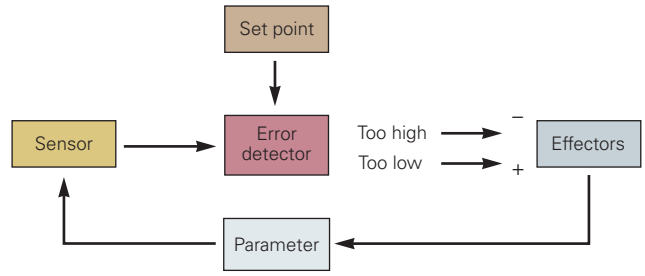
physiological "set points" help control key parameters like body temperature, blood osmolarity, blood pressure, and body fat content.

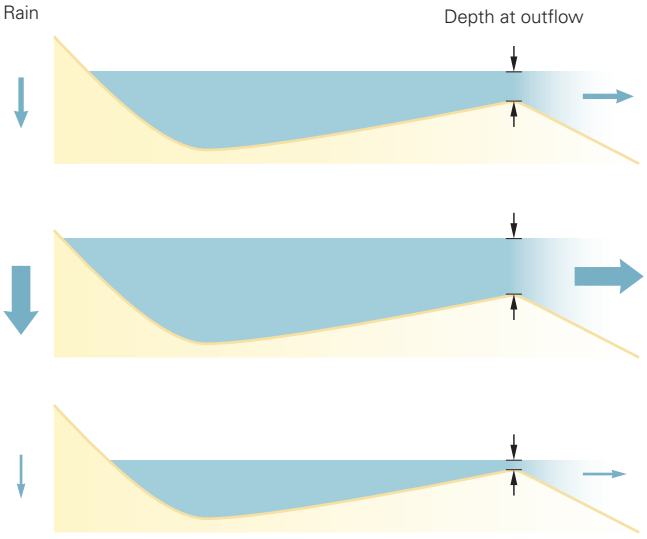
Set point models are appealing because thermostats are so effective in maintaining room temperature at a targeted set point and, by analogy, physiological variables like body temperature are likewise tightly controlled. In such models, a "set point" exists for a parameter, 37°C in the case of body temperature, and at any given moment, the real level of the parameter is assessed and compared with the targeted set point through feedback and error detection (Figure 41–1A). Any deviation above or below triggers counteracting corrective responses—if too hot, cutaneous vasodilatation, sweating, and a dip in the pool; if too cold, vasoconstriction, thermogenesis, shivering, and the donning of a sweater. For regulation of body temperature, the set point and detection of error were historically seen as emergent properties of neurons in the preoptic area of the hypothalamus (POA).

Over time, the set point model required revision because intensive investigation failed to uncover any molecular or neuronal bases for encoding set points and performing error detection. In addition, "set point–like" regulation can, in principle, be achieved without a set point, feedback, or error detection—the so-called "settling point" model (Figure 41–1B). Consider the changing level of a lake. When rainfall is excessive, its level rises; the rivers draining the lake rise and their flow increases. The converse is true when rainfall is low. The changing flow of the rivers draining the lake thus maintains its level near a settling point without requiring an idealized set point, feedback, or error detection. While aspects of the settling point model have appeal, it too is incomplete because homeostatic processes clearly receive important feedback

A Set point model



B Settling point model



C Combined model: settling point of multiple afferent/efferent loops

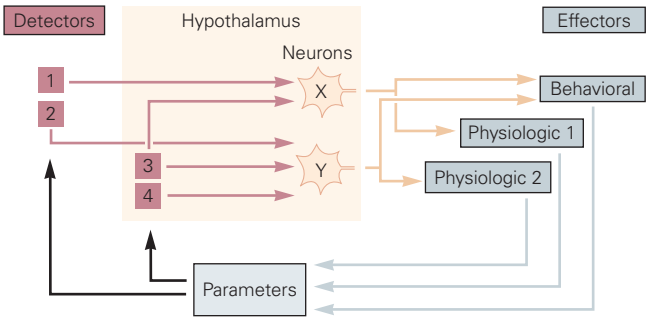


Figure 41–1 (Left) Set points, settling points, and homeostasis.

A. The set point view was inspired by engineering principles. As with a thermostat, constancy is achieved by providing feedback on the existing level of a parameter, determining how it compares to an idealized set point, and then instituting corrective measures to return the parameter to the set point. While popular for many years, it has fallen out of favor as years of research have failed to uncover molecular and neural bases for encoding set points and performing error detection.

B. The settling point model was inspired by observations that many systems achieve constancy in the absence of any feedback or error detection. In this example, the level of outflow of water from a lake is proportional to the depth of the lake. When it rains, the increase or decrease in the level of the lake causes more or less water to flow out of the lake. The level of the lake remains fairly constant without a set point or error detection. A related example is regulation of body weight. Increased food intake leads to increased body weight. As body weight increases, the energy cost of carrying and sustaining that increased weight goes up. Because of this, body weight too should have its settling point. (Reproduced, with permission, from Speakman et al. 2011.)

C. In this model the concepts of feedback in part **A** and settling point in part **B** are combined. The apparent set point is in fact the settling point, an emergent property of multiple feedback-informed afferent/efferent loops.

regarding disturbances, and this feedback produces vital responses that hasten recovery. As we shall see, temperature, osmolarity, and body fat are directly or indirectly "sensed," and this affects the activity of neurons in the hypothalamus that generate counteracting responses.

