PART VII Gastrointestinal Physiology

CHAPTER 26

Neurogastroenterology and Gastrointestinal Motility

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CHAPTER OUTLINE

KEY CONCEPTS

1. The musculature of the digestive tract is mainly smooth muscle.
2. Electrical slow waves and action potentials are the main forms of electrical activity in the gastrointestinal musculature.
3. Gastrointestinal smooth muscles have properties of a functional electrical syncytium.
4. A hierarchy of neural integrative centers in the central nervous system (CNS) and peripheral nervous system (PNS) determines moment-to-moment behavior of the digestive tract.
5. The digestive tract is innervated by the sympathetic, parasympathetic, and enteric divisions of the autonomic nervous system (ANS).
6. Vagus nerves transmit afferent sensory information to the brain and parasympathetic autonomic efferent signals to the digestive tract.
7. Splanchnic nerves transmit sensory information to the spinal cord and sympathetic autonomic efferent signals to the digestive tract.
8. The enteric nervous system (ENS) functions as a minibrain in the gut.
9. Fast and slow excitatory postsynaptic potentials, slow inhibitory postsynaptic potentials, presynaptic inhibition, and presynaptic facilitation are key synaptic events in the ENS.
10. Enteric motor neurons may be excitatory or inhibitory to the musculature.
11. Enteric inhibitory motor neurons to the intestinal circular muscle are continuously active and transiently inactivated to permit muscle contraction.
12. Enteric inhibitory motor neurons to the musculature of sphincters are inactive and transiently activated for timed opening and the passage of luminal contents.
13. A polysynaptic reflex circuit determines the behavior of the intestinal musculature during peristaltic propulsion.
14. Physiological ileus is the normal absence of contractile activity in the intestinal musculature.
15. Peristalsis and relaxation of the lower esophageal sphincter are the main motility events in the esophagus.
16. The gastric reservoir and antral pump have different motor behavior.
17. Vago-vagal reflexes are important in the control of gastric motor functions.
18. Feedback signals from the duodenum determine the rate of gastric emptying.
19. The migrating motor complex is the small intestinal motility pattern of the interdigestive state.

(continued)

20. Mixing movements are the small intestinal motility pattern of the digestive state.
21. Intestinal power propulsion is a protective response to harmful agents.
22. Cramping abdominal pain may be associated with intestinal power propulsion.
23. Motor functions of the large intestine are specialized for storage and dehydration of feces.
24. The physiology of the rectosigmoid region, anal canal, and pelvic floor musculature is important in maintaining fecal continence.

This chapter presents concepts and principles of neurogastroenterology in relation to motor functions of the specialized organs and muscle groups of the digestive tract. **Neurogastroenterology** is a subspecialty of clinical gastroenterology and digestive science. As such, it encompasses the investigative sciences dealing with functions, malfunctions, and malformations in the brain and spinal cord and the sympathetic, parasympathetic, and enteric divisions of the autonomic innervation of the digestive tract. Somatic motor systems are included insofar as pharyngeal phases of swallowing and pelvic floor involvement in defecation and continence are concerned. The basic physiology of smooth muscles, as it relates to enteric neural control of motor movements, is a part of neurogastroenterology. Psychological and psychiatric aspects of gastrointestinal disorders are significant components of the neurogastroenterological domain, especially in relation to projections of discomfort and pain to the digestive tract.

Gastrointestinal (GI) motility refers to wall movement or lack thereof in the digestive tract. The integrated function of multiple tissues and types of cells is necessary for generation of the various patterns of motility found in the organs of the digestive tract. Digestive motor movements involve the application of forces of muscle contraction to material that may be present in the mouth, pharynx, esophagus, stomach, gallbladder, or small and large intestines. The musculature is striated in the mouth, pharynx, upper esophagus, and pelvic floor and in visceral-type smooth muscle elsewhere. Specialized pacemaker cells, called interstitial cells of Cajal, are associated with the smooth musculature. The nervous system, with its different kinds of neurons and glial cells, organizes muscular activity into functional patterns of wall behavior. Functions of the nervous system are influenced by chemical signals released from enterochromaffin cells, enteroendocrine cells, and cells associated with the enteric immune system (e.g., mast cells and polymorphonuclear leukocytes).

Motility in the various organs of the digestive tract is organized to fulfill the specialized function of the individual organ. Esophageal motility, for example, differs from gastric motility, and gastric motility differs from small intestinal motility. The motility in the different organs reflects coordinated contractions and relaxations of the smooth muscle. Contractions are organized to produce the propulsive forces that move the contents along the tract, triturate large particles to smaller particles, mix ingested foodstuff with digestive enzymes, and bring nutrients into contact with the mucosa for efficient absorption. Relaxation of spontaneous tone in the smooth muscle allows sphincters to open and ingested material to be accommodated in reservoirs of the stomach and large intestine. The enteric nervous system (ENS), together with its input from the CNS, organizes motility into patterns of efficient behavior suited to differing digestive states (e.g., fasting and processing of a meal) as well as abnormal patterns such as occur during vomiting.

THE MUSCULATURE OF THE DIGESTIVE TRACT

The smooth muscles of the digestive tract are generally organized in distinct layers. Two important muscle layers for motility in the lower esophagus and small and large intestine are the longitudinal and circular layers (Fig. 26.1). The two layers form the intestinal **muscularis externa**. The stomach has an additional obliquely oriented muscle layer.

The Structure and Function of Circular and Longitudinal Muscles Differ

The circular muscle layer is thicker than the longitudinal layer and more powerful in exerting contractile forces on the contents of the lumen. The long axis of the muscle fibers of circular muscle is oriented in the circumferential direction. Consequently, contraction reduces the diameter of the lumen of an intestinal segment and increases its length. Because the long axis of the muscle fibers is oriented in the longitudinal direction, contraction of the longitudinal muscle coat shortens the segment of intestine where it occurs and expands the lumen.

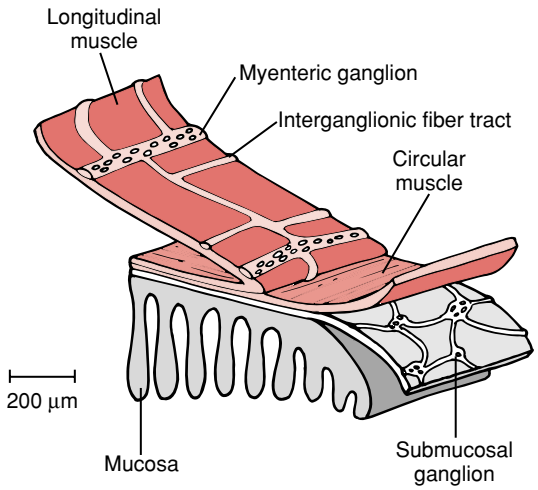

FIGURE 26.1 Structural relationship of the intestinal musculature and the enteric nervous system. Ganglia and interganglionic fiber tracts form the myenteric plexus between the longitudinal and the circular muscle layer and form the submucosal plexus between the mucosa and circular muscle layer.

Both longitudinal and circular muscle layers are innervated by motor neurons of the ENS. The longitudinal muscle layer is innervated mainly by excitatory motor neurons; the circular muscle layer by both excitatory and inhibitory motor neurons. Nonneural pacemaker cells and excitatory motor neurons activate contraction of the circular muscle, and excitatory motor neurons are the main triggers for contraction of the longitudinal muscle. More gap junctions between adjacent muscle fibers are found in the circular layer than in the longitudinal muscle layer. Calcium influx from outside the muscle cells is important for excitation-contraction coupling in longitudinal muscle fibers. Intracellular release from internal stores is more important for excitation-contraction coupling in the muscle fibers of the circular layer.

Smooth Muscles Are Classified as Unitary or Multiunit Types

Smooth muscles are classified based on their behavioral properties and associations with nerves (see Chapter 9). Muscles of the stomach and intestine behave like **unitary type** smooth muscle. These muscles contract spontaneously in the absence of neural or endocrine influence and contract in response to stretch. There are no structured neuromuscular junctions, and neurotransmitters travel over extended diffusion distances to influence relatively large numbers of muscle fibers. The smooth muscle of the esophagus and gallbladder is more like the **multiunit type**. These muscles do not contract spontaneously in the absence of nervous input and do not contract in response to stretch. Activation to contract is by nervous input to relatively small groups of muscle fibers.

Electromechanical and Pharmacomechanical Coupling Trigger Contractions in GI Muscles

GI smooth muscle differs from skeletal muscle in having two mechanisms that initiate the processes leading to contractile shortening and development of tension. In both skeletal muscle and GI smooth muscle, depolarization of the membrane electrical potential leads to the opening of voltage-gated calcium channels, followed by the elevation of cytosolic calcium, which, in turn, activates the contractile proteins. This mechanism is called **electromechanical coupling**. Smooth muscles have an additional mechanism in which the binding of a ligand to its receptor on the muscle membrane leads to the opening of calcium channels and the elevation of cytosolic calcium without any change in the membrane electrical potential. This mechanism is called **pharmacomechanical coupling**. The ligands may be chemical substances released as signals from nerves (neurocrine), from nonneural cells in close proximity to the muscle (paracrine), or from endocrine cells as hormones delivered to the muscle by the blood.

GI and Esophageal Smooth Muscles Have Properties of a Functional Electrical Syncytium

Smooth muscle fibers are connected to their neighbors by **gap junctions**, which are permeable to ions and, thereby, transmit electrical current from muscle fiber to muscle fiber. Ionic connectivity, without cytoplasmic continuity from fiber to fiber, accounts for the **electrical syncytial properties** of smooth muscle, which confers electrical behavior analogous to that of cardiac muscle (see Chapter 13). Electrical activity and associated contractions spread from a point of initiation (e.g., the pacemaker region) in three dimensions throughout the bulk of the muscle. The distance and the direction of electrical activity spread are controlled by the ENS. A failure of nervous control can lead to disordered motility that includes spasm and associated abdominal pain.

Slow Waves and Action Potentials Are Forms of Electrical Activity in GI Muscles

Electrical slow waves are omnipresent and responsible for triggering action potentials in some regions, whereas in other regions (e.g., the gastric antrum and large intestinal circular muscle) they represent the only form of electrical activity (Fig. 26.2). They are always present in the small intestine where they decrease in frequency along a gradient from the duodenum to the ileum. In the gastric antrum, the terms *slow wave* and *action potential* are used interchangeably for the same electrical event. When action potentials are associated with electrical slow waves, they occur during the plateau phase of the slow wave (see Fig. 26.2).

Action potentials in GI smooth muscle are mediated by changes in calcium and potassium conductances. The depolarization phase of the action potential is produced by an all-or-nothing increase in calcium conductance, with the inward calcium current carried by L-type calcium channels. The opening of potassium channels as the calcium channels are closing at or near the peak of the action potential accounts for the repolarization phase. The L-type calcium channels in GI smooth muscle are essentially the same as those found in cardiac and vascular smooth muscle. Therefore, disordered GI motility may be a adverse effect of treating of cardiovascular disease with drugs that block L-type calcium channels.

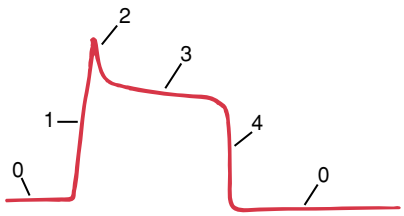

FIGURE 26.2 **Electrical slow waves.** In GI muscles, slow waves occur in four phases determined by specific ionic mechanisms. Phase 0: Resting membrane potential; outward potassium current. Phase 1, the rising phase (upstroke depolarization), activates voltage-gated calcium channels and voltage-gated potassium channels. Phase 3, the plateau phase, balances inward calcium current and outward potassium current. Phase 4, the falling phase (repolarization), inactivates voltage-gated calcium channels and activates calcium-gated potassium channels.

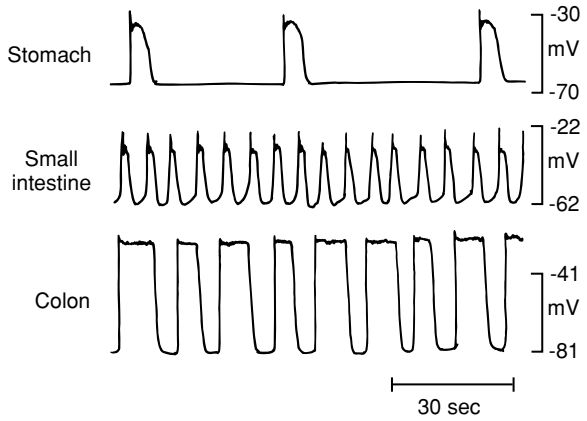

FIGURE 26.3 **Electrical slow-wave frequencies.** Slow waves with similar waveforms occur at different frequencies in the stomach, small intestine, and colon.

Electrical Slow-Wave Frequencies in the Stomach, Small Intestine, and Colon. Electrical slow waves with essentially the same waveform occur at different frequencies in the gastric antrum and small and large intestinal circular muscle when recorded with intracellular electrodes (Fig. 26.3). Slow waves occur at 3/min in the antrum, as high as 18/min in the duodenum, and 6 to 10/min in the colon. The maximum contractile frequency of the muscle does not exceed the frequency of the slow waves, but it may occur at a lower frequency because all slow waves may not trigger contractions. The nervous system determines the nature of the contractile response during each slow wave in the integrated functional state of the whole organ.

