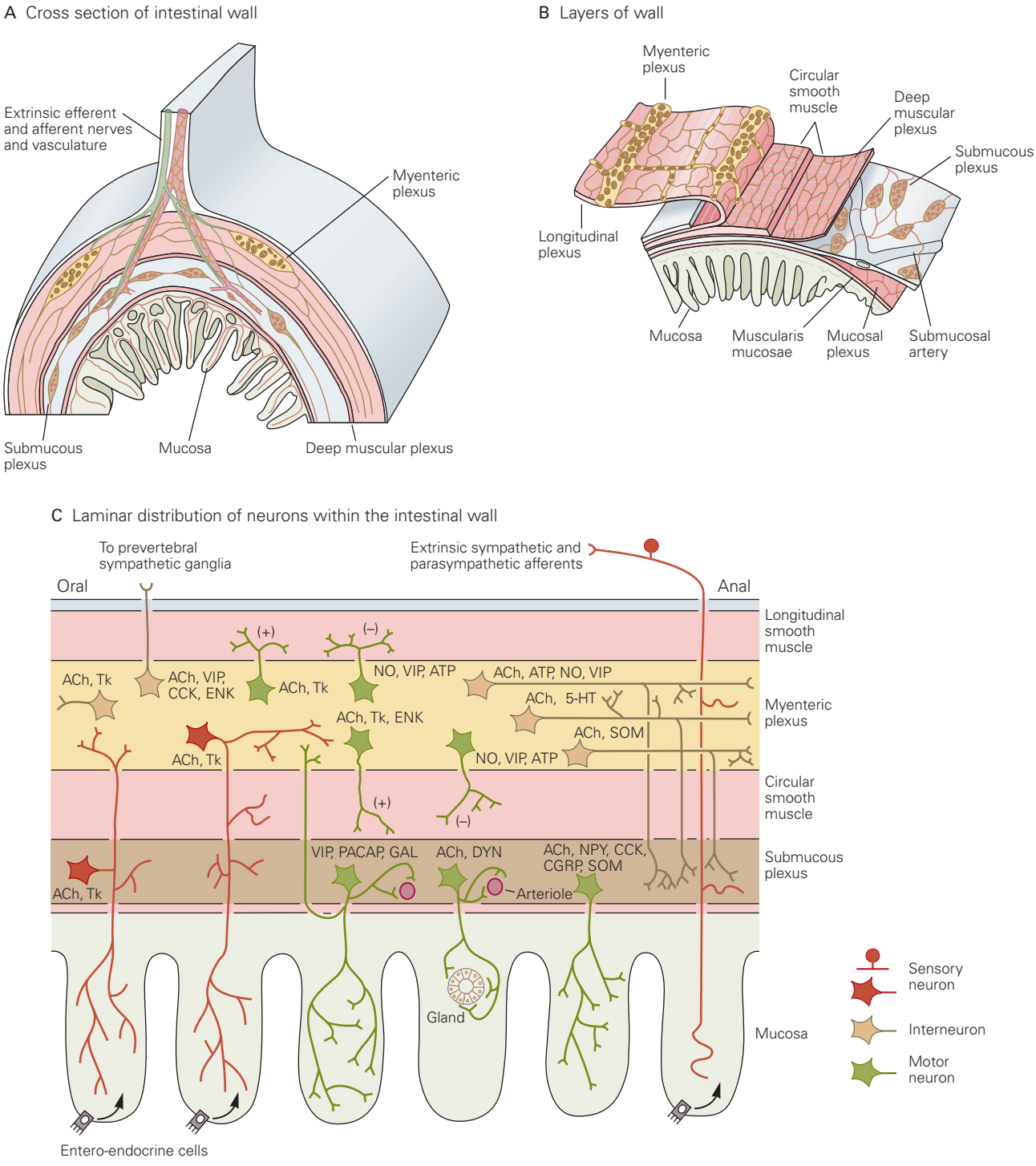

Figure 41–6 Organization of the enteric plexuses in the guinea pig. The myenteric plexus and submucous plexus lie between the layers of intestinal wall (**A** and **B**). At least 14 types of neurons have been identified within the enteric system based on morphology, chemical coding, and functional properties (**C**). Four sets of motor neurons provide excitatory (+) and inhibitory (–) inputs to two smooth muscle layers. Three additional groups of motor neurons control secretions from the mucosa and produce vasodilation. The network also includes two major classes of intrinsic sensory neurons. (Abbreviations: **ACh**, acetylcholine; **ATP**, adenosine triphosphate; **CCK**, cholecystokinin; **CGRP**, calcitonin gene-related polypeptide; **DYN**, dynorphin; **ENK**, enkephalin; **GAL**, galanin; **NO**, nitric oxide; **NPY**, neuropeptide Y; **PACAP**, pituitary adenylate cyclase-activating peptide; **SOM**, somatostatin; **Tk**, tachykinin; **VIP**, vasoactive intestinal peptide; **5-HT**, serotonin.) (Parts A and B adapted, with permission, from Furness and Costa 1980; part C reproduced, with permission, from Furness et al. 2004. Copyright © 2004 Elsevier Ltd.)