Most physiologists today have adopted a "distributed settling point" model that incorporates strong feedback control of multiple sensory/effector loops (Figure 41–1C). With body temperature, for example, there is no single specific set point and no location in the brain where a single set point is encoded and error detection takes place; in short, there is no thermostat. Instead, there are multiple temperature detectors located in different sites (skin, core, and brain), and each is coupled through neuronal pathways that traverse the preoptic area on their way to different body temperature effectors (cutaneous blood vessels, sweat glands, brown fat metabolism, shivering and behavioral pathways). When engaged, each of these effectors impact body temperature. The apparent set point for body temperature is in fact the emergent settling point that results from the combined activities of the multiple feedback-informed afferent/efferent loops. As we will see later, this nuanced model also applies to regulation of blood pressure, blood osmolarity, and body fat.

The Hypothalamus Coordinates Homeostatic Regulation

The hypothalamus integrates the status of physiological parameters with outputs to behavioral, autonomic, and neuroendocrine motor systems and thereby regulates six vital physiological functions (Table 41–1). The hypothalamus lies at the base of the brain immediately above the pituitary gland (Figure 41–2). It is bounded anteriorly (rostrally) by the diagonal band of Broca; dorsally by the anterior commissure, the bed nuclei of the stria terminalis, the zona incerta, and thalamus; and posteriorly (caudally) by the ventral tegmental area and interpeduncular nucleus.

The Hypothalamus Is Commonly Divided Into Three Rostrocaudal Regions

Regions of the hypothalamus are named according to their location and appearance in Nissl-stained sections. The hypothalamus is divided, rostral to caudal, into three regions. (1) The *preoptic hypothalamus* lies above the optic chiasm and contains neurons that control water balance and thirst, temperature, sleep, sexual behavior, and circadian rhythms. (2) The *tuberal hypothalamus* lies above the pituitary and contains neurons controlling pituitary hormone secretion, autonomic outflow, and various behaviors including hunger, sexual behavior, and aggression. (3) The *posterior hypothalamus* includes the posterior and mammillary nuclei, as well as histaminergic neurons in the tuberomammillary nucleus that affect arousal. The functions of other neurons in the posterior hypothalamus areas are less well defined.

The *lateral hypothalamic area* (LHA) spans from the middle to the caudal hypothalamus. It is linked more closely to reward pathways and arousal than to maintenance of homeostasis and specific survival behaviors. Indeed, it is heavily connected with the nucleus accumbens and ventral tegmental area, two areas involved in reward (Chapter 43), and contains neurons that project extensively throughout the cortex. Lastly, LHA neurons expressing the neuropeptide orexin (hypocretin) play a critical role in stabilizing wakefulness (Chapter 44).

Table 41–1 The Hypothalamus Integrates Behavioral (Somatomotor), Autonomic, and Neuroendocrine Responses Involved in Six Vital Functions

1. *Blood pressure and electrolyte composition*. The hypothalamus regulates thirst, salt appetite, and drinking behavior; autonomic control of vasomotor tone; and the release of hormones such as vasopressin (via the paraventricular nucleus).
2. *Energy metabolism*. The hypothalamus regulates hunger and feeding behavior, the autonomic control of digestion, and the release of hormones such as glucocorticoids, growth hormone, and thyroid-stimulating hormone (via the arcuate and paraventricular nuclei).
3. *Reproductive (sexual and parental) behaviors*. The hypothalamus controls autonomic modulation of the reproductive organs and endocrine regulation of the gonads (via the medial preoptic, ventromedial, and ventral premammillary nuclei).
4. *Body temperature*. The hypothalamus influences thermoregulatory behavior (seeking a warmer or cooler environment), controls autonomic body heat conservation/loss mechanisms, and controls secretion of hormones that influence metabolic rate (via the preoptic region).
5. *Defensive behavior*. The hypothalamus regulates the stress response and fight-or-flight response to threats in the environment such as predators (via the paraventricular, anterior hypothalamic, and dorsal premammillary nuclei, and the lateral hypothalamic area).
6. *Sleep–wake cycle*. The hypothalamus regulates the sleep–wake cycle (via a circadian clock in the suprachiasmatic nucleus) and levels of arousal when awake (via the lateral hypothalamic area and tuberomammillary nucleus).