Electrical Slow Waves Without Action Potentials in the Small Intestine. As a general rule, slow waves in the small intestinal circular muscle trigger action potentials and action potentials trigger contractions. Slow waves are omnipresent in virtually all mammalian species and may or may not be accompanied by action potentials. Contractions do not occur in the absence of action potentials. The electrical slow waves in Figure 26.4 were recorded with an extracellular electrode attached to the serosal surface of the intestine. This method records from many circular muscle fibers. Shallow contractions appearing in the absence of action potentials on the slow waves reflect the responses of a few of the total population of muscle fibers under the electrode (Fig. 26.4A). In this case, the action potential currents from the small number of fibers are too small to be detected by the surface electrode. With this method of recording, the size of an action potential appears larger when larger numbers of the total population of muscle fibers are depolarized to action potential threshold by each slow wave. The amplitude of phasic contractions associated with each electrical slow wave increases in direct relation to the number of muscle fibers recruited to firing threshold by each slow-wave cycle (Fig. 26.4B).

Electrical Slow Waves and Interstitial Cells of Cajal. **Interstitial cells of Cajal** (ICCs) are the generators of electrical slow waves in the stomach and small and large intestine (Fig. 26.5). The ICCs are interconnected into networks by gap junctions that impart the properties of a functional electrical syncytium to the network. Gap junctions also electrically connect the ICCs to the circular muscle. Electrical current flows from the ICC network across the gap junctions to depolarize the membrane potential of the circular muscle fibers to the threshold for action potential discharge.

Pacemaker networks of ICCs are located surrounding the small intestinal circular muscle at the border with the longitudinal muscle (myenteric border) and at its border with the submucosa. Slow waves generated by the ICC network at the submucosal border spread passively across gap junctions into the bulk of circular muscle, and those at the myenteric border spread passively into both longitudinal and circular muscle. Muscle fibers of the circular muscle are interconnected by gap junctions that transmit the slow-wave electrical current from fiber to fiber throughout the bulk of the muscle.

CONTROL OF DIGESTIVE FUNCTIONS BY THE NERVOUS SYSTEM

The innervation of the digestive tract controls muscle contraction, secretion, and absorption across the mucosal lining and blood flow inside the walls of the esophagus, stomach, intestines, and gallbladder. Depending on the kind of neurotransmitter released, the neurons can activate or inhibit muscle contraction. The secretion of water, electrolytes, and mucus into the lumen and absorption from the lumen are determined by the innervation. The amount of blood flow within the wall and the distribution of flow between the muscle layers and mucosa are also controlled by nervous activity.

Sensory nerves transmit information on the state of the gut to the brain for processing. Sensory transmission and central processing account for sensations that are localized to the digestive tract. These include sensations of discomfort (such as upper abdominal fullness), abdominal pain, and chest pain (heartburn). Neural interactions include the sensory inflow of information from the gut to the brain and outflow from the brain to the gut. Outflow may originate in higher processing centers of the brain (the frontal cortex) and account for the projection of an individual's emotional state (psychogenic stress) to the gut. This kind of brain-gut interaction underlies the symptoms of diarrhea and lower abdominal discomfort often reported by students anticipating an examination.

A Hierarchy of Neural Integrative Centers Determines the Moment-to-Moment Motor Behavior of the Digestive Tract

The **sympathetic**, **parasympathetic,** and **enteric nervous systems** make up the divisions of the ANS that innervate the digestive tract. Figure 26.6 illustrates how neural control of the gut is hierarchical with five basic levels of integrative organization. Level 1 is the ENS, which behaves like a minibrain in the gut. Level 2 consists of the prevertebral ganglia of the sympathetic nervous system. Levels 3, 4, and 5 are within the CNS. Sympathetic and parasympa-

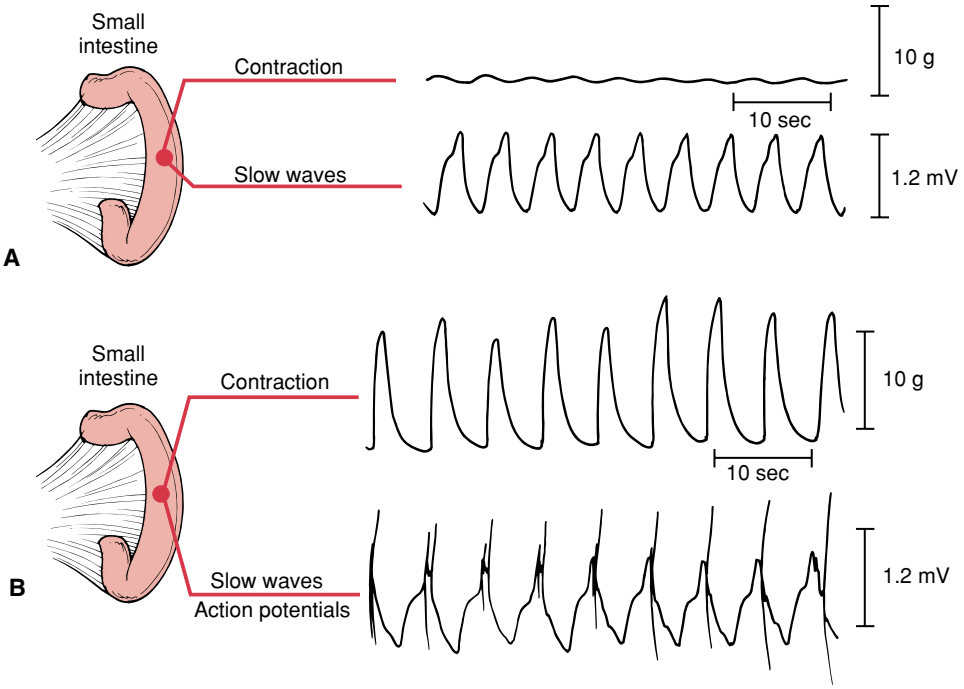

FIGURE 26.4 Electrical slow waves in the small intestine. A, No action potentials appear at the crests of the slow waves, and the muscle contractions associated with each slow wave are small. B, Muscle action potentials appear as sharp upward-downward deflections at the crests of the slow waves. Large-amplitude muscle contractions are associated with each slow wave when action potentials are present. Electrical slow waves trigger action potentials, and action potentials trigger contractions.

thetic signals to the digestive tract originate at levels 3 and 4 (central sympathetic and parasympathetic centers) in the medulla oblongata and represent the final common pathways for the outflow of information from the brain to the gut. Level 5 includes higher brain centers that provide input for integrative functions at levels 3 and 4.

Autonomic signals to the gut are carried from the brain and spinal cord by sympathetic and parasympathetic nervous pathways that represent the **extrinsic component** of innervation. Neurons of the enteric division form the local intramural control networks that make up the **intrinsic component** of the autonomic innervation. The parasympathetic and sympathetic subdivisions are identified by the positions of the ganglia containing the cell bodies of the postganglionic neurons and by the point of outflow from the CNS. Comprehensive autonomic innervation of the digestive tract consists of interconnections between the brain, the spinal cord, and the ENS.

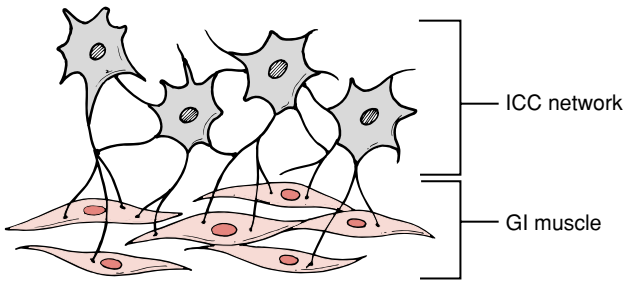

FIGURE 26.5 Interstitial cells of Cajal. ICCs form networks that contact the GI musculature. Electrical slow waves originate in the networks of ICCs. ICCs are the generators (pacemaker sites) of the slow waves. Gap junctions connect the ICCs to the circular muscle. Ionic current flows across the gap junctions to depolarize the membrane potential of the circular muscle fibers to the threshold for the discharge of action potentials.

Autonomic Parasympathetic Neurons Project to the Gut From the Medulla Oblongata and Sacral Spinal Cord

The origins of parasympathetic nerves to the gut are located in both the brainstem and sacral region of the spinal cord (Fig. 26.7). Projections to the digestive tract from these regions of the CNS are **preganglionic efferents**. Neu-

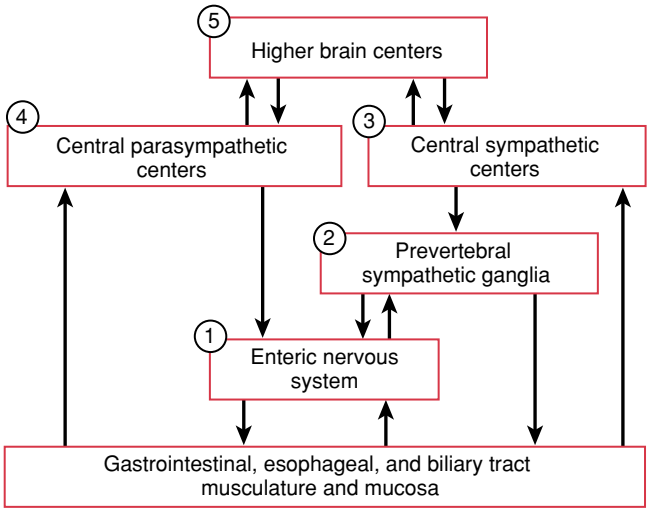

FIGURE 26.6 A hierarchy of neural integrative centers. Five levels of neural organization determine the moment-to-moment motor behavior of the digestive tract. (See text for details.)

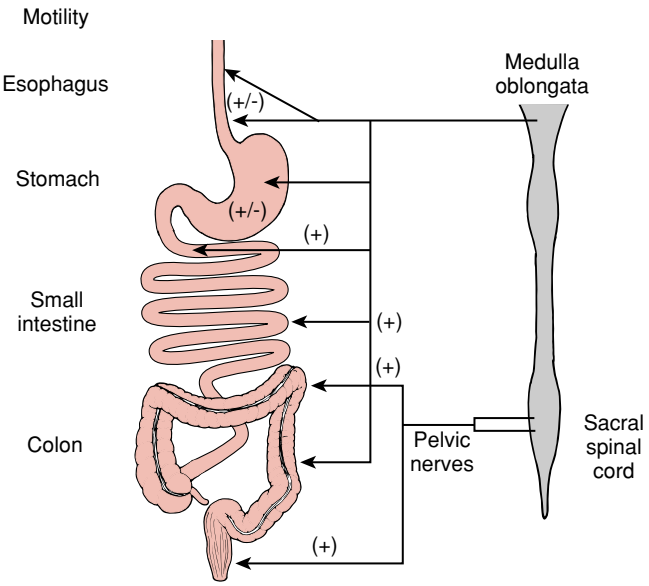

FIGURE 26.7 **Parasympathetic innervation.** Signals from parasympathetic centers in the CNS are transmitted to the enteric nervous system by the vagus and pelvic nerves. These signals may result in contraction (+) or relaxation (−) of the digestive tract musculature.

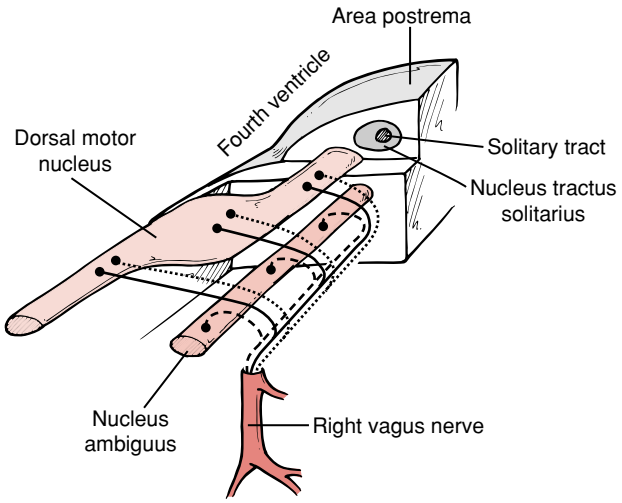

FIGURE 26.8 **Dorsal vagal complex of medulla oblongata.**

ronal cell bodies in the **dorsal motor nucleus** in the medulla oblongata project in the vagus nerves, and those in the sacral region of the spinal cord project in the pelvic nerves to the large intestine. Efferent fibers in the pelvic nerves make synaptic contact with neurons in ganglia located on the serosal surface of the colon and in ganglia of the ENS deeper within the large intestinal wall. Efferent vagal fibers synapse with neurons of the ENS in the esophagus, stomach, small intestine, and colon, as well as in the gallbladder and pancreas.

Efferent vagal nerves transmit signals to the enteric innervation of the GI musculature to control digestive processes both in anticipation of food intake and following a meal. This involves the stimulation and inhibition of contractile behavior in the stomach as a result of activation of the enteric circuits that control excitatory or inhibitory motor neurons, respectively. Parasympathetic efferents to the small and large intestinal musculature are predominantly stimulatory as a result of their input to the enteric microcircuits that control the activity of excitatory motor neurons.

The **dorsal vagal complex** consists of the dorsal motor nucleus of the vagus, **nucleus tractus solitarius**, **area postrema**, and **nucleus ambiguus**; it is the central vagal integrative center (Fig. 26.8). This center in the brain is more directly involved in the control of the specialized digestive functions of the esophagus, stomach, and the functional cluster of duodenum, gallbladder, and pancreas than the distal small intestine and large intestine. The circuits in the dorsal vagal complex and their interactions with higher centers are responsible for the rapid and more precise control required for adjustments to rapidly changing conditions in the upper digestive tract during anticipation, ingestion, and digestion of meals of varied composition.