Table 41–2 Autonomic Neurotransmitters and Their Receptors

Transmitter	Receptor	Responses
Norepinephrine	α_1	Stimulates smooth muscle contraction in arteries, urethra, gastrointestinal tract, iris (pupillary dilation), uterine contractions during pregnancy, ejaculation; glycogenolysis in liver; glandular secretion (salivary glands, lacrimal glands).
	α_2	Presynaptic inhibition of transmitter release from sympathetic and parasympathetic nerve terminals; stimulates contraction in some arterial smooth muscle.
	β_1	Increases heart rate and strength of contraction.
	β_2	Relaxes smooth muscle in airways and gastrointestinal tract; stimulates glycogenolysis in liver.
	β_3	Stimulates lipolysis in white adipocytes and thermogenesis in brown adipocytes; inhibits bladder contraction.
Acetylcholine	Nicotinic	Fast EPSP in autonomic ganglion cells.
	Muscarinic: M_1, M_2, M_3	Glandular secretion; ocular circular muscle (pupillary constriction); ciliary muscles (focus of lens); stimulates endothelial production of NO and vasodilation; slows EPSPs in sympathetic neurons; slows heart rate; presynaptic inhibition at cholinergic nerve terminals; bladder contraction; salivary gland secretion.
Neuropeptide Y	Y_1, Y_2	Stimulates arterial contraction and potentiates responses mediated by α_1-adrenergic receptors; presynaptic inhibition of transmitter release from some postganglionic sympathetic nerve terminals.
NO	Diffuses through membranes; often acts to stimulate intracellular soluble guanylate cyclase	Vasodilation, penile erection, urethral relaxation.
Vasoactive intestinal peptide	VIPAC1, VIPAC2	Glandular secretion and dilation of blood vessels supplying glands.
ATP	P_{2X}, P_{2Y}	Fast and slow excitation of smooth muscle in bladder, vas deferens, and arteries.

ATP, adenosine triphosphate; EPSP, excitatory postsynaptic potential; NO, nitric oxide.

at the postganglionic synapse. For example, ACh and vasoactive intestinal peptide (VIP) are frequently co-released from neurons that control glandular secretion (Figure 41–7C). In salivary glands, the two transmitters act directly to evoke secretion. In addition, VIP causes dilation of the blood vessels supplying the gland. Because cotransmitters can be released in varying proportions that depend on the frequency of presynaptic firing, different patterns of activity can regulate the volume of secretions, their protein and water content, and their viscosity. This regulation operates both through a direct effect on the gland cells and through indirect effects on the glandular blood flow that provides the water contained in secretions.

Understanding the pharmacology of these receptors and the second-messenger signaling pathways they control is important in the treatment of numerous medical conditions, including hypertension, heart failure, asthma, emphysema, allergies, sexual dysfunction, and incontinence.

Autonomic Responses Involve Cooperation Between the Autonomic Divisions

To survive, animals and humans must have "fight-or-flight" responses in order to stand and fight a predator or run away and live to see another day. Walter Cannon, in addition to introducing the concept of

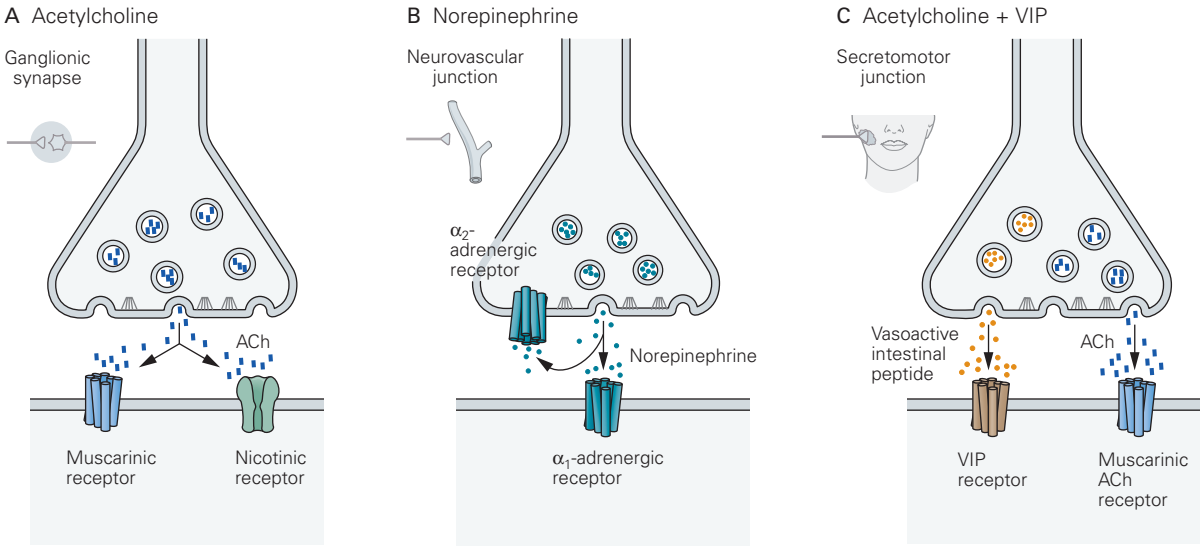

Figure 41–7 Synaptic transmission in the peripheral autonomic system.

A. In sympathetic ganglia, acetylcholine (**ACh**) can activate both nicotinic and muscarinic receptors to produce fast and slow postsynaptic potentials, respectively.

B. At neurovascular junctions, norepinephrine can simultaneously activate postsynaptic α_1-adrenergic receptors to produce vasoconstriction and presynaptic α_2-adrenergic receptors to inhibit further transmitter release.

C. Cotransmission involves the co-activation of more than one type of receptor by more than one transmitter. Parasympathetic postganglionic nerve terminals in the salivary glands release both ACh and vasoactive intestinal peptide (**VIP**) to control secretion. At some autonomic synapses with end organs, three or more receptor types are activated.

homeostasis, also appreciated that this fight-or-flight response is a critical sympathetic function.