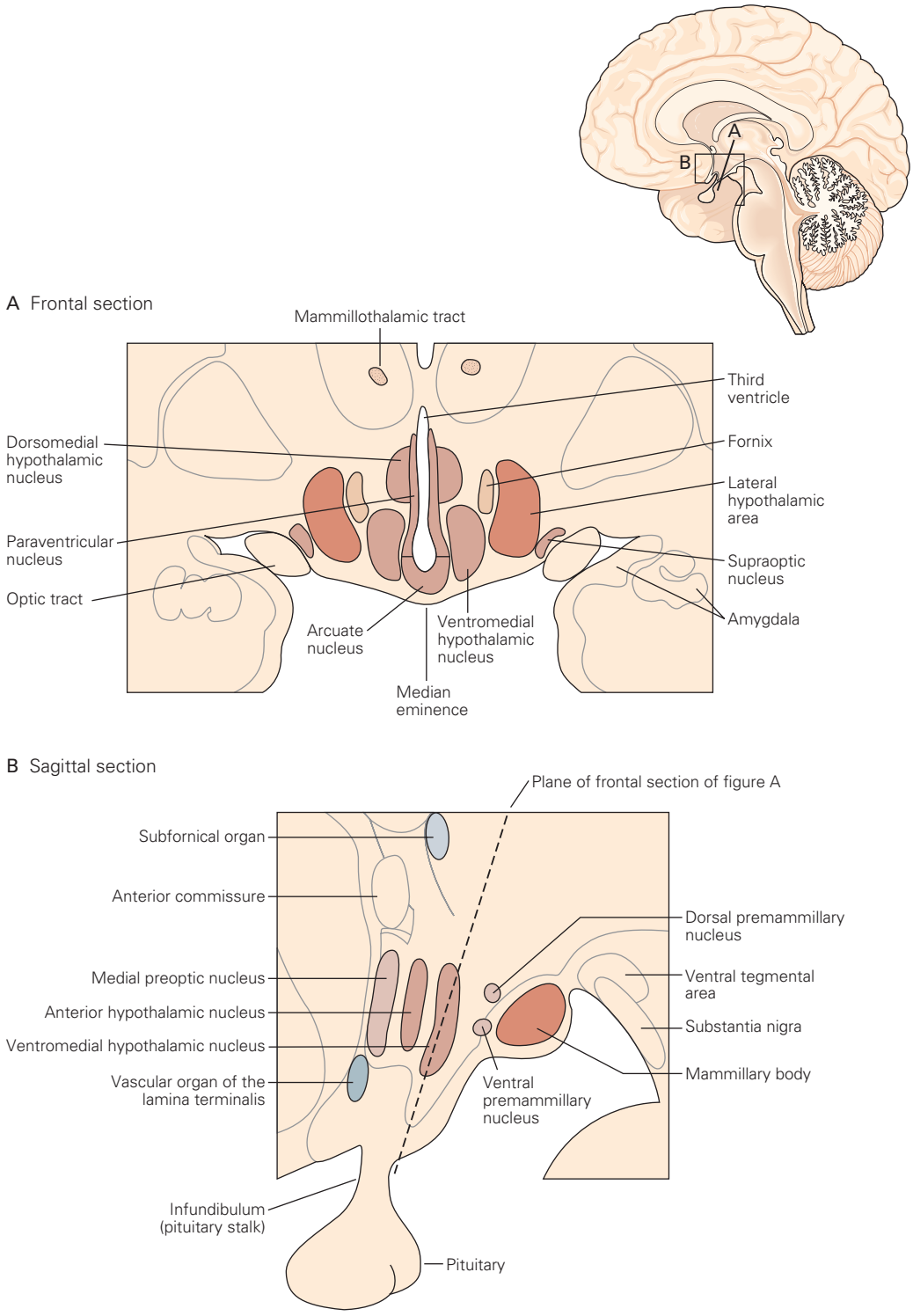


Figure 41–2 The structure of the hypothalamus.

A. Frontal view of the hypothalamus (section along plane A shown in the sagittal view of the brain, upper right). The third ventricle is in the midline; the paraventricular, dorsomedial, and arcuate nuclei adjacent to the ventricle form the neuroendocrine motor zone and periventricular region at this level. The ventromedial nucleus is part of the medial column of hypothalamic nuclei, and the lateral hypothalamic area is the lateral zone component represented in the part of the hypothalamus shown here.

B. Sagittal (rostrocaudal) view of the medial column of hypothalamic nuclei, showing the adjacent (caudal) substantia nigra and ventral tegmental area of the midbrain. The functional significance of key hypothalamic nuclei is summarized in Table 41–1.

Modality-Specific Hypothalamic Neurons Link Interoceptive Sensory Feedback With Outputs That Control Adaptive Behaviors and Physiological Responses

General principles of hypothalamic function have emerged over several decades. Neurons in the periphery and brain respond when parameters under homeostatic control are disturbed. Such neurons can respond directly to the stimulus or indirectly to changes in hormones and other factors that track the regulated parameter. This sensory information is then relayed to functionally appropriate regulatory neurons in a particular site (or sites) within the hypothalamus. Once the information is integrated by hypothalamic neurons, the results are then conveyed downstream to motor circuits that control specific behaviors and physiological responses. The result is a coordinated corrective response (eg, warmth-seeking plus heat production and retention, thirst plus water retention by the kidney, or hunger plus decreased energy expenditure).

Our understanding of the functions of hypothalamic neurons has been refined recently using optogenetic and chemogenetic techniques in active animals. By selectively activating subsets of hypothalamic neurons, one can evoke specific behaviors and physiological responses, even when the need is totally absent. Key regulatory neurons for body temperature are located in the median preoptic nucleus (MnPO). Water balance is regulated by neurons in three sites—the MnPO, the vascular organ of the lamina terminalis (OVLT), and the subfornical organ (SFO)—and energy balance by neurons in the arcuate nucleus (Figure 41–2A).