Vago-Vagal Reflex Circuits Consist of Sensory Afferents, Second-Order Interneurons, and Efferent Neurons

A reflex circuit known as the **vago-vagal reflex** underlies moment-to-moment adjustments required for optimal digestive function in the upper digestive tract (see Clinical Focus Box 26.1). The afferent side of the reflex arc consists of vagal afferent neurons connected with a variety of sensory receptors specialized for the detection and signaling of mechanical parameters, such as muscle tension and mucosal brushing, or luminal chemical parameters, including glucose concentration, osmolality, and pH. Cell bodies of the vagal afferents are in the **nodose ganglia**. The afferent neurons are synaptically connected with neurons in the dorsal motor nucleus of the vagus and in the nucleus of the tractus solitarius. The nucleus of the tractus solitarius, which lies directly above the dorsal motor nucleus of the vagus (see Fig. 26.8), makes synaptic connections with the neuronal pool in the vagal motor nucleus. A synaptic meshwork formed by processes from neurons in both nuclei tightly links the two into an integrative center. The dorsal vagal neurons are second- or third-order neurons representing the efferent arm of the reflex circuit. They are the final common pathways out of the brain to the enteric circuits innervating the effector systems.

Efferent vagal fibers form synapses with neurons in the ENS to activate circuits that ultimately drive the outflow of signals in motor neurons to the effector systems. When the effector system is the musculature, its innervation consists of both inhibitory and excitatory motor neurons that participate in reciprocal control. If the effector systems are gastric glands or digestive glands, the secretomotor neurons are excitatory and stimulate secretory behavior.

The circuits for CNS control of the upper GI tract are organized much like those dedicated to the control of skeletal muscle movements (see Chapter 5), where fundamental reflex circuits are located in the spinal cord. Inputs to the spinal reflex circuits from higher order integrative

CLINICAL FOCUS BOX 26.1

Delayed Emptying and Rapid Emptying: Disorders of Gastric Motility

Disorders of gastric motility can be divided into the broad categories of delayed and rapid emptying. The generalized symptoms of both disorders overlap (Fig. 26.A).

Delayed gastric emptying is common in diabetes mellitus and may be related to disorders of the vagus nerves, as part of a spectrum of autonomic neuropathy. Surgical vagotomy results in a rapid emptying of liquids and a delayed emptying of solids. As mentioned earlier, vagotomy impairs adaptive relaxation and results in increased contractile tone in the reservoir (see Fig. 26.29). Increased pressure in the gastric reservoir more forcefully presses liquids into the antral pump. Paralysis with a loss of propulsive motility in the antrum occurs after a vagotomy. The result is **gastroparesis**, which can account for the delayed emptying of solids after a vagotomy. When selective vagotomy is performed as a treatment for peptic ulcer disease, the pylorus is enlarged surgically **(pyloroplasty)** to compensate for postvagotomy gastroparesis.

Delayed gastric emptying with no demonstrable underlying condition is common. Up to 80% of patients with anorexia nervosa have delayed gastric emptying of solids. Another such condition is **idiopathic gastric stasis**, in which no evidence of an underlying condition can be found. Motility-stimulating drugs (e.g., cisapride) are used successfully in treating these patients. In children, **hypertrophic pyloric stenosis** impedes gastric emptying. This is a thickening of the muscles of the pyloric canal associated with a loss of enteric neurons. The absence of inhibitory motor neurons and the failure of the circular muscles to relax account for the obstructive stenosis.

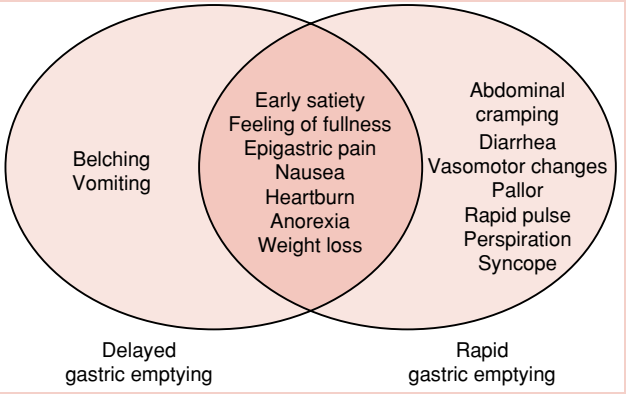

FIGURE 26.A **Symptoms of disordered gastric emptying. Some of the symptoms of delayed and rapid gastric emptying overlap.**

Rapid gastric emptying often occurs in patients who have had both vagotomy and gastric antrectomy for the treatment of peptic ulcer disease. These individuals have rapid emptying of solids and liquids. The pathological effects are referred to as the **dumping syndrome**, which results from the "dumping" of large osmotic loads into the proximal small intestine.

centers in the brain (motor cortex and basal ganglia) complete the neural organization of skeletal muscle motor control. Memory, the processing of incoming information from outside the body, and the integration of proprioceptive information are ongoing functions of higher brain centers responsible for the logical organization of outflow to the skeletal muscles by way of the basic spinal reflex circuit. The basic connections of the vago-vagal reflex circuit are like somatic motor reflexes, in that they are "fine-tuned" from moment to moment by input from higher integrative centers in the brain.

Autonomic Sympathetic Neurons Project to the Gut From Thoracic and Upper Lumbar Segments of the Spinal Cord

Sympathetic innervation to the gut is located in thoracic and lumbar regions of the spinal cord (Fig. 26.9). The nerve cell bodies are in the intermediolateral columns. Efferent sympathetic fibers leave the spinal cord in the ventral roots to make their first synaptic connections with neurons in **prevertebral sympathetic ganglia** located in the abdomen. The prevertebral ganglia are the **celiac**, **superior mesenteric**, and **inferior mesenteric ganglia**. Cell bodies in the prevertebral ganglia project to the digestive tract where they synapse with neurons of the ENS in addition to innervating the blood vessels, mucosa, and specialized regions of the musculature.

Sympathetic input generally functions to shunt blood from the splanchnic to the systemic circulation during exercise and stressful environmental change, coinciding with the suppression of digestive functions, including motility and secretion. The release of **norepinephrine** (NE) from sympathetic postganglionic neurons is the principal mediator of these effects. NE acts directly on sphincteric muscles to increase tension and keep the sphincter closed. Presynaptic inhibitory action of NE at synapses in the control circuitry of the ENS is primarily responsible for inactivation of motility.

Suppression of synaptic transmission by the sympathetic nerves occurs at both fast and slow excitatory synapses in the neural networks of the ENS. This inactivates the neural circuits that generate intestinal motor behavior. Activation of the sympathetic inputs allows only continuous discharge of inhibitory motor neurons to the nonsphincteric muscles. The overall effect is a state of paralysis of intestinal motility in conjunction with reduced intestinal blood flow. When this state occurs transiently, it is called **physiological ileus** and, when it persists abnormally, is called **paralytic ileus**.

Splanchnic Nerves Transmit Sensory Information to the Spinal Cord and Efferent Sympathetic Signals to the Digestive Tract

The splanchnic nerves are mixed nerves that contain both sympathetic efferent and sensory afferent fibers. Sensory

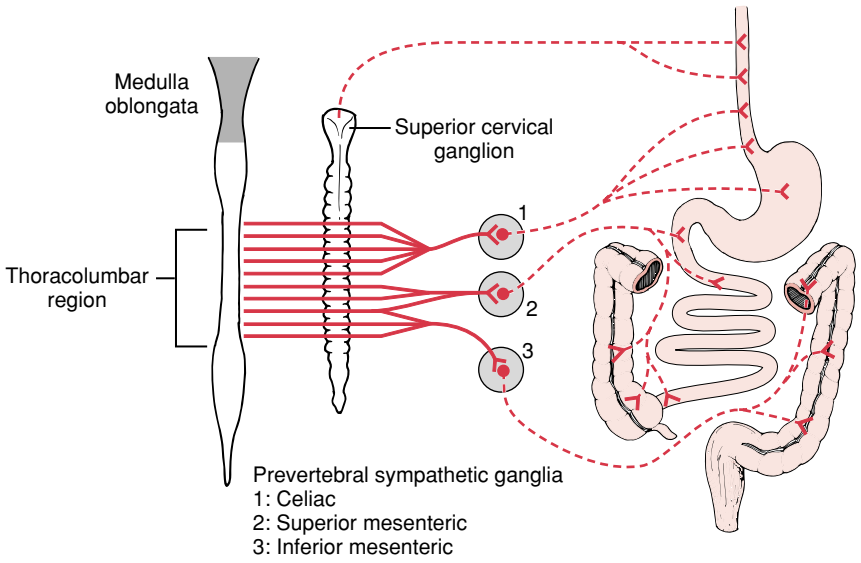

FIGURE 26.9 Sympathetic innervation.

nerves course side by side with the sympathetic fibers; nevertheless, they are not part of the sympathetic nervous system. The term sympathetic afferent, which is sometimes used, is incorrect.

Sensory afferent fibers in the splanchnic nerves have their cell bodies in dorsal root spinal ganglia. They transmit information from the GI tract and gallbladder to the CNS for processing. These fibers transmit a steady stream of information to the local processing circuits in the ENS, to prevertebral sympathetic ganglia, and to the CNS. The gut has mechanoreceptors, chemoreceptors, and thermoreceptors. Mechanoreceptors sense mechanical events in the mucosa, musculature, serosal surface, and mesentery. They supply both the ENS and the CNS with information on stretch-related tension and muscle length in the wall and on the movement of luminal contents as they brush the mucosal surface. Mesenteric mechanoreceptors code for gross movements of the organ. Chemoreceptors generate information on the concentration of nutrients, osmolality, and pH in the luminal contents. Recordings of sensory information exiting the gut in afferent fibers reveal that most receptors are multimodal, in that they respond to both mechanical and chemical stimuli. The presence in the GI tract of pain receptors (nociceptors) equivalent to C fibers and A-delta fibers elsewhere in the body is likely, but not unequivocally confirmed, except for the gallbladder. The sensitivity of splanchnic afferents, including nociceptors, may be elevated when inflammation is present in intestine or gallbladder.

The Enteric Division of the ANS Functions as a Minibrain in the Gut

The ENS is a minibrain located close to the effector systems it controls. Effector systems of the digestive tract are the musculature, secretory glands, and blood vessels. Rather than crowding the vast numbers of neurons required for controlling digestive functions into the cranium as part of the cephalic brain and relying on signal transmission over long and unreliable pathways, the integrative microcircuits are located at the site of the effectors. The circuits at the effector sites have evolved as an organized array of different kinds of neurons interconnected by chemical synapses. Function in the circuits is determined by the generation of action potentials within single neurons and chemical transmission of information at the synapses.

The enteric microcircuits in the various specialized regions of the digestive tract are wired with large numbers of neurons and synaptic sites where information processing occurs. Multisite computation generates output behavior from the integrated circuits that could not be predicted from properties of their individual neurons and synapses. As in the brain and spinal cord, emergence of complex behaviors is a fundamental property of the neural networks of the ENS.

The processing of sensory signals is one of the major functions of the neural networks of the ENS. Sensory signals are generated by sensory nerve endings and coded in the form of action potentials. The code may represent the status of an effector system (such as tension in a muscle), or it may signal a change in an environmental parameter, such as luminal pH. Sensory signals are computed by the neural networks to generate output signals that initiate homeostatic adjustments in the behavior of the effector system.

The cell bodies of the neurons that make up the neural networks are clustered in ganglia that are interconnected by fiber tracts to form a plexus. The structure, function, and neurochemistry of the ganglia differ from other ANS ganglia. Unlike autonomic ganglia elsewhere in the body, where they function mainly as relay-distribution centers for signals transmitted from the brain and spinal cord, enteric ganglia are interconnected to form a nervous system with mechanisms for the integration and processing of information like those found in the CNS. This is why the ENS is sometimes referred to as the "minibrain-in-the-gut."

Myenteric and Submucous Plexuses Are Parts of the ENS

The ENS consists of ganglia, primary interganglionic fiber tracts, and secondary and tertiary fiber projections to the

effector systems (i.e., musculature, glands, and blood vessels). These structural components of the ENS are interlaced to form a plexus. Two ganglionated plexuses are the most obvious constituents of the ENS (see Fig. 26.1). The **myenteric plexus**, also known as **Auerbach's plexus**, is located between the longitudinal and circular muscle layers of most of the digestive tract. The **submucous plexus**, also known as **Meissner's plexus**, is situated in the submucosal region between the circular muscle and mucosa. The submucous plexus is most prominent as a ganglionated network in the small and large intestines. It does not exist as a ganglionated plexus in the esophagus and is sparse in the submucosal space of the stomach.

Motor innervation of the intestinal crypts and villi originates in the submucous plexus. Neurons in submucosal ganglia send fibers to the myenteric plexus and also receive synaptic input from axons projecting from the myenteric plexus. The interconnections link the two networks into a functionally integrated nervous system.

Sensory Neurons, Interneurons, and Motor Neurons Form the Microcircuits of the ENS

The heuristic model for the ENS is the same as that for the brain and spinal cord (Fig. 26.10). In fact, the ENS has as many neurons as the spinal cord. Like the CNS, sensory neurons, interneurons, and motor neurons in the ENS are connected synaptically for the flow of information from sensory neurons to interneuronal integrative networks to motor neurons to effector systems. The ENS organizes and coordinates the activity of each effector system into meaningful behavior of the integrated organ. Bidirectional communication occurs between the central and enteric nervous systems.