Two important ideas underlie this insight. First, the sympathetic and parasympathetic systems play complementary, even antagonistic, roles; the sympathetic system promotes arousal, defense, and escape, whereas the parasympathetic system promotes eating and procreation. Second, actions of the sympathetic system are relatively diffuse; they influence all parts of the body and once turned on can persist for some time. These ideas are behind the popular notion of the "adrenaline rush" produced by excitement, as by a roller coaster ride.

We now know that extreme sympathetic responses such as "fight-or-flight" can have long-term pathological consequences resulting in the syndrome known as post-traumatic stress disorder (Chapter 61). This disorder was first recognized in soldiers during World War I, when it was referred to as "shell shock." A variety of life-threatening experiences, ranging from sexual abuse and domestic violence to aircraft disasters, can also induce post-traumatic stress disorder, which affects millions of people in the United States alone.

Because the fight-or-flight model assumes antagonistic roles for the sympathetic and parasympathetic systems, Cannon's model led to an overemphasis on the extremes of autonomic behavior. Actually, during everyday life, the different divisions of the autonomic system are tightly integrated. In addition, we now know that the sympathetic system is less diffusely organized than first envisioned by Cannon. Even within the sympathetic division, subsets of neurons control specific targets, and these pathways can be activated independently.

As in the somatic motor system, reflexes in the autonomic motor system are elicited through sensory pathways and are hierarchically organized. An important feature of this organization is that it allows for coordination between the different divisions of the autonomic system. The interplay between different systems in simple autonomic behaviors is analogous to the role of antagonist muscles in locomotion. To walk, one must alternately contract antagonist muscles that flex and extend a joint. Similarly, the sympathetic and parasympathetic systems are often partners in the regulation of end organs. In most cases, ranging from the simplest reflexes to more complex behaviors, all three peripheral divisions of the autonomic system work together. We illustrate this organization with two examples: control of the bladder (micturition reflex) and regulation of blood pressure.

Bladder Control

The micturition reflex is an example of a physiological cycle resulting from coordination between sympathetic and parasympathetic systems. In this cycle, the bladder is emptied by the parasympathetic pathway, which contracts the bladder and relaxes the urethra. The sympathetic system allows the bladder to fill by stimulating the urethra and inhibiting the parasympathetic pathway, thus inhibiting the reflex for bladder emptying. The sensory feedback required for this behavior is integrated with the motor outflow at both spinal and supraspinal levels (Figure 41–8).

Spinal components of the reflex are most influential during the storage phase of the micturition cycle, when sympathetic and somatic motor effects predominate. When the bladder is full, its distension triggers a sensory signal sufficient to activate the pontine micturition center (PMC). Descending signals from the PMC then increase parasympathetic outflow. Somatic control of the external urinary sphincter, which consists of striated muscle, contributes to both phases of the micturition cycle and is a voluntary behavior that originates through forebrain mechanisms (Figure 41–8). Patients with spinal cord injuries at the cervical or thoracic levels retain the reflex but not voluntary control of urination, because the connections between the bladder and the pons are severed.

Blood Pressure Regulation

The baroreceptor reflex is one of the simplest mechanisms for regulating blood pressure and further illustrates coordinated homeostatic control by antagonist sympathetic and parasympathetic pathways. It prevents orthostatic hypotension and fainting by compensating for rapid hydrostatic effects produced by changes in posture. When a recumbent person stands up, the sudden elevation of the head above the heart causes a transient decrease of cerebral blood pressure that is rapidly sensed by baroreceptors in the carotid sinus in the neck (Figure 41–9). Other important pressure sensors are located in the aortic arch and in the pulmonary circulation.

When neurons in the ventrolateral medulla detect the decrease in afferent baroreceptor activity produced by low blood pressure, they produce a reflexive suppression of parasympathetic activity to the heart and stimulation of sympathetic activity to the heart and vascular system. These changes in autonomic tone restore blood pressure by increasing heart rate, the strength of cardiac contractions, and the overall vascular resistance to blood flow through arterial vasoconstriction.

Under the converse condition of elevated arterial pressure, the increase in baroreceptor activity enhances parasympathetic inhibition of the heart and decreases sympathetic stimulation of cardiac function and vascular resistance. In general, the parasympathetic component of the baroreceptor reflex has a more rapid onset and is briefer than the sympathetic component. Consequently, parasympathetic activity is critical for the rapid response of baroreceptor reflexes but less important than sympathetic activity for long-term blood pressure regulation.

Visceral Sensory Information Is Relayed to the Brain Stem and Higher Brain Structures

Visceral sensory information reaches the brain mainly through two cranial nerves (IX and X), which end in caudal segments of the nucleus of the solitary tract (NTS), and through the abdominal splanchnic nerves, which end in the spinal cord (Chapter 40). The splanchnic information is transmitted to the brain through the spinothalamic tract (Chapter 4), which branches out along the way and also sends afferents to the NTS and lateral parabrachial nucleus.

The NTS relays sensory information in two different directions. First, it projects to networks in the brain stem and spinal cord that control and coordinate autonomic reflexes (as we saw for the baroreceptor reflex). In this way, visceral sensory signals relayed through the NTS regulate vagal motor control of the heart and gastrointestinal tract directly. Some neurons in the NTS project to neurons in the ventrolateral medullary reticular formation that control blood pressure by differentially regulating blood flow in particular vascular beds (Figure 41–9). Second, the NTS sends ascending projections to the forebrain, relaying visceral information to higher structures (Figure 41–10A). These higher structures, including the hypothalamus, use this information to coordinate autonomic, neuroendocrine, and behavioral responses.