Modality-Specific Hypothalamic Neurons Also Receive Descending Feedforward Input Regarding Anticipated Homeostatic Challenges

In addition to input from sensory signals that provide important feedback regarding the status of the body, key regulatory neurons in the hypothalamus receive "top-down" feedforward inputs from neurons that anticipate future homeostatic challenges. For example, when food-deprived animals detect cues that predict the availability of food, there is a rapid drop in the firing of hunger-promoting neurons in the arcuate nucleus even before food is ingested. Such top-down feedforward control prepares the body for anticipated homeostatic challenges. In addition, such rapid regulation, by countering an aversive state represented by high activity in deficiency-driven neurons, could be important for motivating deficiency-based behaviors such as thirst and hunger (discussed below).

Next, we examine two effectors arms of the hypothalamus—the autonomic motor system and the neuroendocrine system.

The Autonomic System Links the Brain to Physiological Responses

Although the autonomic motor system implements many of the physiological responses initiated by the hypothalamus, the autonomic system is also regulated by circuits in the brain stem and spinal cord (Chapter 40). As a consequence, autonomic functions vary in their dependence on the hypothalamus. For example, micturition is largely independent of the hypothalamus, while blood pressure regulation depends heavily on circuits in the brain stem but can also be modulated by the hypothalamus. In contrast, thermogenesis by brown adipose tissue is largely subservient to the hypothalamus.

Visceral Motor Neurons in the Autonomic System Are Organized Into Ganglia

Unlike the somatic motor system, in which motor neurons are located in the ventral spinal cord and brain stem, the cell bodies of autonomic motor neurons are found in enlargements of peripheral nerves called ganglia.[1] The autonomic motor neurons innervate secretory epithelial cells in glands, smooth and cardiac muscle, and adipose tissue.

Efforts to understand the principles of organization of autonomic ganglia began in 1880 in England with the work of Walter Gaskell and were later continued by John N. Langley. They stimulated autonomic nerves and observed the responses of end organs (eg, vasoconstriction, piloerection, sweating, pupillary constriction). They used nicotine to block signals from individual ganglia to test interactions between ganglia. Langley proposed that specific chemical substances must be released by preganglionic neurons of the autonomic ganglia and that these substances act by binding to receptors on the postganglionic neurons, which target the end organs. These ideas set the stage for the later investigations of chemical synaptic transmission.

[1]The peripheral nerves also have sensory ganglia, located on the dorsal roots of the spinal cord and on five of the cranial nerves: trigeminal (V), facial (VII), vestibulocochlear (VIII), glossopharyngeal (IX), and vagus (X) (Chapter 40).

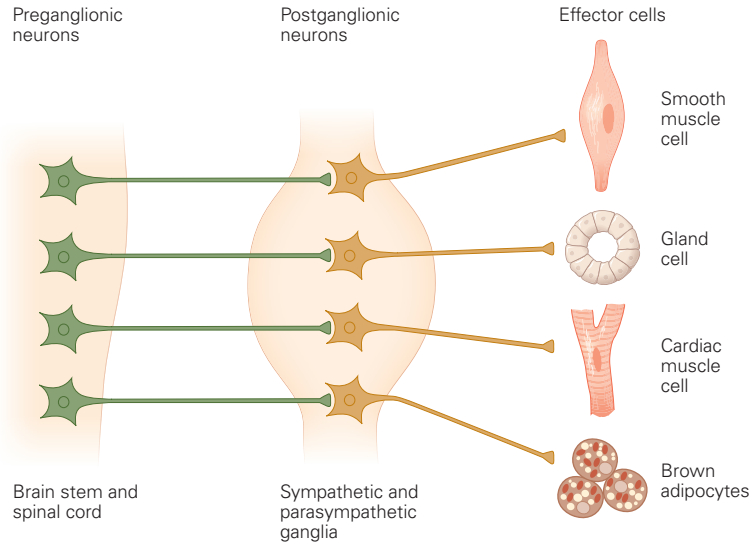


Figure 41–3 **Distinct cell types in peripheral autonomic pathways selectively control target cells with different phenotypes.** Autonomic motor neurons lie outside the central nervous system in ganglia controlled by preganglionic neurons in the spinal cord and brain stem. These downstream neurons within parasympathetic and sympathetic ganglia regulate three types of effector cells: smooth muscle, gland cells, and cardiac muscle. Additionally, downstream neurons found only in sympathetic ganglia selectively control brown adipocytes and immune cells in lymphoid tissue. This figure illustrates the three basic cell types—preganglionic neurons, downstream ganglionic neurons, and different target effector cells—that control function.

Langley also distinguished the autonomic and somatic motor systems and in so doing, created much of our current nomenclature.

The autonomic system is divided into three divisions: sympathetic, parasympathetic, and enteric. All neurons in sympathetic and parasympathetic ganglia are controlled by *preganglionic neurons* whose cell bodies are located in the spinal cord and brain stem. The preganglionic neurons synthesize and release the neurotransmitter acetylcholine (ACh), which acts on nicotinic ACh receptors on *postganglionic neurons*, producing fast excitatory postsynaptic potentials and initiating action potentials that propagate to synapses with effector cells in *end organs* (Figure 41–3). The sympathetic and parasympathetic systems are differentiated by five criteria:

1. The segmental organization of their preganglionic neurons in the spinal cord and brain stem
2. The peripheral locations of their ganglia
3. The types and locations of end organs they innervate
4. The effects they produce on end organs
5. The neurotransmitters employed by their postganglionic neurons

Preganglionic Neurons Are Localized in Three Regions Along the Brain Stem and Spinal Cord

The parasympathetic pathways arise from a cranial nerve zone in the brain stem and a second zone in sacral segments of the spinal cord (Figure 41–4). These parasympathetic zones surround a sympathetic zone that extends continuously in thoracic and lumbar segments of the cord.

