?
5. What effect does sympathetic stimulation have on sweating? Blood vessel caliber? Bronchiole caliber? Heart rate?
6. Name the two major classes of adrenergic receptors. What signaling mechanisms do they use?
7. What are prevertebral ganglia? Name three. What does the adrenal medulla secrete? What stimulates its secretion?
8. Where are the preganglionic parasympathetic neurons? Where are the ganglionic neurons? Are the preganglionic fibers long or short? Are the postganglionic fibers long or short?
9. What neurotransmitters are used at the preganglionic parasympathetic nerve terminal? Postganglionic? What types of receptors are present at the two locations?
10. What effect does parasympathetic stimulation have on sweating? Blood vessel caliber? Bronchiole caliber? Intestinal motility? Lacrimation? What is SLUDE?