SYNAPTIC TRANSMISSION

Multiple kinds of synaptic transmission occur in the microcircuits of the ENS. Both fast synaptic potentials with durations less than 50 msec and slow synaptic potentials lasting several seconds can be recorded in cell bodies of enteric ganglion cells. These synaptic events may be excitatory postsynaptic potentials (EPSPs) or inhibitory postsynaptic potentials (IPSPs). They can be evoked by experimental stimulation of presynaptic axons, or they may occur spontaneously. Presynaptic inhibitory and facilitatory events can involve axoaxonal, paracrine, or endocrine forms of transmission, and they occur at both fast and slow synaptic connections.

Figure 26.11 shows three kinds of synaptic events that occur in enteric neurons. The synaptic potentials in this illustration were evoked by placing fine stimulating electrodes on interganglionic fiber tracts of the myenteric or submucous plexus and applying electrical shocks to stimulate presynaptic axons and release the neurotransmitter at the synapse.

Enteric Slow EPSPs Have Specific Properties Mediated by Metabotropic Receptors

The slow EPSP in Figure 26.11 was evoked by repetitive shocks (5 Hz) applied to the fiber tract for 5 seconds. Slowly activating depolarization of the membrane potential with a time course lasting longer than 2 minutes after termination of the stimulus is apparent. Repetitive discharge of action potentials reflects enhanced neuronal excitability during the EPSP. The record shows hyperpolarizing after-potentials associated with the first four spikes of the train. As the slow EPSP develops, the hyperpolarizing after-potentials are suppressed and can be seen to recover at the end of the spike train as the EPSP subsides. Suppression of the after-potentials is part of the mechanism of slow synaptic excitation that permits the neuron to convert from low to high states of excitability.

Slow EPSPs are mediated by multiple chemical messengers acting at a variety of different **metabotropic receptors**. Different kinds of receptors, each of which mediates slow synaptic-like responses, are found in varied combinations

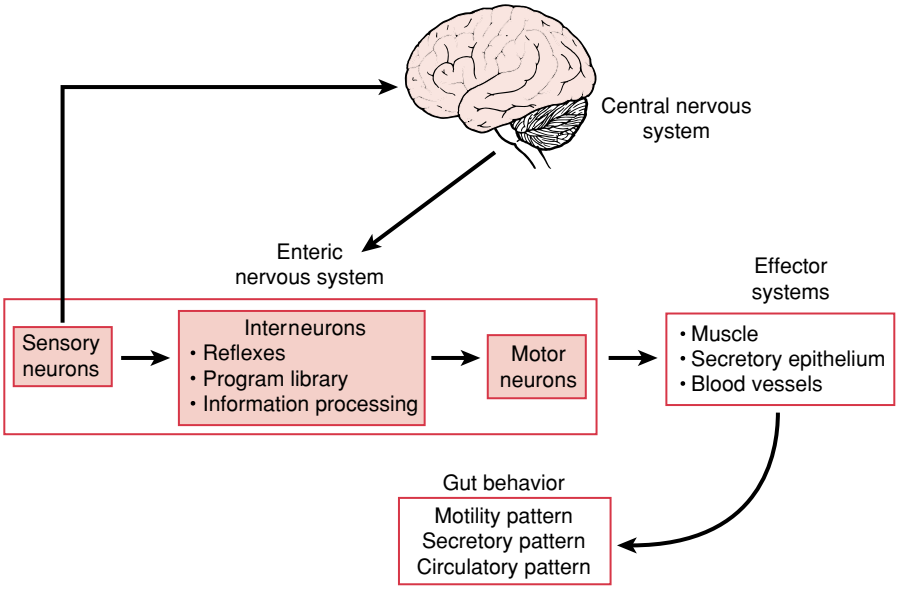

FIGURE 26.10 Enteric nervous system. Sensory neurons, interneurons, and motor neurons are synaptically interconnected to form the microcircuits of the ENS. As in the CNS, information flows from sensory neurons to interneuronal integrative networks to motor neurons to effector systems.

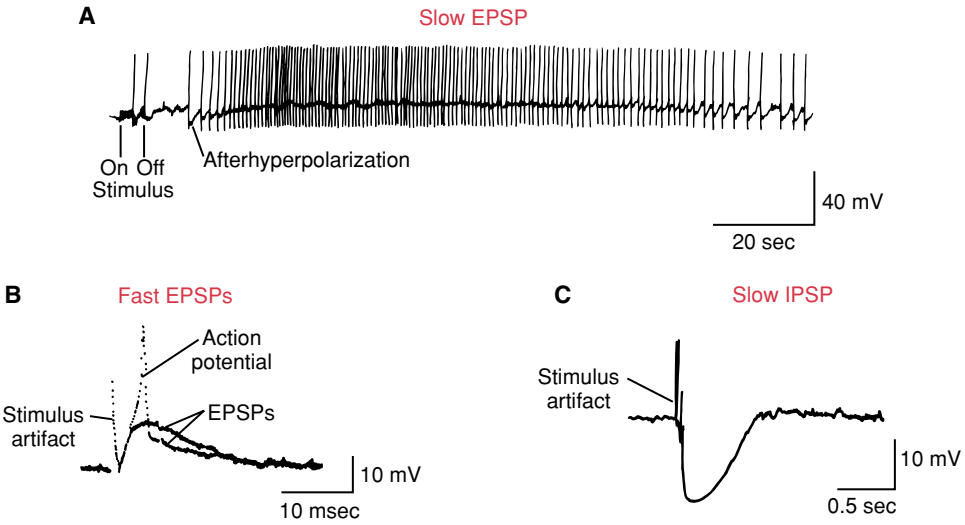

FIGURE 26.11 **Synaptic events in enteric neurons.** Slow EPSPs, fast EPSPs, and slow IPSPs all occur in enteric neurons. **A,** The slow EPSP was evoked by repetitive electrical stimulation of the synaptic input to the neuron. Slowly activating membrane depolarization of the membrane potential continues for almost 2 minutes after termination of the stimulus. During the slow EPSP, repetitive discharge of action potentials reflects enhanced neuronal excitability. **B,** The fast EPSPs were also evoked by single electrical shocks applied to the axon that synapsed with the recorded neuron. Two fast EPSPs were evoked by successive stimuli and are shown as superimposed records. Only one of the EPSPs reached the threshold for the discharge of an action potential. **C,** The slow IPSP was evoked by the stimulation of an inhibitory input to the neuron.

on each individual neuron. A common mode of signal transduction involves receptor activation of adenylyl cyclase and second messenger function of cAMP, which links several different chemical messages to the behavior of a common set of ionic channels responsible for generation of the slow EPSP responses. Serotonin, substance P, and acetylcholine (ACh) are examples of enteric neurotransmitters that evoke slow EPSPs. **Paracrine mediators** released from nonneural cells in the gut also evoke slow EPSP-like responses when released in the vicinity of the ENS. Histamine, for example, is released from mast cells during hypersensitivity reactions to antigens and acts at the histamine H_2-receptor subtype to evoke slow EPSP-like responses in enteric neurons. Subpopulations of enteric neurons in specialized regions of the gut (e.g., the upper duodenum) have receptors for hormones, such as gastrin and cholecystokinin, that also evoke slow EPSP-like responses.

Slow EPSPs Are a Mechanism for Prolonged Neural Excitation or Inhibition of GI Effector Systems

The long-lasting discharge of spikes during the slow EPSP drives the release of neurotransmitter from the neuron's axon for the duration of the spike discharge. This may result in either prolonged excitation or inhibition at neuronal synapses and neuroeffector junctions in the gut wall.

Contractile responses within the musculature and secretory responses within the mucosal epithelium are slow events that span time courses of several seconds from start to completion. The train-like discharge of spikes during slow EPSPs is the neural correlate of long-lasting responses of the gut effectors during physiological stimuli. Figure 26.12 illustrates how the occurrence of slow EPSPs in excitatory motor neurons to the intestinal musculature or the mucosa results in prolonged contraction of the muscle or prolonged secretion from the crypts. The occurrence of slow EPSPs in inhibitory motor neurons to the musculature results in prolonged inhibition of contraction. This response is observed as a decrease in contractile tension.

Enteric Fast EPSPs Have Specific Properties Mediated by Inotropic Receptors

Fast EPSPs (see Fig. 26.11B) are transient depolarizations of membrane potential that have durations of less than 50 msec. They occur in the enteric neural networks throughout the digestive tract. Most fast EPSPs are mediated by ACh acting at **inotropic nicotinic receptors**. Ionotropic receptors are those coupled directly to ion channels. Fast EPSPs function in the rapid transfer and transformation of neurally coded information between the elements of the enteric microcircuits. They are "bytes" of information in the information-processing operations of the logic circuits.

Enteric Slow IPSPs Have Specific Properties Mediated by Multiple Chemical Receptors

The slow IPSP of Figure 26.11 was evoked by stimulation of an interganglionic fiber tract in the submucous plexus. This hyperpolarizing synaptic potential will suppress excitability (decrease the probability of spike discharge), compared with enhanced excitability during the slow EPSP.

Several different chemical messenger substances that may be peptidergic, purinergic, or cholinergic produce slow IPSP-like effects. Enkephalins, dynorphin, and morphine are all slow IPSP mimetics. This action is limited to subpopulations of neurons. Opiate receptors of the μ sub-

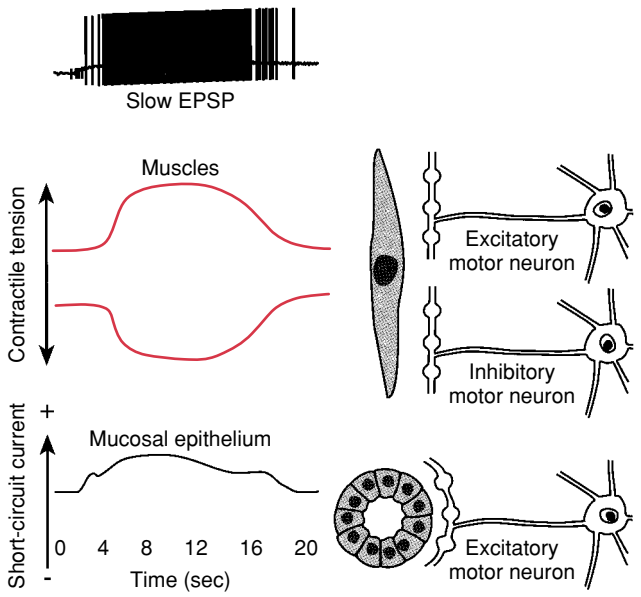

FIGURE 26.12 **The functional significance of slow EPSPs.** Slow EPSPs in excitatory motor neurons to the muscles or mucosal epithelium result in prolonged muscle contraction or mucosal crypt secretion. Stimulation of secretion in experiments is seen as an increase in ion movement (short-circuit current). Slow IPSPs in inhibitory motor neurons to the muscles result in prolonged inhibition of contractile activity, which is observed as decreased contractile tension.

type predominate on myenteric neurons in the small intestine; the receptors on neurons of the intestinal submucous plexus belong to the δ-opiate receptor subtype. The effects of opiates and opioid peptides are blocked by the antagonist naloxone. Addiction to morphine may be seen in enteric neurons, and withdrawal is observed as high-frequency spike discharge upon the addition of naloxone during chronic morphine exposure.

NE acts at β_2-adrenergic receptors to mimic slow IPSPs. This action occurs primarily in neurons of the submucous plexus that are involved in controlling mucosal secretion. The stimulation of sympathetic nerves evokes slow IPSPs that are blocked by β_2-adrenergic receptor antagonists in submucosal neurons. Slow IPSPs in submucosal neurons is a mechanism by which the sympathetic innervation suppresses intestinal secretion during physical exercise when blood is shunted from the splanchnic to systemic circulation.

Galanin is a 29-amino acid polypeptide that simulates slow synaptic inhibition when applied to any of the neurons of the myenteric plexus. The application of adenosine, ATP, or other purinergic analogs also mimics slow IPSPs. The inhibitory action of adenosine is at adenosine α_1 receptors. Inhibitory actions of adenosine α_1 agonists result from the suppression of the enzyme adenylyl cyclase and the reduction in intraneuronal cAMP.

Presynaptic Inhibitory Receptors Are Found at Enteric Synapses and Neuromuscular Junctions

Presynaptic inhibition (Fig. 26.13) is an important function at fast nicotinic synapses, at slow excitatory synapses, and at sympathetic inhibitory synapses in the neural networks of the submucous plexus and at excitatory neuromuscular junctions. It is a specialized form of neurocrine transmission whereby neurotransmitter released from an axon acts at receptors on a second axon to prevent the release of neurotransmitter from the second axon. Presynaptic inhibition, resulting from actions of paracrine or endocrine mediators on receptors at presynaptic release sites, is an alternative mechanism for modulating synaptic transmission.

Presynaptic inhibition in the ENS is mediated by multiple substances and their receptors, with variable combinations of the receptors involved at each release site. The chemical messenger substances may be peptidergic, aminergic, or cholinergic. NE acts at presynaptic β_2-adrenergic receptors to suppress fast EPSPs at nicotinic synapses, slow EPSPs, and cholinergic transmission at neuromuscular junctions. Serotonin suppresses both fast and slow EPSPs in the myenteric plexus. Opiates or opioid peptides suppress some fast EPSPs in the intestinal myenteric plexus.