Visceral sensory information is relayed from the NTS to the forebrain via direct and indirect projections (Figure 41–10A). The major indirect pathway involves the lateral parabrachial nucleus, which receives afferents from the NTS and sends efferents to higher structures, including the amygdala, hypothalamus, bed nucleus of the stria terminalis, insular cortex, and infralimbic/prelimbic cortex. The direct projections from the NTS target many of these same forebrain sites. The rostral NTS is an important part of the afferent taste pathway (Chapter 29). Information

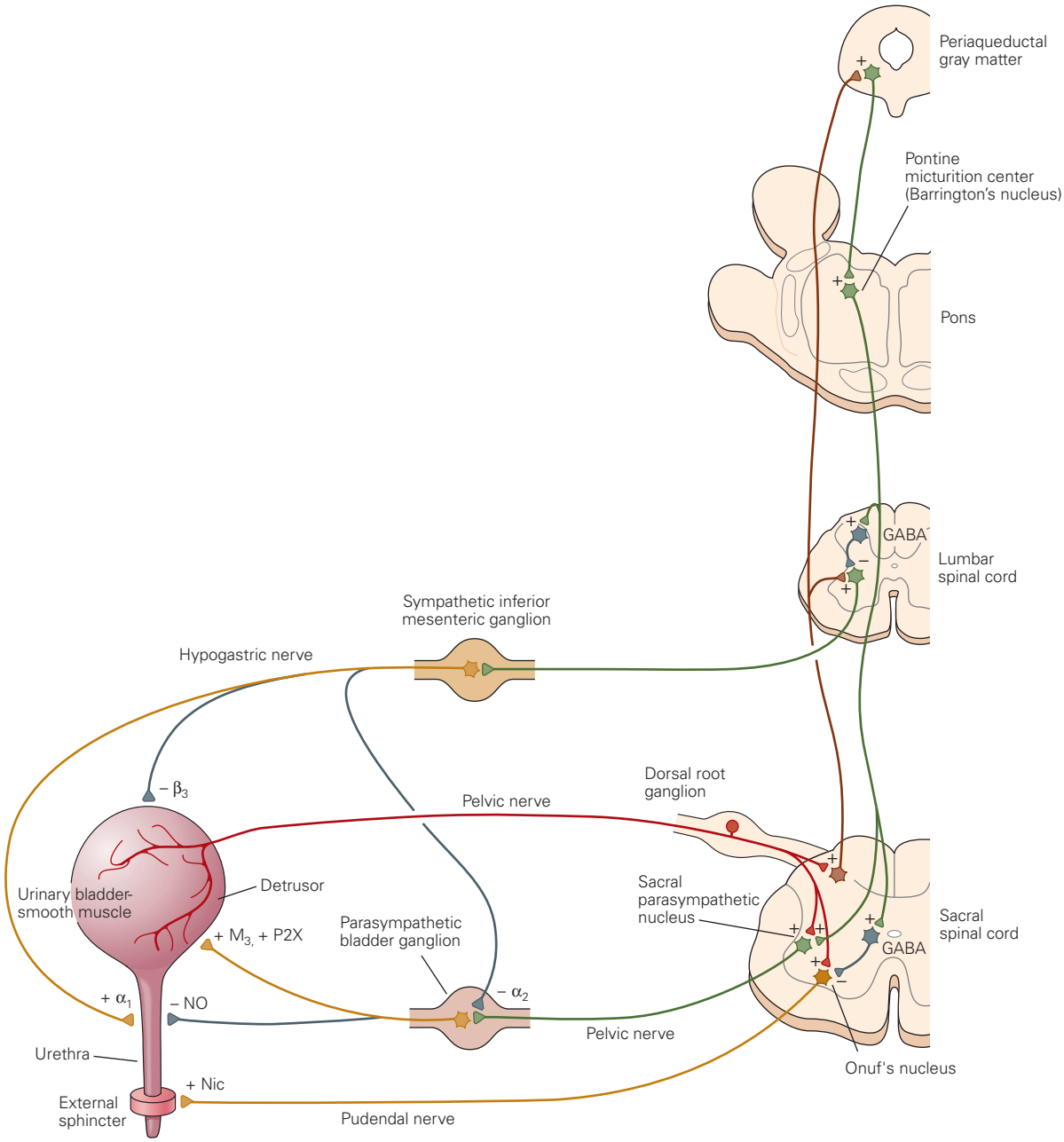

Figure 41–8 **The micturition reflex requires interplay between the parasympathetic and sympathetic divisions of the autonomic system.** (Adapted from DeGroat, Booth, and Yoshimura 1993.)

When bladder volume is low, urinary outflow is inhibited because activity in the sympathetic pathway is greater than activity in the parasympathetic pathway. Mild distension of the detrusor (storage portion of the bladder) initiates a low level of sensory activity, which reflexively activates spinal preganglionic neurons. The resulting low level of preganglionic activity is effectively transmitted and amplified by the sympathetic inferior mesenteric ganglion but filtered out by the parasympathetic bladder ganglion because of differences in patterns of synaptic convergence in the two ganglia. The resulting predominance of sympathetic tone keeps the detrusor relaxed and the urethra constricted. Sympathetic postganglionic fibers also reduce parasympathetic activity by inhibiting preganglionic release of acetylcholine. In addition to their effects on the autonomic outflow, the sensory signals are sufficient to keep the external urinary sphincter closed.