The cranial parasympathetic pathways arise from preganglionic neurons in the general visceral motor nuclei of four cranial nerves: the oculomotor (N. III) in the midbrain and the facial (N. VII), glossopharyngeal (N. IX), and vagus (N. X) in the medulla. The cranial parasympathetic nuclei are described in Chapter 40 together with the mixed cranial nerves (eg, the facial, glossopharyngeal, and vagus). The spinal parasympathetic pathway originates in preganglionic neurons in sacral segments S2–S4. Their cell bodies are located in intermediate regions of the gray matter, and their axons project in peripheral nerves through the ventral roots.

The sympathetic preganglionic cell column extends between the cervical and lumbosacral enlargements of the spinal cord, corresponding to the first thoracic segment and third lumbar segment (Figure 41–4). Most of the cell bodies of sympathetic preganglionic neurons are located in the intermediolateral cell column; others are found in the central autonomic area surrounding the central canal and in a band connecting the central area with the intermediolateral cell column. The axons of preganglionic sympathetic neurons project from the spinal cord through the nearest ventral root and then run with small connecting nerves known as rami communicantes before terminating on postganglionic cells in the paravertebral sympathetic chain (Figure 41–5).

Sympathetic Ganglia Project to Many Targets Throughout the Body

The sympathetic motor system regulates systemic physiological parameters such as blood pressure and body temperature by influencing target cells within virtually every tissue throughout the body (Figure 41–4).

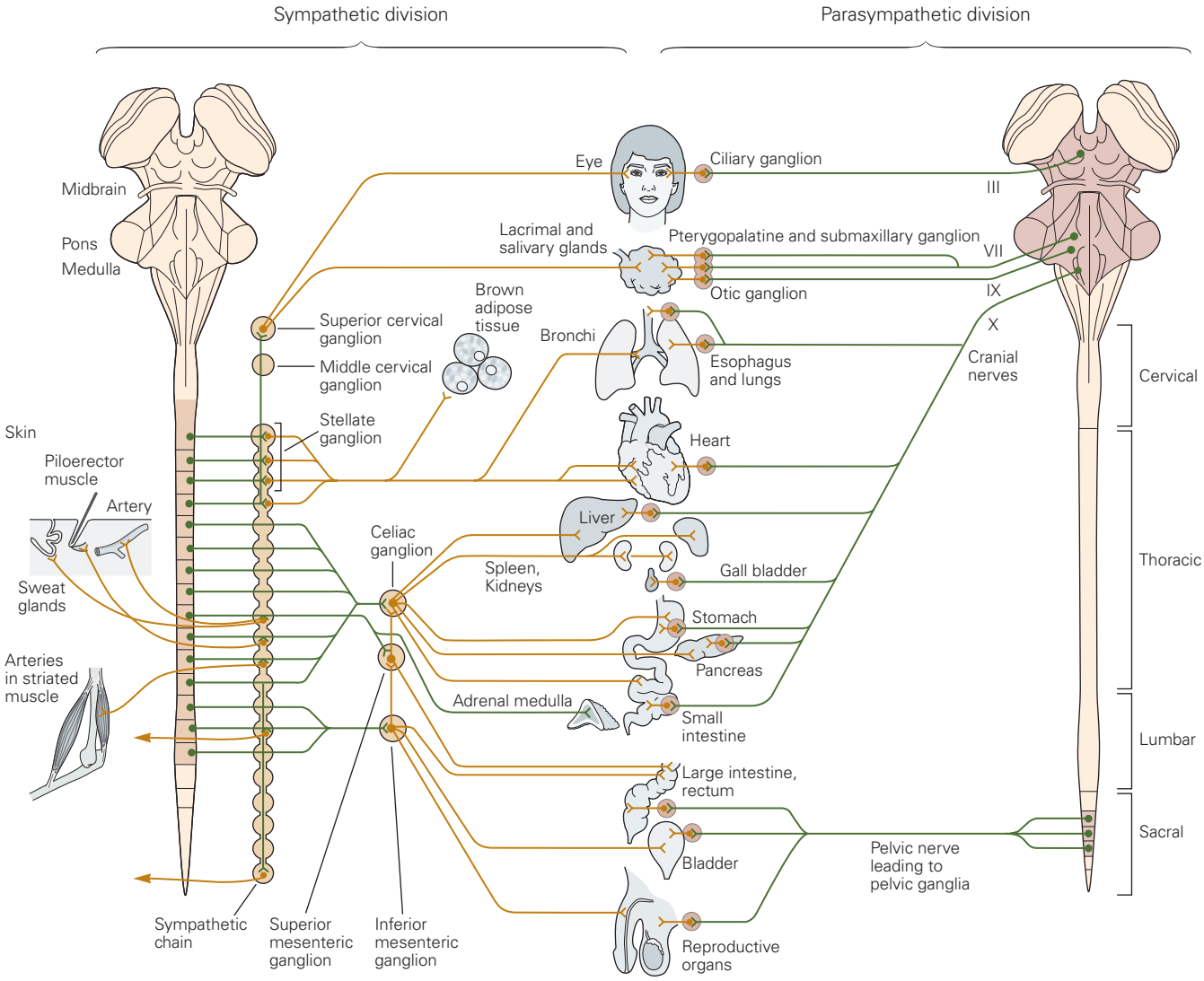


Figure 41–4 Sympathetic and parasympathetic divisions of the autonomic motor system. The sympathetic ganglia lie close to the spinal column and supply virtually every tissue in the body. Some tissues, such as skeletal muscle, are regulated only indirectly through their arterial blood supply. The parasympathetic ganglia are located near their targets, which do not include the skin or skeletal muscle.