ACh acts at muscarinic presynaptic receptors to suppress fast EPSPs in the myenteric plexus. This is a form of autoinhibition where ACh released at synapses with nicotinic postsynaptic receptors feeds back onto presynaptic

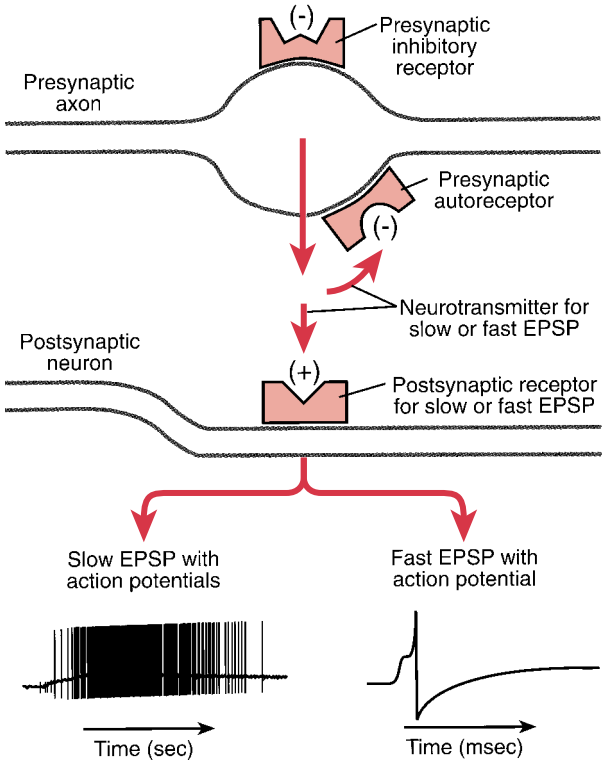

FIGURE 26.13 **Presynaptic inhibition.** Presynaptic inhibitory receptors are found on axons at neurotransmitter release sites for both slow and fast EPSPs. Different neurotransmitters act through the presynaptic inhibitory receptors to suppress axonal release of the transmitters for slow and fast EPSPs. Presynaptic autoreceptors are involved in a special form of presynaptic inhibition whereby the transmitter for slow or fast EPSPs accumulates at the synapse and acts on the autoreceptor to suppress further release of the neurotransmitter. (+), excitatory receptor; (−), inhibitory receptor.

CLINICAL FOCUS BOX 26.2

Chronic Intestinal Pseudoobstruction

Intestinal pseudoobstruction is characterized by symptoms of intestinal obstruction in the absence of a mechanical obstruction. The mechanisms for controlling orderly propulsive motility fail while the intestinal lumen is free from obstruction. This syndrome may result from abnormalities of the muscles or ENS. Its general symptoms of colicky abdominal pain, nausea and vomiting, and abdominal distension simulate mechanical obstruction.

Pseudoobstruction may be associated with degenerative changes in the ENS. Failure of propulsive motility reflects the loss of the neural networks that program and control the organized motility patterns of the intestine. This disorder can occur in varying lengths of intestine or in the entire length of the small intestine. Contractile behavior of the circular muscle is hyperactive but disorganized in the denervated segments. This behavior reflects the absence of inhibitory nervous control of the muscles, which are self-excitable when released from the braking action of enteric inhibitory motor neurons.

Paralytic ileus, another form of pseudoobstruction, is characterized by prolonged motor inhibition. The electrical slow waves are normal, but muscular action potentials and contractions are absent. Prolonged ileus commonly occurs after abdominal surgery. The ileus results from suppression of the synaptic circuits that organize propulsive motility in the intestine. A probable mechanism is presynaptic inhibition and the closure of synaptic gates (see Fig. 26.22).

Continuous discharge of the inhibitory motor neurons accompanies suppression of the motor circuits. This activity of the inhibitory motor neurons prevents the circular muscle from responding to electrical slow waves, which are undisturbed in ileus.

muscarinic receptors to suppress ACh release in negative-feedback fashion (see Fig. 26.13). Histamine acts at histamine H_3 presynaptic receptors to suppress fast EPSPs. Presynaptic inhibition mediated by paracrine or endocrine release of mediators is significant in pathophysiological states, such as inflammation. The release of histamine from intestinal mast cells in response to sensitizing allergens is an important example of paracrine-mediated presynaptic suppression in the enteric neural networks.

Presynaptic inhibition operates normally as a mechanism for selective shutdown or deenergizing of a microcircuit (see Clinical Focus Box 26.2). Preventing transmission among the neural elements of a circuit inactivates the circuit. For example, a major component of shutdown of gut function by the sympathetic nervous system involves the presynaptic inhibitory action of NE at fast nicotinic synapses.

Presynaptic Facilitation Enhances the Synaptic Release of Neurotransmitters and Increases the Amplitude of EPSPs

Presynaptic facilitation refers to an enhancement of synaptic transmission resulting from the actions of chemical mediators at neurotransmitter release sites on enteric axons (Fig. 26.14). The phenomenon is known to occur at fast excitatory synapses in the myenteric plexus of the small intestine and gastric antrum and at noradrenergic inhibitory synapses in the submucous plexus. It is also an action of cholecystokinin in the ENS of the gallbladder. Presynaptic facilitation is evident as an increase in amplitude of fast EPSPs at nicotinic synapses and reflects an enhanced ACh release from axonal release sites. At noradrenergic inhibitory synapses in the submucous plexus, it involves the elevation of cAMP in the postganglionic sympathetic fiber and appears as an enhancement of the slow IPSPs evoked by the stimulation of sympathetic postganglionic fibers.

Therapeutic agents that improve motility in the GI tract are known as **prokinetic drugs**. Presynaptic facilitation is the mechanism of action of some prokinetic drugs. Such drugs act to facilitate nicotinic transmission at the fast excitatory synapses in the enteric neural networks that control propulsive motor function. In both the stomach and the intestine, increases in EPSP amplitudes and rates of rise decrease the probability of transmission failure at the synapses, thereby increasing the speed of information transfer. This mechanism "energizes" the network circuits

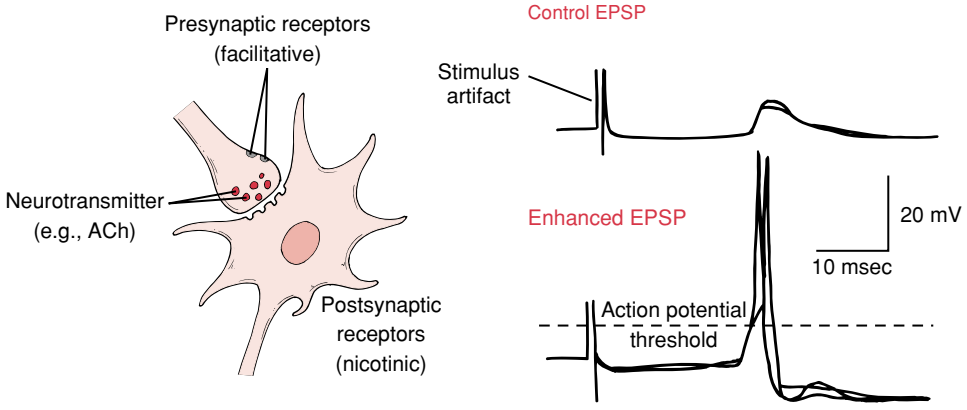

FIGURE 26.14 Presynaptic facilitation. Presynaptic facilitation enhances release of ACh and increases the amplitude of fast EPSPs at a nicotinic synapse.

and enhances propulsive motility (i.e., gastric emptying and intestinal transit).

ENTERIC MOTOR NEURONS

Motor neurons innervate the muscles of the digestive tract and, like spinal motor neurons, are the final pathways for signal transmission from the integrative microcircuits of the minibrain-in-the-gut (see Figs. 26.10 and 26. 15). The motor neuron pool of the ENS consists of excitatory and inhibitory neurons.

The neuromuscular junction is the site where neurotransmitters released from axons of motor neurons act on muscle fibers. Neuromuscular junctions in the digestive tract are simpler structures than the motor endplates of skeletal muscle (see Chapter 8). Most motor axons in the digestive tract do not release neurotransmitter from terminals as such; instead, release is from varicosities that occur along the axons. The neurotransmitter is released from the varicosities all along the axon during propagation of the action potential. Once released, the neurotransmitter diffuses over relatively long distances before reaching the muscle and/or interstitial cells of Cajal. This structural organization is an adaptation for the simultaneous application of a chemical neurotransmitter to a large number of muscle fibers from a small number of motor axons.

Excitatory Motor Neurons Evoke Muscle Contraction and Secretion in the Intestinal Crypts of Lieberkühn

Excitatory motor neurons release neurotransmitters that evoke contraction and increased tension in the GI muscles. ACh and substance P are the principal excitatory neurotransmitters released from enteric motor neurons to the musculature.

Two mechanisms of excitation-contraction coupling are involved in the neural initiation of muscle contraction in the GI tract. Transmitters from excitatory motor axons may trigger muscle contraction by depolarizing the muscle membrane to the threshold for the discharge of action potentials or by the direct release of calcium from intracellular stores. Neurally evoked depolarizations of the muscle membrane potential are called **excitatory junction potentials** (EJPs) (see Fig. 26.15). Direct release of calcium by the neurotransmitter fits the definition of pharmacomechanical coupling. In this case, occupation of receptors on the muscle plasma membrane by the neurotransmitter leads to the release of intracellular calcium, with calcium-triggered contraction independent of any changes in membrane electrical activity.

Cell bodies of the excitatory motor neurons are present in the myenteric plexus. In the small and large intestines, they project in the aboral direction to innervate the circular muscle.

Secretomotor neurons excite secretion of H_2O, electrolytes, and mucus from the crypts of Lieberkühn. ACh and VIP are the principal excitatory neurotransmitters. The cell bodies of secretomotor neurons are in the submucosal plexus. Excitation of these neurons, for example, by histamine release from mast cells during allergic responses, can lead to **neurogenic secretory diarrhea**. Suppression of excitability, for example, by morphine or other opiates, can lead to constipation.

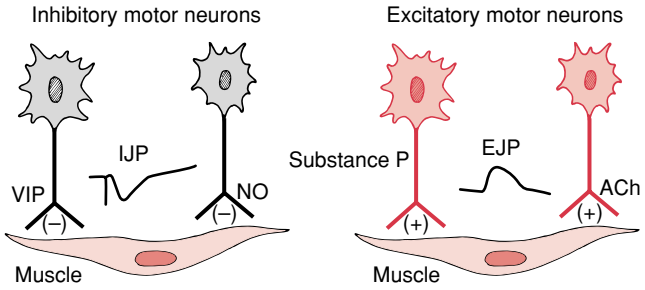

FIGURE 26.15 **Enteric motor neurons.** Motor neurons are final pathways from the ENS to the GI musculature. The motor neuron pool of the ENS consists of both excitatory and inhibitory neurons. Release of VIP or NO from inhibitory motor neurons evokes IJPs. Release of ACh or substance P from excitatory motor neurons evokes EJPs. VIP, vasoactive intestinal peptide; NO, nitric oxide; IJP, inhibitory junction potential; EJP, excitatory junction potential.

Inhibitory Motor Neurons Suppress Muscle Contraction

Inhibitory neurotransmitters released from inhibitory motor neurons activate receptors on the muscle plasma membranes to produce **inhibitory junction potentials** (IJPs) (see Fig. 26.15). IJPs are hyperpolarizing potentials that move the membrane potential away from the threshold for the discharge of action potentials and, thereby, reduce the excitability of the muscle fiber. Hyperpolarization during IJPs prevents depolarization to the action potential threshold by the electrical slow waves and suppresses propagation of action potentials among neighboring muscle fibers within the electrical syncytium.

Early evidence suggested a purine nucleotide, possibly ATP, as the inhibitory transmitter released by enteric inhibitory motor neurons. Consequently, the term *purinergic neuron* temporarily became synonymous with enteric inhibitory motor neuron. The evidence for ATP as the inhibitory transmitter is now combined with evidence for vasoactive intestinal peptide (VIP), pituitary adenylyl cyclase–activating peptide, and nitric oxide (NO) as inhibitory transmitters. Enteric inhibitory motor neurons with VIP and/or NO synthase innervate the circular muscle of the stomach, intestines, gallbladder and the various sphincters. Cell bodies of inhibitory motor neurons are present in the myenteric plexus. In the stomach and small and large intestines, they project in the aboral direction to innervate the circular muscle.

The longitudinal muscle layer of the small intestine does not appear to have inhibitory motor innervation. In contrast to the circular muscle, where inhibitory neural control is essential, enteric neural control of the longitudinal muscle during peristalsis may be exclusively excitatory.

Inhibitory Motor Neurons Control the Myogenic Intestinal Musculature

The need for inhibitory neural control is determined by the specialized physiology of the musculature. As mentioned earlier, the intestinal musculature behaves like a self-excitable electrical syncytium as a result of cell-to-cell communication across gap junctions and the presence of a pacemaker system. Action potentials triggered anywhere in the muscle will spread from muscle fiber to muscle fiber in three dimensions throughout the syncytium, which can be the entire length of the bowel. Action potentials trigger contractions as they spread. A nonneural pacemaker system of electrical slow waves (i.e., interstitial cells of Cajal) accounts for the self-excitable characteristic of the electrical syncytium. In the integrated system, the electrical slow waves are an extrinsic factor to which the circular muscle responds.