When filling causes the bladder to reach a critical volume, the associated increase in sensory activity reaches a threshold that allows impulses to pass through the pontine micturition center (Barrington's nucleus). Descending activity from this nucleus then further excites the parasympathetic outflow. The resulting increase in parasympathetic preganglionic firing promotes summation of fast excitatory postsynaptic potentials and initiation of postsynaptic action potentials in the bladder ganglion as it switches to its "on" state. During the emptying process, descending pathways also inhibit the sympathetic and somatic outflows through inhibitory spinal interneurons. Inhibition of somatic motor neurons in Onuf's nucleus causes relaxation and opening of the external sphincter. In this figure, the sacral spinal cord is enlarged relative to the other slices.

(Abbreviations: α_1, alpha-1 adrenergic receptor, α_2, alpha-2 adrenergic receptor, β_3, beta-3 adrenergic receptor, **GABA**, γ-aminobutyric acid; M_3, muscarinic ACh receptor 3; **nic**, nicotinic receptor; **NO**, nitric oxide; **P2X**, purinergic receptor.)

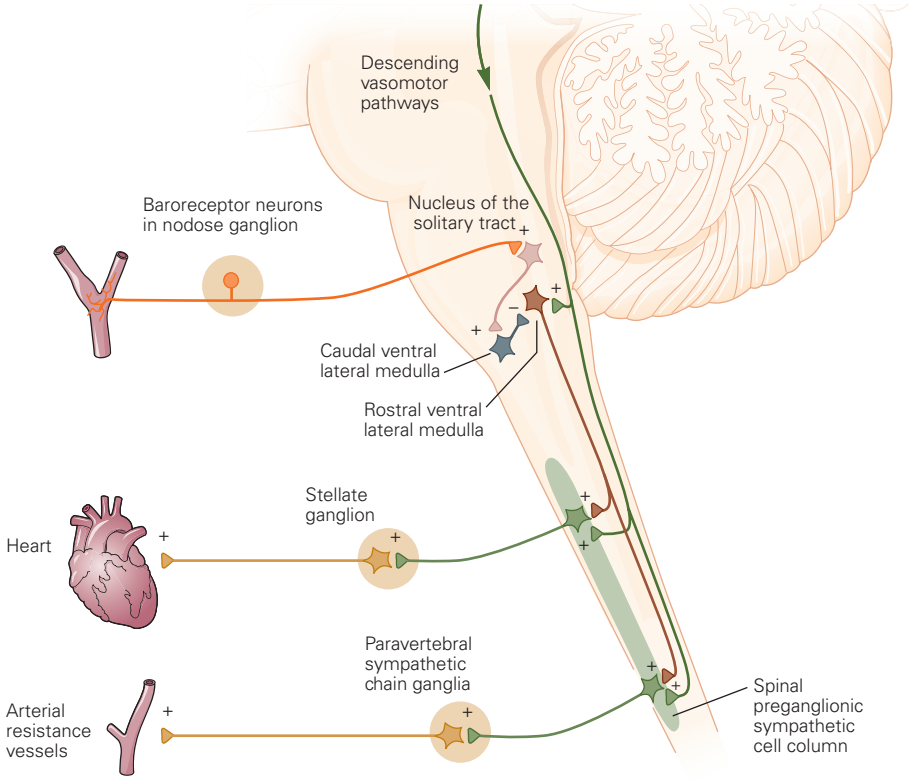

Figure 41–9 The baroreceptor reflex behaves as a negative feedback loop with gain. Arterial blood pressure is sensed by baroreceptors, a type of stretch receptor neuron, in the carotid sinus near the base of the brain. After integration in the medulla, this information provides negative feedback control of the cardiovascular system. The sympathetic component of the circuit includes outputs that stimulate the heart's pumping capacity (cardiac output) by increasing heart rate and the strength of contractions. In addition, sympathetic stimulation causes arteries to contract, which raises the hydraulic resistance to blood flow. Together, the effects of increased cardiac output and increased vascular resistance raise mean arterial blood pressure. Inhibitory projections from the caudal to the rostral ventral lateral medulla create negative feedback so that an increase in blood pressure inhibits sympathetic activity, whereas a decrease raises sympathetic activity. Although omitted for simplicity, parasympathetic neurons in the cardiac ganglion also contribute to the reflex by creating an inhibitory cardiac input that is functionally antagonistic to the sympathetic pathway (Figure 41–10). During baroreceptor reflexes, parasympathetic activity within the heart is therefore increased by hypertension and reduced by hypotension.

in this pathway is relayed via the medial parabrachial nucleus to the taste area of insular cortex.

Central Control of Autonomic Function Can Involve the Periaqueductal Gray, Medial Prefrontal Cortex, and Amygdala

The periaqueductal gray, which surrounds the cerebral aqueduct in the midbrain, receives inputs from most parts of the central autonomic network and projects to the medullary reticular formation to initiate integrated behavioral and autonomic responses. For example, in the defensive "fight-or-flight" response, the periaqueductal gray helps redirect blood flow from the digestive system to the hind limbs, thus enhancing running (Figure 41–10B).

The medial prefrontal cerebral cortex is a visceral sensory-motor region. It includes two functional areas that interact with each other: the rostral insular cortex and the rostromedial tip of the cingulate gyrus (also referred to as the infralimbic and prelimbic areas). Stimulation here can produce a variety of autonomic effects including contractions of the stomach and changes in blood pressure. These visceral sensory and motor areas of cortex send descending projections to the parts of the central autonomic network in the brain stem discussed above.