This regulation depends on synaptic input from the spinal cord and from supraspinal structures that control the activity of the preganglionic neurons.

Important groups of supraspinal neurons that excite preganglionic sympathetic activity are located in the rostral ventrolateral medulla, the raphe pallidus in the brain stem, and the paraventricular nucleus in the hypothalamus. Preganglionic neurons integrate these descending inputs along with local segmental sensory inputs and form synapses with neurons in paravertebral and prevertebral sympathetic ganglia (Figure 41–5).

Ganglionic neurons in turn form synapses with a variety of end organs, including blood vessels, heart, bronchial airways, piloerector muscles, brown fat, and salivary and sweat glands. Sympathetic neurons also regulate immune function through projections to primary lymphoid tissue in the bone marrow and thymus and to secondary lymphoid cells in the spleen. A subset of preganglionic neurons synapse on chromaffin cells in the medulla of the adrenal gland (Figure 41–5), which secrete epinephrine (adrenaline) and norepinephrine (noradrenaline) into the circulation as hormones to act on distant targets.

The paravertebral and prevertebral sympathetic ganglia differ in both location and organization. Paravertebral ganglia are distributed segmentally,

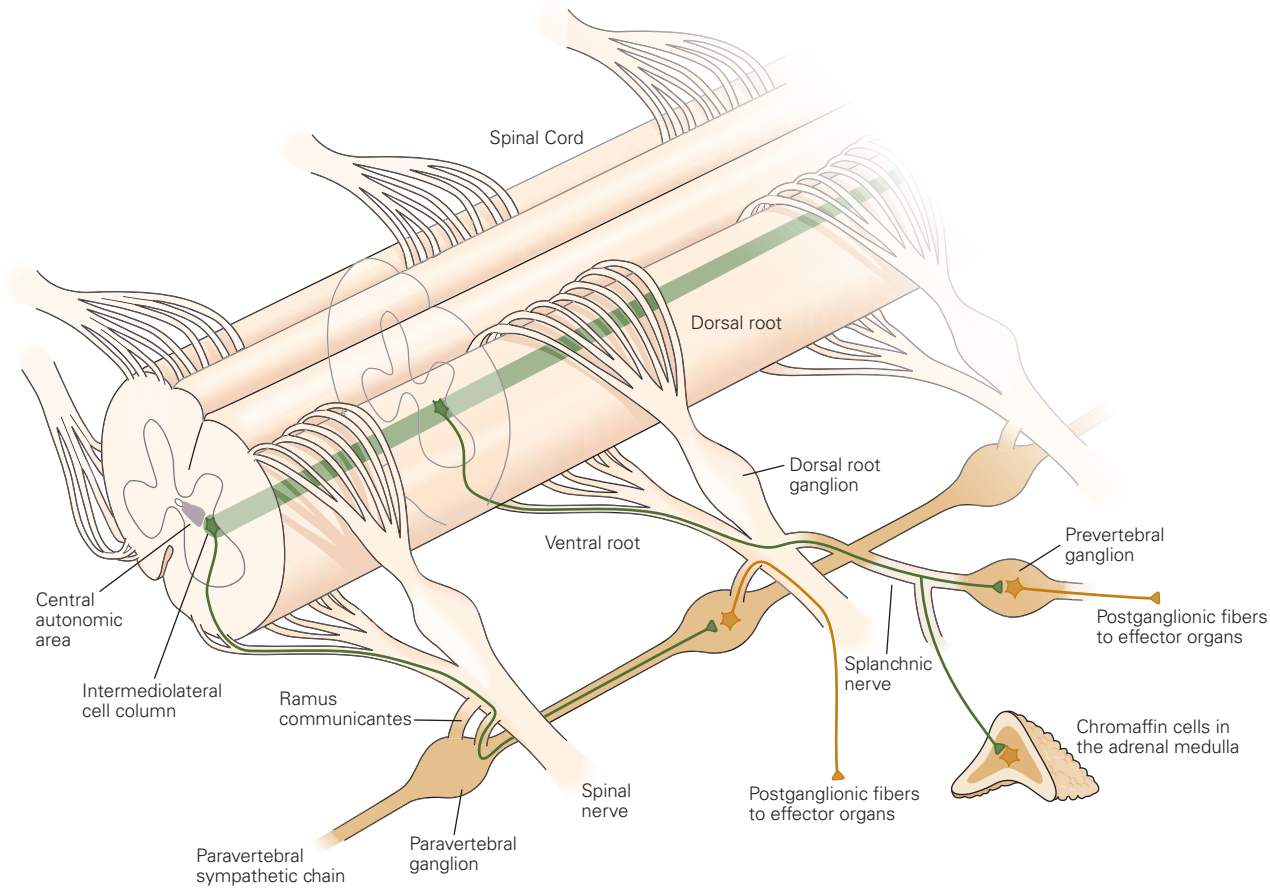


Figure 41–5 The sympathetic outflow is organized into groups of paravertebral and prevertebral ganglia. The axons of preganglionic cells in the spinal cord reach postganglionic neurons by way of ventral roots and the paravertebral sympathetic chain. The axons either form synapses on postganglionic neurons in paravertebral ganglia or project out of the chain into splanchnic nerves. Preganglionic axons in the splanchnic nerves form synapses with postganglionic neurons in prevertebral ganglia and with chromaffin cells in the adrenal medulla.