Why does the circular muscle fail to respond with action potentials and contractions to all slow-wave cycles? Why don't action potentials and contractions spread in the syncytium throughout the entire length of intestine each time they occur? Answers to these questions lie in the functional significance of enteric inhibitory motor neurons.

Inhibitory Motor Neurons to the Circular Muscle. Figure 26.16A shows the spontaneous discharge of action potentials occurring in bursts, as recorded extracellularly from a neuron in the myenteric plexus of the small intestine. This kind of continuous discharge of action potentials by subsets of intestinal inhibitory motor neurons occurs in all mammals. The result is continuous inhibition of myogenic activity because, in intestinal segments where neuronal discharge in the myenteric plexus is prevalent, muscle action potentials and associated contractile activity are absent or occur only at reduced levels with each electrical slow wave. The continuous release of the inhibitory neurotransmitters VIP and NO can be detected in intestinal preparations in this case. When the inhibitory neuronal discharge is blocked experimentally with tetrodotoxin, every cycle of the electrical slow wave triggers an intense discharge of action potentials. Figure 26.16B shows how phasic contractions, occurring at slow-wave frequency, progressively increase to maximal amplitude during a blockade of inhibitory neural activity after the application of tetrodotoxin in the small intestine. This response coincides with a progressive increase in baseline tension.

Tetrodotoxin is an effective pharmacological tool for demonstrating ongoing inhibition because it selectively blocks neural activity without affecting the muscle. This action is a result of a selective blockade of sodium channels in neurons. The rising phase of the muscle action potentials is caused by an inward calcium current that is unaffected by tetrodotoxin.

As a general rule, any treatment or condition that removes or inactivates inhibitory motor neurons results in tonic contracture and continuous, uncoordinated contractile activity of the circular musculature. Several circumstances that remove the inhibitory neurons are associated with conversion from a hypoirritable condition of the circular muscle to a hyperirritable state. These include the application of local anesthetics, hypoxia from restricted blood flow to an intestinal segment, an autoimmune attack on enteric neurons, congenital absence in Hirschsprung's disease, treatment with opiate drugs, and inhibition of NO synthase (see Clinical Focus Boxes 26.3 and 26.4).

Inhibitory Motor Neurons and the Strength of Contractions Evoked by Electrical Slow Waves. The strength of circular muscle contraction evoked by each slow-wave cycle is a function of the number of inhibitory motor neurons in an active state. The circular muscle in an intestinal segment can respond to the electrical slow waves only when the inhibitory motor neurons are inactivated by inhibitory synaptic input from other neurons in the control circuits. This means that inhibitory neurons determine when the constantly running slow waves initiate a contraction, as well as the strength of the contraction that is initiated by each slow-wave cycle. The strength of each contraction is determined by the proportion of muscle fibers in the population that can respond during a given slow-wave cycle, which, in turn, is determined by the proportion exposed to inhibitory transmitters released by motor neurons. With maximum inhibition, no contractions can occur in response to a slow wave (see Fig.26.4A); contractions of maximum strength occur after all inhibition is removed and all of the muscle fibers in a segment are activated by each slow-wave cycle (see Fig. 26.4B). Contractions between the two extremes are graded in strength according to the number of

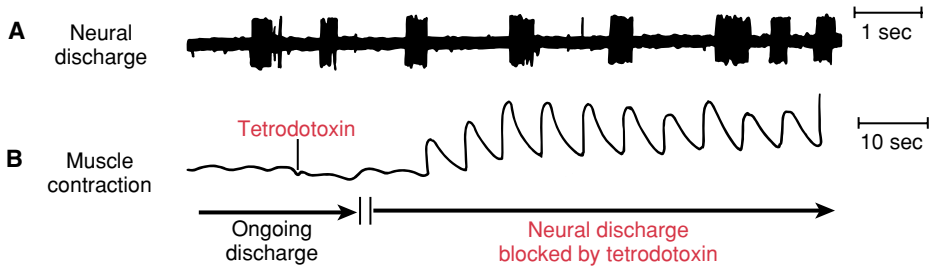

FIGURE 26.16 **Inhibitory motor neurons.** Ongoing firing of a subpopulation of inhibitory motor neurons to the intestinal circular muscle prevents electrical slow waves from triggering the action potentials that trigger contractions. When the inhibitory neural discharge is blocked with tetrodotoxin, every cycle of the electrical slow wave triggers discharge of action potentials and large-amplitude contractions. **A**, Electrical record of ongoing burst-like firing. **B**, Record of muscle contractile activity before and after application of tetrodotoxin.

CLINICAL FOCUS BOX 26.3

Hirschsprung's Disease and Incontinence: Motor Disorders of the Large Intestine and Anorectum

Hirschsprung's disease is a developmental disorder that is present at birth but may not be diagnosed until later childhood. It is characterized by defecation difficulty or failure. The disease is often called **congenital megacolon**, because the proximal colon may become grossly enlarged with impacted feces, or **congenital aganglionosis**, because the ganglia of the ENS fail to develop in the terminal region of the large intestine. Mutations in RET or endothelin genes account for the disease in some patients.

Enteric neurons may be absent in the rectosigmoid region only, in the descending colon, or in the entire colon. The aganglionic region appears constricted as a result of continuous contractile activity of the circular muscle, whereas the normally innervated intestine proximal to the aganglionic segment is distended with feces.

The constricted terminal segment of the large intestine in Hirschsprung's disease presents a functional obstruction to the forward passage of fecal material. Constriction and narrowing of the lumen of the segment reflects uncontrolled myogenic contractile activity in the absence of inhibitory motor neurons

Incontinence is an inappropriate leakage of feces and flatus to a degree that it disables the patient by disrupting routine daily activities. As discussed earlier, the mechanisms for maintaining continence involve the coordinated interactions of several different components. Consequently, sensory malfunction, incompetence of the internal anal sphincter, or disorders of neuromuscular mechanisms of the external sphincter and pelvic floor muscles can be factors in the pathophysiology of incontinence.

Sensory malfunction renders the patient unaware of the filling of the rectum and stimulation of the anorectum, in which case he or she does not perceive the need for voluntary control over the muscular mechanisms of continence. This condition is tested clinically by distending an intrarectal balloon. The healthy subject will perceive the distension with an instilled volume of 15 mL or less, whereas the sensory-deprived patient either will not report any sensation at all or will require much larger volumes before becoming aware of the distension.

Incompetence of the internal anal sphincter is usually related to a surgical or mechanical factor or perianal disease, such as prolapsing hemorrhoids. Disorders of the neuromuscular mechanisms of the external sphincter and pelvic floor muscles may also result from surgical or mechanical trauma, such as during childbirth.

Physiological deficiencies of the skeletal motor mechanisms can be a significant factor in the common occurrence of incontinence in older adults. Whereas the resting tone of the internal anal sphincter does not seem to decrease with age, the strength of contraction of the external anal sphincter does weaken. Moreover, the striated muscles of the external anal sphincter and pelvic floor lose contractile strength with age. This condition occurs in parallel with a deterioration of nervous function, reflected by decreased conduction velocity in fibers of the pelvic nerves. Clinical examination with intra-anal manometry reveals a decreased ability of the patient with disordered voluntary muscle function to increase intra-anal pressure when asked to "squeeze" the intra-anal catheter.

inhibitory motor neurons that are inactivated by the ENS minibrain during each slow wave.

Control by Inhibitory Motor Neurons of the Length of Intestine Occupied by a Contraction and the Direction of Propagation of Contractions. The state of activity of inhibitory motor neurons determines the length of a contracting segment by controlling the distance of spread of action potentials within the three-dimensional electrical geometry of the muscular syncytium (Fig. 26.17). This occurs coincidently with control of contractile strength. Contractions can only occur in segments where ongoing inhibition has been inactivated, while it is prevented in adjacent segments where the inhibitory innervation is ac-

CLINICAL FOCUS BOX 26.4

Dysphagia, Diffuse Spasm, and Achalasia: Motor Disorders of the Esophagus

Failure of peristalsis in the esophageal body or failure of the lower esophageal sphincter to relax will result in **dysphagia** or difficulty in swallowing. Some people show abnormally high pressure waves as peristalsis propagates past the recording ports on manometric catheters. This condition, called **nutcracker esophagus**, is sometimes associated with chest pain that may be experienced as angina-like pain.

In **diffuse spasm**, organized propagation of the peristaltic behavioral complex fails to occur after a swallow. Instead, the act of swallowing results in simultaneous contractions all along the smooth muscle esophagus. On manometric tracings, this response is observed as a synchronous rise in intraluminal pressure at each of the recording sensors.

In **achalasia** of the lower esophageal sphincter, the sphincter fails to relax normally during a swallow. As a result, the ingested material does not enter the stomach and accumulates in the body of the esophagus. This leads to **megaesophagus**, in which distension and gross enlargement of the esophagus are evident. In advanced untreated cases of achalasia, peristalsis does not occur in response to a swallow.

Achalasia is a disorder of inhibitory motor neurons in the lower esophageal sphincter. The number of neurons in the lower esophageal sphincter is reduced, and the levels of the inhibitory neurotransmitter VIP and the enzyme NO synthase are diminished. This degenerative disease results in a loss of the inhibitory mechanisms for relaxing the sphincter with appropriate timing for a successful swallow.

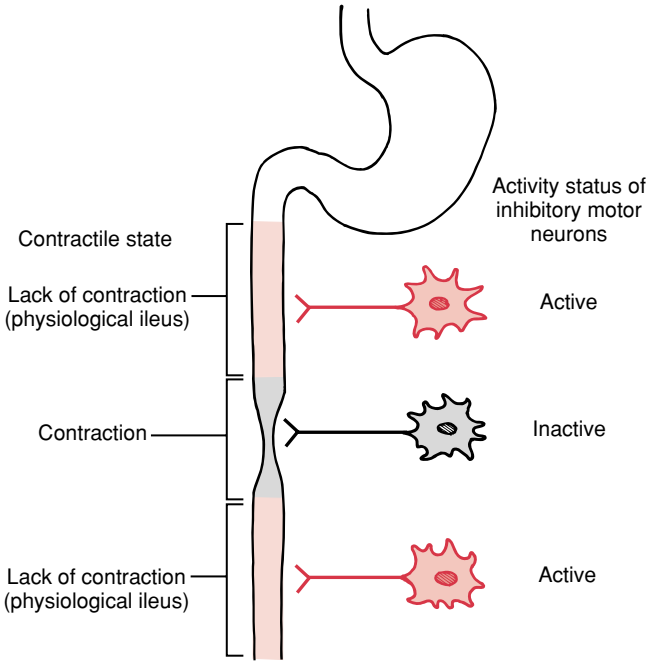

FIGURE 26.17 Inhibitory control of the intestinal musculature. Myogenic contraction occurs in segments of intestine where inhibitory motor neurons are inactive. Physiological ileus occurs in segments of intestine where the inhibitory neurons are actively firing.

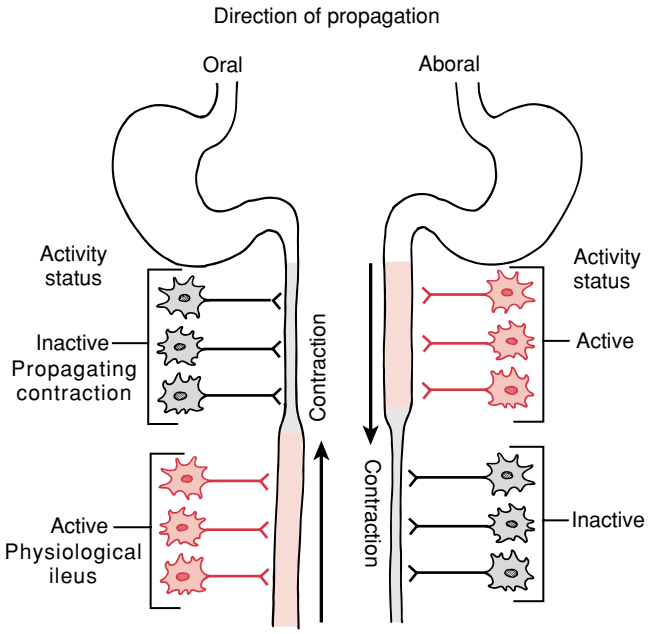

FIGURE 26.18 Inhibitory control of the direction of propagation of contractions. Contractions propagate into intestinal segments where inhibitory motor neurons are inactivated. Sequential inactivation in the oral direction permits oral propagation of contractions. Sequential inactivation in the aboral direction permits aboral propagation.

tive. The oral and aboral boundaries of a contracted segment reflect the transition zone from inactive to active inhibitory motor neurons. This is the mechanism by which the ENS generates short contractile segments during the digestive (mixing) pattern of small intestinal motility and longer contractile segments during propulsive motor patterns, such as "power propulsion" that travels over extended distances along the intestine.

As a result of the functional syncytial properties of the musculature, inhibitory motor neurons are necessary for control of the direction in which contractions travel along the intestine. The directional sequence in which inhibitory motor neurons are inactivated determines whether contractions propagate in the oral or aboral direction (Fig. 26.18). Normally, the neurons are inactivated sequentially in the aboral direction, resulting in contractile activity that propagates and moves the intraluminal contents distally. During vomiting, the integrative microcircuits of the ENS inactivate inhibitory motor neurons in a reverse sequence, allowing small intestinal propulsion to travel in the oral direction and propel the contents toward the stomach (see Clinical Focus Box 26.5).