Finally, visceral regions of cortex, along with many subcortical parts of the central autonomic

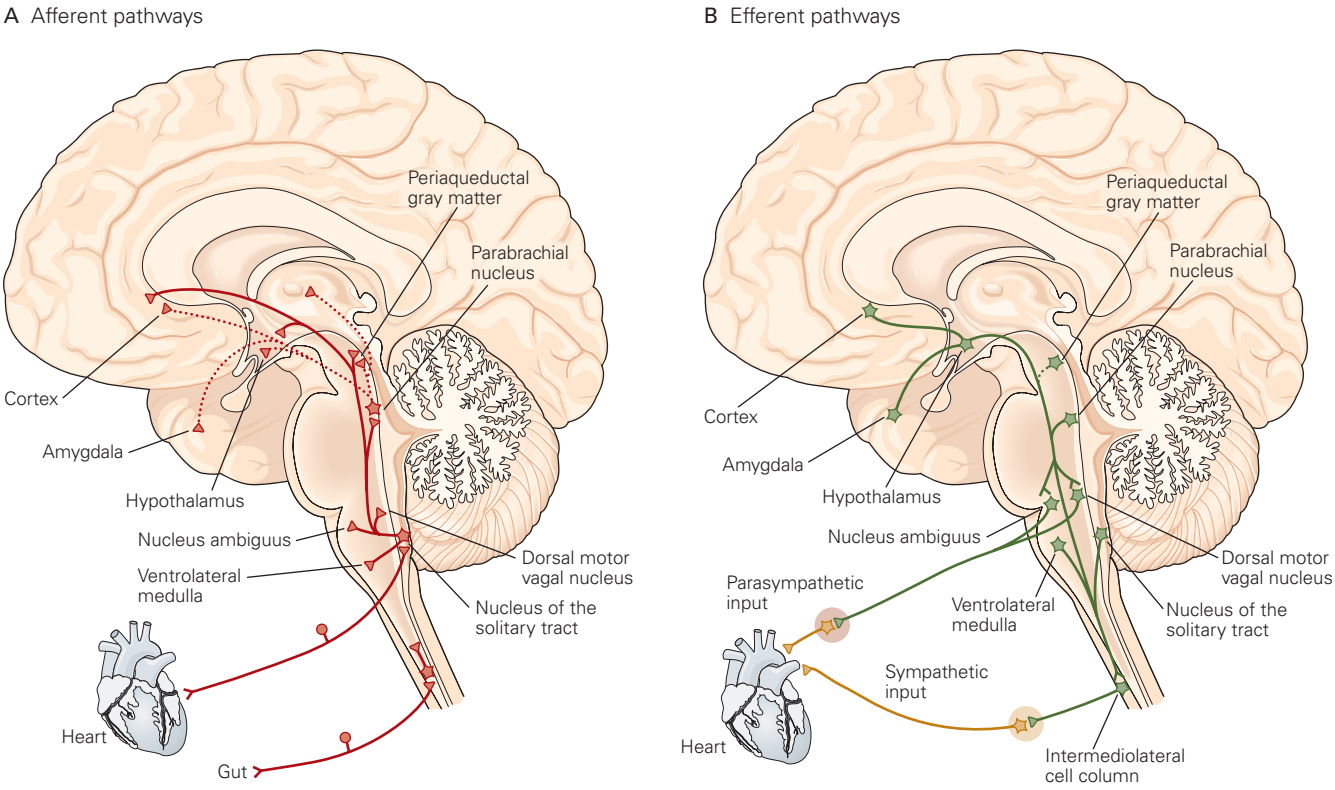

Figure 41–10 **The central autonomic network.** Nearly all of the cell groups illustrated here are interconnected with one another, forming the central autonomic network.

A. Visceral information (**solid lines**) is distributed to the brain from the nucleus of the solitary tract and from ascending spinal pathways activated by the splanchnic nerves (from the gut, for example). The nucleus of the solitary tract distributes this information to preganglionic parasympathetic neurons (the dorsal motor vagal nucleus and nucleus ambiguus), to regions of the ventrolateral medulla that coordinate autonomic and respiratory reflexes, and to more rostral parts of the central autonomic network in the pons (parabrachial nucleus), midbrain (periaqueductal gray), and forebrain. The parabrachial nucleus also projects to many of the more rostral components of the central autonomic network, including visceral and gustatory nuclei of the thalamus (**dotted lines**). Other pathways from the spinal cord (not shown) also transmit visceral information to many parts of the central autonomic network, including the nucleus of the solitary tract, parabrachial nucleus, periaqueductal gray, hypothalamus, amygdala, and cortex. The spinal cord also projects to the main somatosensory nucleus of the thalamus (ventral posterolateral nucleus).

B. All of the efferent pathways shown here (except perhaps for the periaqueductal gray) project directly to autonomic preganglionic neurons. In the hypothalamus, the descending division of the paraventricular nucleus and three cell clusters in the lateral zone project heavily to both parasympathetic and sympathetic preganglionic neurons. Other pathways (not shown) arise from certain monoaminergic cell groups in the brain stem, including noradrenergic neurons in the A5 region and serotonergic neurons in the raphe nuclei.

network, interact with the amygdala. Complex pathways between certain amygdalar cell groups underlie certain conditioned emotional responses—learned associations between specific stimuli and behaviors with accompanying autonomic responses. When a rat learns that a mild electric shock follows an auditory cue, the auditory cue alone comes to produce the elevated heart rate and freezing that was originally elicited by the shock alone (Chapters 42 and 53). Such learned responses are prevented by selective lesions of the amygdalar region, which projects to the hypothalamus and lower brain stem parts of the central autonomic network.