extending bilaterally as two chains from the first cervical segment to the last sacral segment. The chains lie lateral to the vertebral column at its ventral margin and generally contain one ganglion per segment (Figures 41–4 and 41–5). Two important exceptions are the superior cervical and stellate ganglia. The superior cervical ganglion is a coalescence of several cervical ganglia and supplies sympathetic innervation to the entire head, including the cerebral vasculature. The stellate ganglion, which innervates the heart and lungs, is a coalescence of ganglia from lower cervical segments and the first thoracic segment. These sympathetic pathways have an orderly somatotopic relation to one another from their segmental origin in preganglionic neurons to their terminus in peripheral targets.

The prevertebral ganglia are midline structures that lie close to the arteries for which they are named (Figures 41–4 and 41–5). In addition to sending sympathetic signals to visceral organs in the abdomen and pelvis, these ganglia also receive sensory feedback from their end organs.

Parasympathetic Ganglia Innervate Single Organs

In contrast to sympathetic ganglia, which regulate many targets and lie some distance from their targets close to the spinal cord, parasympathetic ganglia generally innervate single end organs and lie near to or within the end organs they regulate (Figure 41–4). In addition, the parasympathetic system does not influence lymphoid tissue, skin, or skeletal muscle except in the head, where it regulates vascular beds in the jaw, lip, and tongue.

The cranial and sacral parasympathetic ganglia innervate different targets. The cranial outflow includes four ganglia in the head (Chapter 40). The oculomotor

(III) nerve projects to the ciliary ganglion, which controls pupillary size and focus by innervating the iris and ciliary muscles. The facial (VII) nerve and a small component of the glossopharyngeal (IX) nerve project to the pterygopalatine (or sphenopalatine) ganglion, which promotes production of tears by the lacrimal glands and mucus by the nasal and palatine glands. Cranial nerve IX and a small component of nerve VII project to the otic ganglion. Its postganglionic neurons innervate the parotid, the largest salivary gland. Nerve VII also projects to the submandibular ganglion, which controls secretion of saliva by the submaxillary and sublingual glands.

The vagus (X) nerve projects broadly to parasympathetic ganglia in the heart, lungs, liver, gallbladder, and pancreas. It also projects to the stomach, small intestine, and more rostral segments of the gastrointestinal tract. The caudal parasympathetic outflow supplies the large intestine, rectum, bladder, and reproductive organs.

The Enteric Ganglia Regulate the Gastrointestinal Tract

The entire gastrointestinal tract, from the esophagus to the rectum—and including the pancreas and gallbladder—is controlled by the system of enteric ganglia. This system, by far the largest and most complex division of the autonomic nervous system, contains as many as 100 million neurons.

The enteric system has been studied most extensively in the small intestine of the guinea pig. Its activity is coordinated by two interconnected plexuses, small islands of interconnected neurons. The myenteric plexus controls smooth muscle movements of the gastrointestinal tract; the submucous plexus controls mucosal function (Figure 41–6). Working together, this distributed network of ganglia coordinates the orderly peristaltic propulsion of gastrointestinal contents and controls the secretions of the stomach and intestines and other components of digestion. In addition, the enteric system regulates local blood flow and also immune function in Peyer's patches. The enteric system is modulated by external inputs from sympathetic prevertebral ganglia and from parasympathetic components of the vagus nerve.

Unlike the sympathetic and parasympathetic divisions of the autonomic system, the enteric plexus contains interneurons and sensory neurons in addition to motor neurons. This intrinsic neural circuitry can maintain the basic functions of the gut even after the splanchnic sympathetic and vagal parasympathetic pathways are cut. Through splanchnic nerves and the afferent portion of the vagus nerve, the gastrointestinal tract also sends sensory information about the physiological status of the tract to the spinal cord and brain stem.

Acetylcholine and Norepinephrine Are the Principal Transmitters of Autonomic Motor Neurons

All preganglionic neurons in the sympathetic and parasympathetic systems use ACh as their excitatory neurotransmitter, activating ionotropic nicotinic ACh receptors on ganglionic neurons. These receptors resemble those at the neuromuscular junction in having nonselective cation pores, but they are encoded by different genes.

Activation of the ganglionic neurons triggers action potentials that propagate to postganglionic synapses with end organs in the periphery. At these end organ synapses, parasympathetic neurons release ACh, which activates muscarinic G protein–coupled receptors; sympathetic neurons release norepinephrine, which activates α- and β-adrenergic G protein–coupled receptors. The postsynaptic action can be either excitatory or inhibitory, depending on the type of target cell and its receptors (Table 41–2). Notable exceptions to this organization are the sympathetic postganglionic neurons that control sweat glands. They assume a cholinergic phenotype after birth.