The Inhibitory Innervation of GI Sphincters Is Transiently Activated for Timed Opening and the Passage of Luminal Contents

The circular muscle of sphincters remains tonically contracted to occlude the lumen and prevent the passage of contents between adjacent compartments, such as between stomach and esophagus. Inhibitory motor neurons are normally inactive in the sphincters and are switched on with timing appropriate to coordinate the opening of the sphincter with physiological events in adjacent regions

CLINICAL FOCUS BOX 26.5

Emesis

During **emesis** (vomiting), powerful propulsive peristalsis starts in the midjejunum and travels to the stomach. As a result, the small intestinal contents are propelled rapidly and continuously toward the stomach. As the propulsive complex advances, the gastroduodenal junction and the stomach wall relax, allowing passage of the intestinal contents into the stomach. At the same time, the longitudinal muscle of the esophagus and the gastroesophageal junction dilates. The overall result is the formation of a funnel-like cavity that allows the free flow of gastric contents into the esophagus as intra-abdominal pressure is increased by contraction of the diaphragm and abdominal muscles during retching.

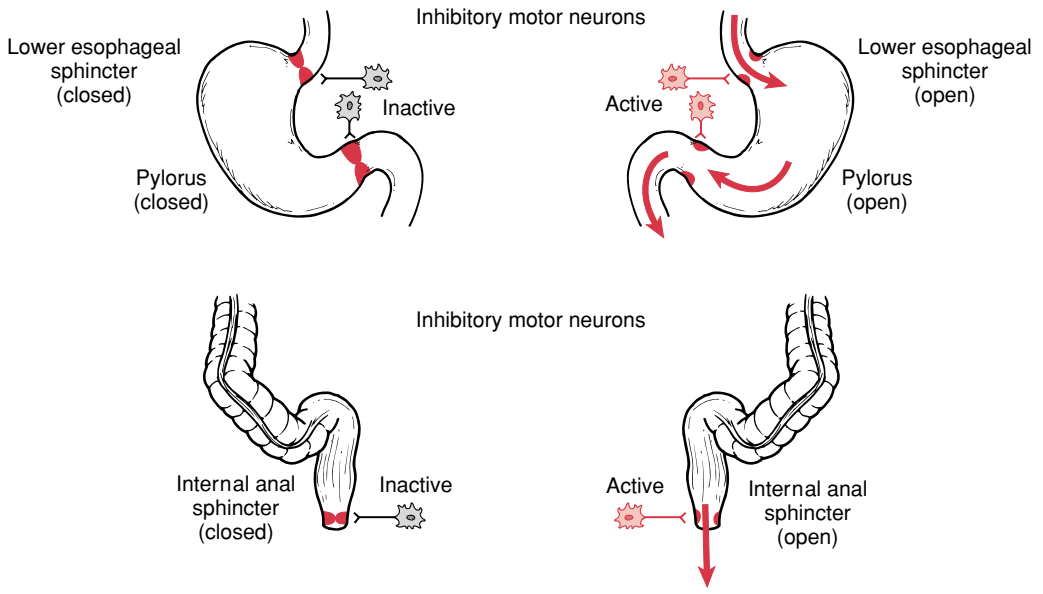

FIGURE 26.19 Inhibitory control of sphincters. GI sphincters are closed when their inhibitory innervation is inactive. The sphincters are opened by active firing of the inhibitory motor neurons.

(Fig. 26.19). When this occurs, the inhibitory neurotransmitter relaxes the ongoing muscle contraction in the sphincteric muscle and prevents excitation and contraction in the adjacent muscle from spreading into and closing the sphincter.

BASIC PATTERNS OF GI MOTILITY

Motility in the digestive tract accounts for the propulsion, mixing, and reservoir functions necessary for the orderly processing of ingested food and the elimination of waste products. **Propulsion** is the controlled movement of ingested foods, liquids, GI secretions, and sloughed cells from the mucosa through the digestive tract. It moves the food from the stomach into the small intestine and along the small intestine, with appropriate timing for efficient digestion and absorption. Propulsive forces move undigested material into the large intestine and eliminate waste through defecation. **Trituration**, the crushing and grinding of ingested food by the stomach, decreases particle size, increasing the surface area for action by digestive enzymes in the small intestine. **Mixing movements** blend pancreatic, biliary, and intestinal secretions with nutrients in the small intestine and bring products of digestion into contact with the absorptive surfaces of the mucosa. **Reservoir functions** are performed by the stomach and colon. The body of the stomach stores ingested food and exerts steady mechanical forces that are important determinants of gastric emptying. The colon holds material during the time required for the absorption of excess water and stores the residual material until defecation is convenient.

Each of the specialized organs along the digestive tract exhibits a variety of motility patterns. These patterns differ depending on factors such as time after a meal, awake or sleeping state, and the presence of disease. Motor patterns that accomplish propulsion in the esophagus and small and large intestines are derived from a basic peristaltic reflex circuit in the ENS.

Peristalsis Is a Stereotyped Propulsive Motor Reflex

Peristalsis is the organized propulsion of material over variable distances within the intestinal lumen. The muscle layers of the intestine behave in a stereotypical pattern during peristaltic propulsion (Fig. 26.20). This pattern is determined by the integrated circuits of the ENS. During peristalsis, the longitudinal muscle layer in the segment ahead of the advancing intraluminal contents contracts while the circular muscle layer simultaneously relaxes. The intestinal tube behaves like a cylinder with constant surface area. The shortening of the longitudinal axis of the cylinder is accompanied by a widening of the cross-sectional diameter. The simultaneous shortening of the longitudinal muscle and relaxation of the circular muscle results in expansion of the lumen, which prepares a **receiving segment** for the forward-moving intraluminal contents during peristalsis.

The second component of stereotyped peristaltic behavior is contraction of the circular muscle in the segment behind the advancing intraluminal contents. The longitudi-

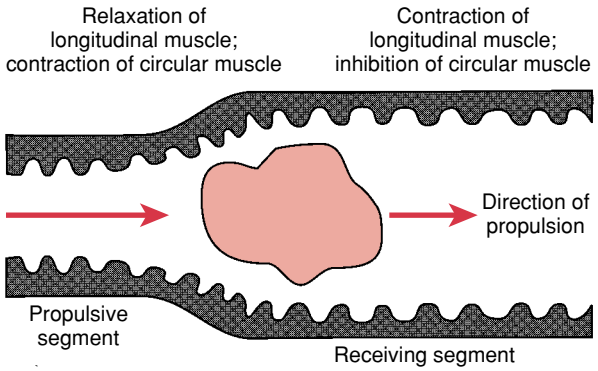

FIGURE 26.20 Peristaltic propulsion. Peristaltic propulsion involves formation of a propulsive and a receiving segment, mediated by reflex control of the intestinal musculature.

nal muscle layer in this segment relaxes simultaneously with contraction of the circular muscle, resulting in the conversion of this region to a **propulsive segment** that propels the luminal contents ahead, into the receiving segment. Intestinal segments ahead of the advancing front become receiving segments and then propulsive segments in succession as the peristaltic complex of propulsive and receiving segments travels along the intestine.

A Polysynaptic Reflex Circuit Determines Peristalsis

The peristaltic reflex (i.e., the formation of propulsive and receiving segments) can be triggered experimentally by distending the intestinal wall or by "brushing" the mucosa. Involvement of the reflex in the neural organization of peristaltic propulsion is similar to the reflexive behavior mediated by the CNS for somatic movements of skeletal muscles. Reflex circuits with fixed connections in the spinal cord automatically reproduce a stereotypical pattern of behavior each time the circuit is activated (e.g., the myotatic reflex; see Chapter 5). Connections for the reflex remain, irrespective of the destruction of adjacent regions of the spinal cord. The peristaltic reflex circuit is similar, but the basic circuit is repeated along and around the intestine. Just as the monosynaptic reflex circuit of the spinal cord is the terminal circuit for the production of almost all skeletal muscle movements (see Chapter 5), the same basic peristaltic circuitry underlies all patterns of propulsive motility. Blocks of the same basic circuit are connected in series along the length of the intestine and repeated in parallel around the circumference. The basic peristaltic circuit consists of synaptic connections between sensory neurons, interneurons, and motor neurons. Distances over which peristaltic propulsion travels are determined by the number of blocks recruited in sequence along the bowel. Synaptic gates between blocks of the basic circuit determine whether or not recruitment occurs for the next circuit in the sequence.

The basic circuit for peristalsis is repeated serially along the intestine (Fig. 26.21). Synaptic gates connect the blocks of basic circuitry and provide a mechanism for controlling the distance over which the peristaltic behavioral complex travels. When the gates are opened, neural signals pass between successive blocks of the basic circuit, resulting in propagation of the peristaltic event over extended distances. Long-distance propulsion is prevented when all gates are closed (see Clinical Focus Box 26.1).

Presynaptic mechanisms are involved in gating the transfer of signals between sequentially positioned blocks of peristaltic reflex circuitry. Synapses between the neurons that carry excitatory signals to the next block of circuitry function as gating points for controlling the distance over which peristaltic propulsion travels (Fig. 26.22). Messenger substances that act presynaptically to inhibit the release of transmitter at the excitatory synapses close the gates to the transfer of information, determining the distance of propagation. Drugs that facilitate the release of neurotransmitters at the excitatory synapses (e.g., cisapride) have therapeutic application by increasing the probability of information transfer at the synaptic gates, enhancing propulsive motility.

Peristaltic Propulsion in the Upper Small Intestine During Vomiting. The enteric neural circuits can be programmed to produce peristaltic propulsion in either direction along the intestine. If forward passage of the intraluminal contents is impeded in the large intestine, reverse peristalsis propels the bolus over a variable distance away from the obstructed segment. **Retroperistalsis** then stops and forward peristalsis moves the bolus again in the direction of the obstruction. During the act of vomiting, retroperistalsis occurs in the small intestine. In this case, as well as in the obstructed intestine, the coordinated muscle behavior of peristalsis is the same except that it is organized by the nervous system to travel in the oral direction (see Clinical Focus Box 26.5).

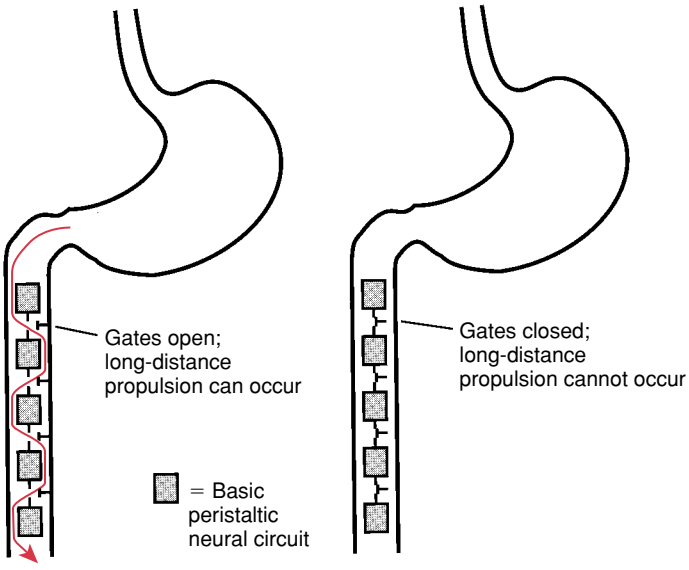

FIGURE 26.21 Operation of synaptic gates between basic blocks of peristaltic circuitry. Opening the gates between successive blocks of the basic circuit results in extended propagation of the propulsive event. Long-distance propulsion is prevented when all gates are closed.

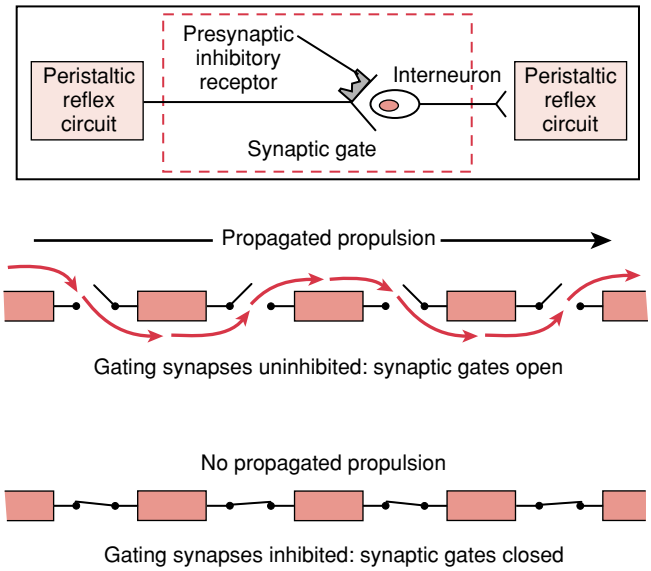

FIGURE 26.22 **Control of the distance and direction of peristaltic propulsion.** Synaptic gates determine distance and direction of propagation of propulsive motility. Presynaptic inhibitory receptors determine the open and closed states of the gates. When the gating synapses are uninhibited (i.e., no presynaptic inhibition), propagation proceeds in the direction in which the gates are open. The gates are closed by activation of presynaptic inhibitory receptors.

Ileus Reflects the Operation of a Program in the ENS

Physiological ileus is the absence of motility in the small and large intestine. It is a fundamental behavioral state of the intestine in which quiescence of motor function is neurally programmed. The state of physiological ileus disappears after ablation (removal) of the ENS. When enteric neural functions are destroyed by pathological processes, disorganized and nonpropulsive contractile behavior occurs continuously because of the myogenic electrical properties (see Clinical Focus Box 26.2).