The Neuroendocrine System Links the Brain to Physiological Responses Through Hormones

Another effector arm of the hypothalamus is the neuroendocrine system, which controls secretion of hormones by the pituitary gland. The pituitary has two functionally and anatomically distinct subdivisions,

the anterior and posterior pituitary. The posterior pituitary is an extension of the brain and contains hormone-secreting axon terminals of hypothalamic neurons. These terminals secrete vasopressin or oxytocin directly into the systemic circulation. The anterior pituitary, on the other hand, is entirely nonneuronal and is composed of five types of endocrine cells. Hormone secretion from these cells is controlled by stimulatory and inhibitory factors released by hypothalamic neurons into a specialized circulatory system that carries blood from the base of the brain (median eminence) to the anterior pituitary.

Hypothalamic Axon Terminals in the Posterior Pituitary Release Oxytocin and Vasopressin Directly Into the Blood

Large neurons in the paraventricular and supraoptic nuclei form the magnocellular component of the neuroendocrine motor system of the hypothalamus (Figure 41–11). The magnocellular neurons send their axons through the hypothalamo-hypophysial tract to the posterior pituitary, or *neurohypophysis* (Figure 41–12). Approximately one-half of these neurons synthesize and secrete vasopressin (the antidiuretic hormone) into the general circulation; the other half synthesize and secrete oxytocin, a structurally similar hormone. Both hormones circulate to organs, where vasopressin controls blood pressure and water reabsorption by the kidney and oxytocin controls uterine smooth muscle and milk release.

Vasopressin and oxytocin are nine-amino acid peptide hormones. Like other peptide hormones, they are synthesized in the cell body as larger prohormones (Chapter 16) and then cleaved within Golgi transport vesicles before traveling down the axon to release sites in the posterior pituitary. The genes for these peptides have similar sequences and probably arose by duplication.

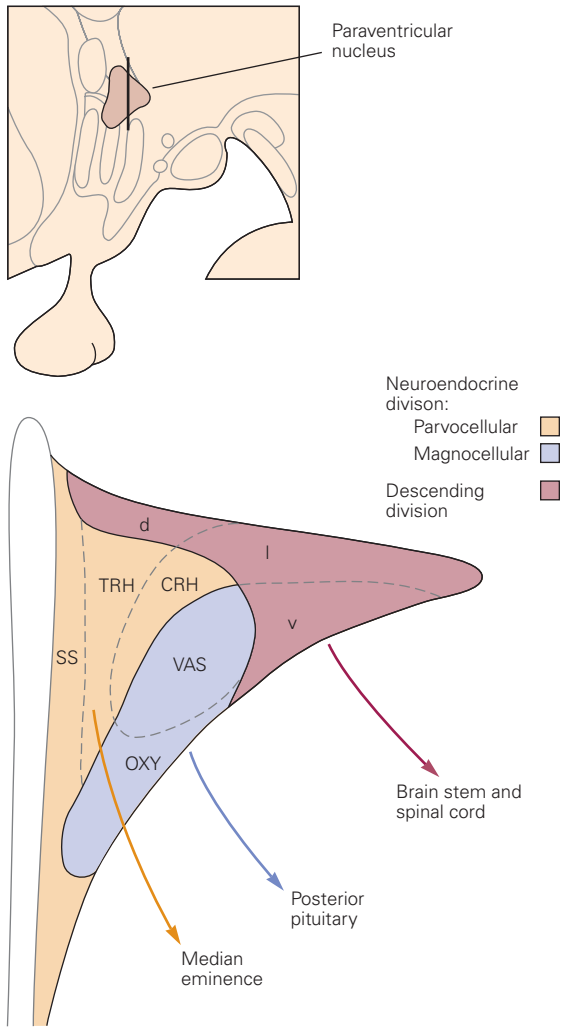

Figure 41–11 **The paraventricular nucleus in the hypothalamus is a microcosm of neuroendocrine, autonomic, and sensory-motor integration.** The three structural-functional divisions of the paraventricular nucleus are shown. The *magnocellular neuroendocrine division* comprises two distinct although partly interdigitated pools of neurons that normally release vasopressin (**VAS**) or oxytocin (**OXY**). Their axons course through the internal zone of the median eminence and terminate in the posterior pituitary. Two other populations of magnocellular vasopressin and oxytocin neurons lie in the supraoptic nucleus along the base of the brain.

The *parvocellular neuroendocrine division* includes three major, separate (although partly interdigitated) pools of neurons that control anterior pituitary hormone secretion. Their axons end in the external zone of the median eminence, where they release their peptide neurotransmitters—somatostatin (**SS**), growth hormone-inhibiting hormone (GIH), thyrotropin-releasing hormone (**TRH**), or corticotropin-releasing hormone (**CRH**)—into the hypophysial portal veins.

The *descending division* has three parts—dorsal (**d**), lateral (**l**), and ventral (**v**)—each comprising topographically organized conventional neurons that project to the brain stem and spinal cord. Their axons terminate in many parts of the central autonomic network in the brain stem (Figure 41–10), the marginal zone (lamina I) of the dorsal horn of the spinal cord and spinal trigeminal nucleus, and a number of regions in the brain stem reticular formation and periaqueductal gray matter. The descending division modulates autonomic outflow (and inflow), the inflow of nociceptive information, and eating and drinking behaviors. Appropriate integration of magnocellular neuroendocrine, parvocellular neuroendocrine, autonomic, and behavioral responses is mediated primarily by external inputs rather than by interneurons or extensive recurrent axon collaterals of projection neurons. Circulating steroid and thyroid hormones also produce selective effects on particular types of neurons in the paraventricular nucleus.