In addition to acting on different receptors in different postsynaptic cells, one transmitter can activate different receptor types in the same postsynaptic cell. This principle was first discovered in sympathetic ganglia where ACh activates both nicotinic and muscarinic postsynaptic receptors to produce both a fast and slow excitatory postsynaptic potential (Figure 41–7A and Chapter 14). In some cases, one transmitter can activate both a postsynaptic receptor as well as a receptor on the presynaptic terminals from which the transmitter was released. Such presynaptic responses can cause either presynaptic inhibition or presynaptic facilitation (Figure 41–7B and Chapter 15). This specialization of synaptic transmission in sympathetic and parasympathetic neurons leads to functional diversity in the regulation of end organ function.

Cholinergic and adrenergic synaptic transmission in the peripheral autonomic motor system is often modulated by the co-release of various neuropeptides, nitric oxide, or adenosine triphosphate, which by activating multiple receptor types further contribute to functional diversity (Table 41–2 and Figure 41–7C). The motor responses elicited in end organs depend on the identity of the postganglionic neurotransmitters and the pre- and postsynaptic receptors

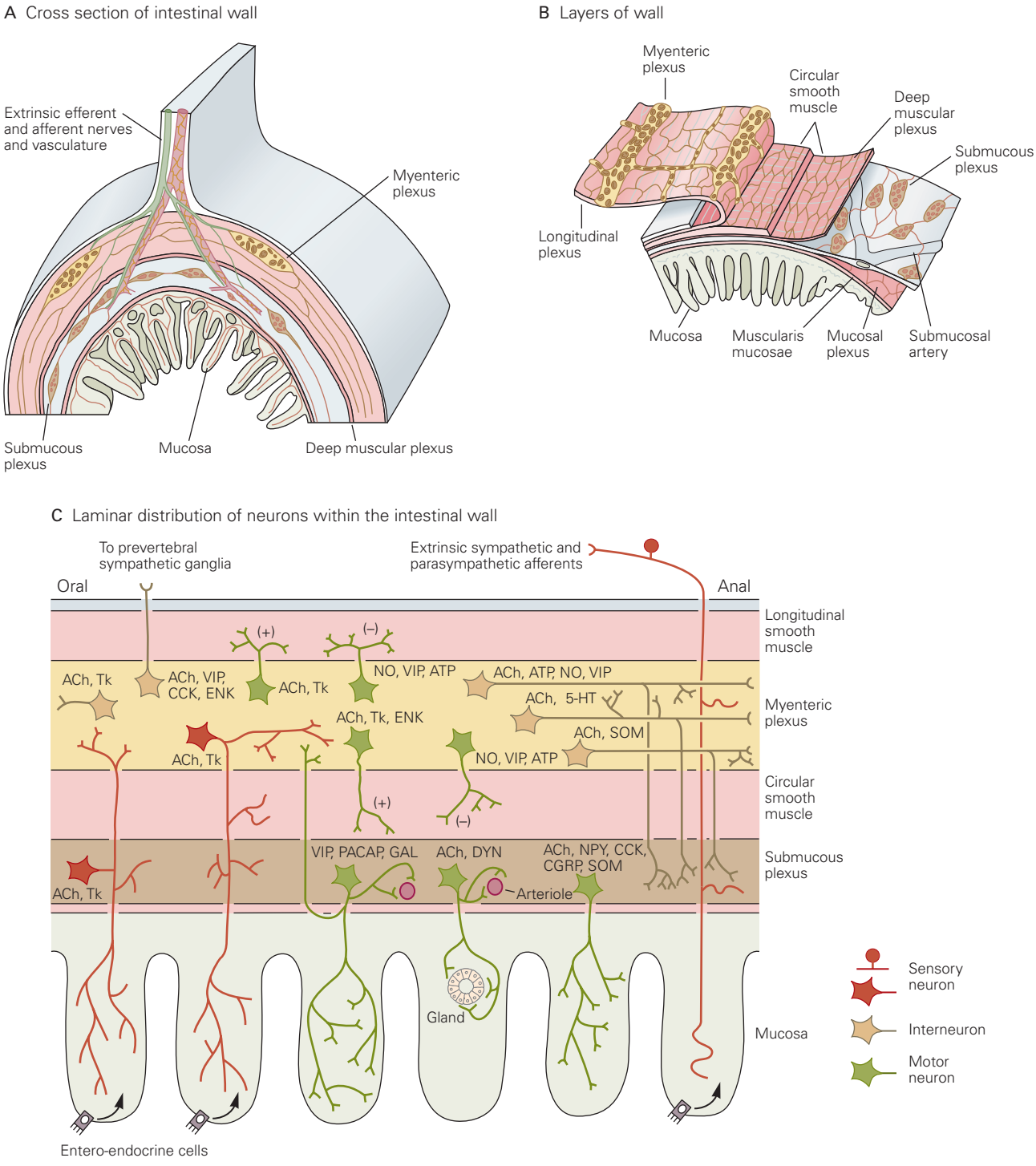


Figure 41–6 Organization of the enteric plexuses in the guinea pig. The myenteric plexus and submucous plexus lie between the layers of intestinal wall (**A** and **B**). At least 14 types of neurons have been identified within the enteric system based on morphology, chemical coding, and functional properties (**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.)