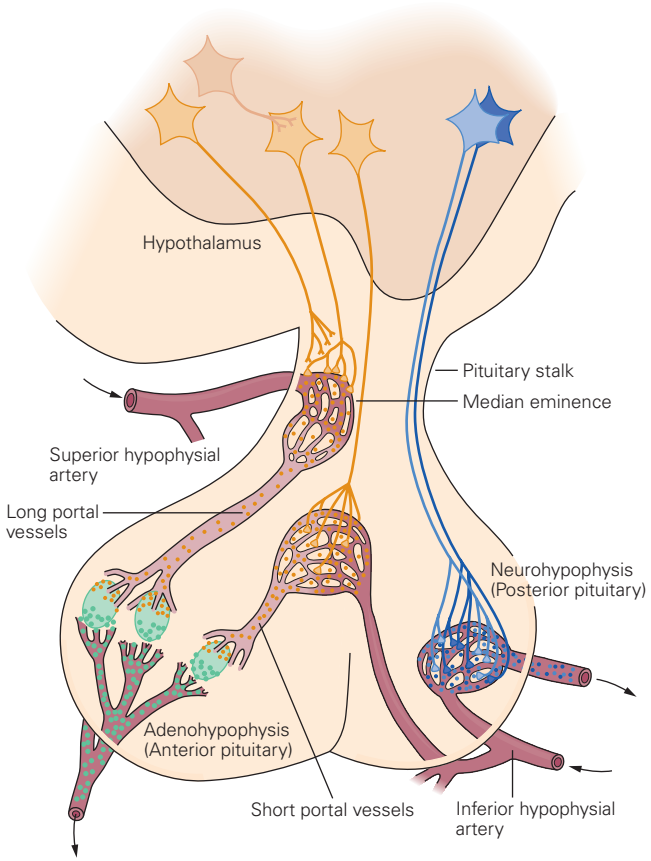

Figure 41–12 The hypothalamus controls the pituitary gland both directly and indirectly through neuroendocrine neurons. Neurons in the magnocellular neuroendocrine system (**blue**) send their axons directly to the posterior pituitary (neurohypophysis) where they release the peptides vasopressin and oxytocin into the general circulation. Neurons in the parvocellular neuroendocrine system (**yellow**) send their axons to the hypophysial portal system in the median eminence and pituitary stalk. Portal veins transport hypothalamic hormones (peptides and dopamine) to the anterior pituitary (adenohypophysis) where they increase the release of hormones from five classic types of endocrine cells (Figure 41–11). The output of neuroendocrine neurons is regulated in large part by inputs from other regions of the brain. (Adapted from Reichlin 1978, and Gay 1972.)

Endocrine Cells in the Anterior Pituitary Secrete Hormones in Response to Specific Factors Released by Hypothalamic Neurons

In the 1950s, Geoffrey Harris proposed that the anterior pituitary, or *adenohypophysis*, is regulated indirectly by the hypothalamus. He showed that the hypophysial portal veins, which carry blood from the hypothalamic median eminence to the anterior pituitary, transport factors released from hypothalamic neurons that control anterior pituitary hormone secretion (Figure 41–12). In the 1970s, Andrew Schally, Roger Guillemin, and Wylie Vale determined the structure of a group of hypothalamic peptide hormones that control pituitary hormone secretion from the five classic endocrine cell types in the anterior pituitary. These hormones, which are released into the median eminence by hypothalamic neurons, fall into two classes: releasing hormones and release-inhibiting hormones. Only one anterior pituitary hormone, prolactin, is under predominantly inhibitory control (mediated by dopamine).

The *parvocellular neuroendocrine motor zone* of the hypothalamus is centered along the wall of the third ventricle (Figure 41–2A) and contains neurons that project to and release their hormones into the median eminence. The parvocellular neurons releasing *gonadotropin-releasing hormone* (GnRH) are atypical in that they are scattered in a continuum extending from the medial septum through to the mediobasal hypothalamus. They are controlled by upstream neurons that release *kisspeptin*. The remaining parvocellular neuroendocrine neurons lie within the paraventricular and arcuate nuclei and the short periventricular region between them (Figures 41–2 and 41–11).

Distinct pools of neurons in and around the paraventricular nucleus release *corticotropin-releasing hormone* (CRH), *thyrotropin-releasing hormone* (TRH), or *somatostatin* (or growth hormone release-inhibiting hormone) (Figure 41–11). The CRH neurons control the release of anterior pituitary adrenocorticotropic hormone (ACTH), which in turn controls the release of cortisol (glucocorticoids) from the adrenal cortex. Thus, this pool of CRH neurons is the "final common pathway" for all centrally mediated glucocorticoid stress hormonal responses. The arcuate nucleus contains two pools of parvocellular neuroendocrine neurons. One group releases *growth hormone–releasing hormone* (GHRH) and the other dopamine, which inhibits prolactin secretion. Some of the dopaminergic neurons are distributed dorsally as far as the paraventricular nucleus.

The axons of all these parvocellular neuroendocrine neurons travel in the hypothalamo-hypophysial tract and end in the specialized proximal end of the pituitary stalk, the median eminence (Figure 41–12). There, in a region of capillary loops in the external zone of the median eminence, the axon terminals release the various hypophysiotropic factors. While the median eminence is within the brain, it is considered outside the blood–brain barrier. This is due to the fenestrated nature of the median eminence