Quiescence of the intestinal circular muscle is believed to reflect the operation of a neural program in which all the gates within and between basic peristaltic circuits are held shut (see Fig. 26.22). In this state, the inhibitory motor neurons remain in a continuously active state and responsiveness of the circular muscle to the electrical slow waves is suppressed. This normal condition, physiological ileus, is in effect for varying periods of time in different intestinal regions, depending on such factors as the time after a meal.

The normal state of motor quiescence becomes pathological when the gates for the particular motor patterns are rendered inoperative for abnormally long periods. In this state of paralytic ileus, the basic circuits are locked in an inoperable state while unremitting activity of the inhibitory motor neurons suppresses myogenic activity (see Clinical Focus Box 26.1).

Sphincters Prevent the Reflux of Luminal Contents

Smooth muscle sphincters are found at the gastroesophageal junction, gastroduodenal junction, opening of the bile duct, ileocolonic junction, and termination of the large intestine in the anus. They consist of rings of smooth muscle that remain in a continuous state of contraction. The effect of the tonic contractile state is to occlude the lumen in a region that separates two specialized compartments. With the exception of the internal anal sphincter, sphincters function to prevent the backward movement of intraluminal contents.

The **lower esophageal sphincter** prevents the reflux of gastric acid into the esophagus. Incompetence results in chronic exposure of the esophageal mucosa to acid, which can lead to heartburn and dysplastic changes that may become cancerous. The **gastroduodenal sphincter** or **pyloric sphincter** prevents the excessive reflux of duodenal contents into the stomach. Incompetence of this sphincter can result in the reflux of bile acids from the duodenum. Bile acids are damaging to the protective barrier in the gastric mucosa; prolonged exposure can lead to gastric ulcers.

The **sphincter of Oddi** surrounds the opening of the bile duct as it enters the duodenum. It acts to prevent the reflux of intestinal contents into the ducts leading from the liver, gallbladder, and pancreas. Failure of this sphincter to open leads to distension, which is associated with the biliary tract pain that is felt in the right upper abdominal quadrant.

The **ileocolonic sphincter** prevents the reflux of colonic contents into the ileum. Incompetence can allow the entry of bacteria into the ileum from the colon, which may result in bacterial overgrowth. Bacterial counts are normally low in the small intestine. The **internal anal sphincter** prevents the uncontrolled movement of intraluminal contents through the anus.

The ongoing contractile tone in the smooth muscle sphincters is generated by **myogenic mechanisms**. The contractile state is an inherent property of the muscle and independent of the nervous system. Transient relaxation of the sphincter to permit the forward passage of material is accomplished by activation of inhibitory motor neurons (see Fig. 26.19). **Achalasia** is a pathological state in which smooth muscle sphincters fail to relax. Loss of the ENS and its complement of inhibitory motor neurons in the sphincters can underlie achalasia (see Clinical Focus Box 26.4).

MOTILITY IN THE ESOPHAGUS

The esophagus is a conduit for the transport of food from the pharynx to the stomach. Transport is accomplished by peristalsis, with propulsive and receiving segments produced by neurally organized contractile behavior of the longitudinal and circular muscle layers.

The esophagus is divided into three functionally distinct regions: the upper esophageal sphincter, the esophageal body, and the lower esophageal sphincter. Motor behavior of the esophagus involves striated muscle in the upper esophagus and smooth muscle in the lower esophagus.

Peristalsis and Relaxation of the Lower Esophageal Sphincter Are the Main Motility Events in the Esophagus

Esophageal peristalsis may occur as primary peristalsis or secondary peristalsis. **Primary peristalsis** is initiated by the voluntary act of swallowing, irrespective of the presence of food in the mouth. **Secondary peristalsis** occurs when the primary peristaltic event fails to clear the bolus from the body of the esophagus. It is initiated by activation of mechanoreceptors and can be evoked experimentally by distending a balloon in the esophagus.

When not involved in the act of swallowing, the muscles of the esophageal body are relaxed and the lower esophageal sphincter is tonically contracted. In contrast to the intestine, the relaxed state of the esophageal body is not produced by the ongoing activity of inhibitory motor neurons. Excitability of the muscle is low and there are no electrical slow waves to trigger contractions. The activation of excitatory motor neurons rather than myogenic mechanisms accounts for the coordinated contractions of the esophagus during a swallow.

Manometric Catheters Monitor Esophageal Motility and Diagnose Disordered Motility

Esophageal motor disorders are diagnosed clinically with **manometric catheters**, multiple small catheters fused into a single assembly with pressure sensors positioned at various levels (see Clinical Focus Box 26.4). They are placed into the esophagus via the nasal cavity. Manometric catheters record a distinctive pattern of motor behavior following a swallow (Fig. 26.23). At the onset of the swallow, the lower esophageal sphincter relaxes. This is recorded as a fall in pressure in the sphincter that lasts throughout the swallow and until the esophagus empties its contents into the stomach. Signals for relaxation of the lower esophageal sphincter are transmitted by the vagus nerves. The pressure-sensing ports along the catheter assembly show transient increases in pressure as the segment with the sensing port becomes the propulsive segment of the peristaltic pattern as it passes on its way to the stomach.

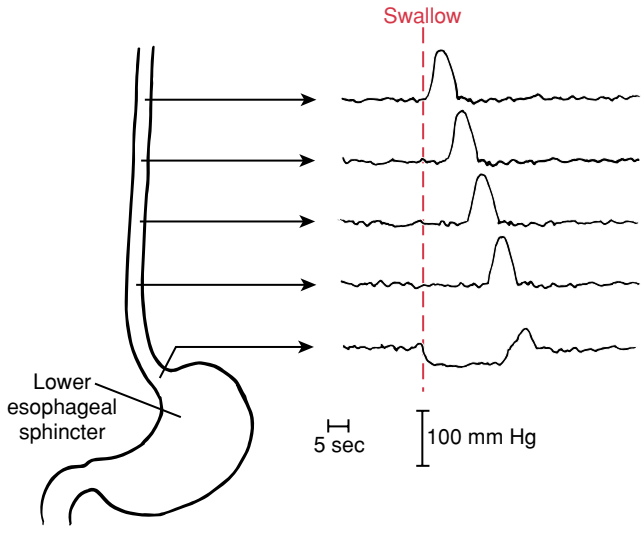

FIGURE 26.23 Manometric recordings of pressure events in the esophageal body and lower esophageal sphincter following a swallow. The propulsive segment of the peristaltic behavioral complex produces a positive pressure wave at each recording site in succession as it travels down the esophagus. Pressure falls in the lower esophageal sphincter shortly after the onset of the swallow, and the sphincter remains relaxed until the propulsive complex has transported the swallowed material into the stomach.

GASTRIC MOTILITY

The functional regions of the stomach do not correspond to the anatomic regions. The anatomic regions are the **fundus**, **corpus (body)**, **antrum**, and **pylorus** (Fig. 26.24). Functionally, the stomach is divided into a proximal **reservoir** and distal **antral pump** on the basis of distinct differences in motility between the two regions. The reservoir consists of the fundus and approximately one third of the corpus; the antral pump includes the caudal two thirds of the corpus, the antrum, and the pylorus.

Differences in motility between the reservoir and antral pump reflect adaptations for different functions. The muscles of the proximal stomach are adapted for maintaining continuous contractile tone (tonic contraction) and do not contract phasically. By contrast, the muscles of the antral pump contract phasically. The spread of phasic contractions in the region of the antral pump propels the gastric contents toward the gastroduodenal junction. Strong propulsive waves of this nature do not occur in the proximal stomach.

Motor Behavior of the Antral Pump Is Initiated by a Dominant Pacemaker

Gastric action potentials determine the duration and strength of the phasic contractions of the antral pump and are initiated by a dominant pacemaker located in the cor-

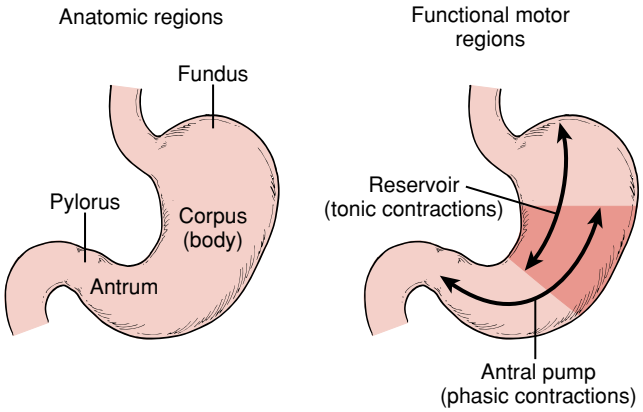

FIGURE 26.24 The stomach: three anatomic and two functional regions. The reservoir is specialized for receiving and storing a meal. The musculature in the region of the antral pump exhibits phasic contractions that function in the mixing and trituration of the gastric contents. No distinctly identifiable boundary exists between the reservoir and antral pump.

pus distal to the midregion. Once started at the pacemaker site, the action potentials propagate rapidly around the gastric circumference and trigger a ring-like contraction. The action potentials and associated ring-like contraction then travel more slowly toward the gastroduodenal junction.

Electrical syncytial properties of the gastric musculature account for the propagation of the action potentials from the pacemaker site to the gastroduodenal junction. The pacemaker region in humans generates action potentials and associated antral contractions at a frequency of 3/min. The gastric action potential lasts about 5 seconds and has a rising phase (depolarization), a plateau phase, and a falling phase (repolarization) (see Fig. 26.2).

The Gastric Action Potential Triggers Two Kinds of Contractions

The gastric action potential is responsible for two components of the propulsive contractile behavior in the antral pump. A **leading contraction**, with a relatively constant amplitude, is associated with the rising phase of the action potential, and a **trailing contraction**, of variable amplitude, is associated with the plateau phase (Fig. 26.25). Gastric action potentials are generated continuously by the pacemaker, but they do not trigger a trailing contraction when the plateau phase is reduced below threshold voltage. Trailing contractions appear when the plateau phase is above threshold. They increase in strength in direct relation to increases in the amplitude of the plateau potential above threshold.

The leading contractions produced by the rising phase of the gastric action potential have negligible amplitude as they propagate to the pylorus. As the rising phase reaches the terminal antrum and spreads into the pylorus, contraction of the pyloric muscle closes the orifice between the stomach and duodenum. The trailing contraction follows the leading contraction by a few seconds. As the trailing contraction approaches the closed pylorus, the gastric contents are forced into an antral compartment of ever-decreasing volume and progressively increasing pressure. This results in jet-like **retropulsion** through the orifice formed by the trailing contraction (Fig. 26.26). Trituration and reduction in particle size occur as the material is forcibly retropelled through the advancing orifice and back into the gastric reservoir to await the next propulsive cycle. Repetition at 3 cycles/min reduces particle size to the 1- to 7-mm range that is necessary before a particle can be emptied into the duodenum during the digestive phase of gastric motility.

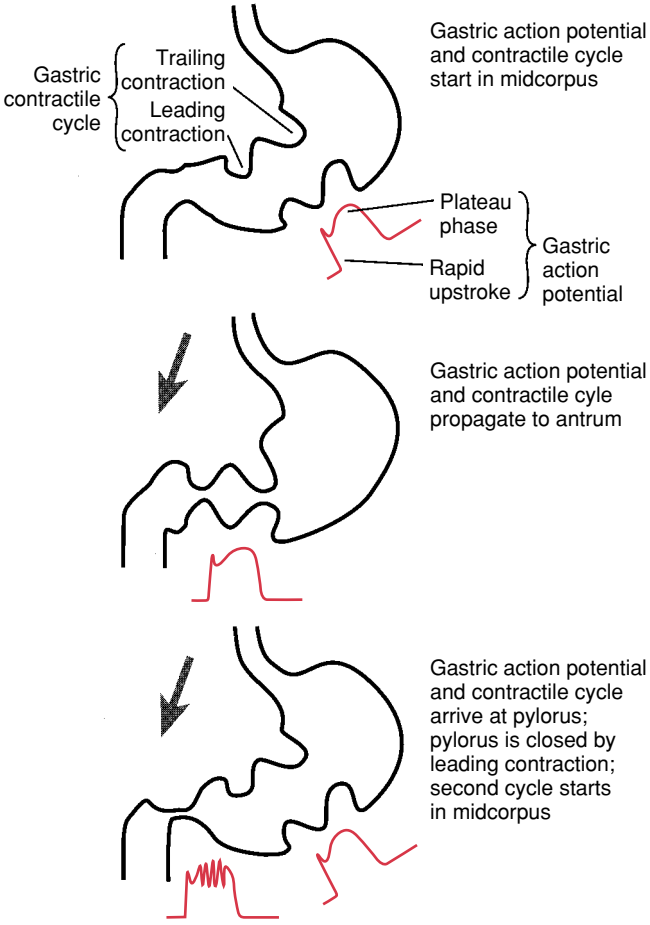

FIGURE 26.25 **Contractile cycle of the antral pump.** The rising phase of the gastric action potential accounts for the leading contraction that propagates toward the pylorus during one contractile cycle. The plateau phase accounts for the trailing contraction of the cycle. (Modified from Szurszewski JH. Electrical basis for gastrointestinal motility. In: Johnson LR, Christensen J, Jackson M, et al., eds. Physiology of the Gastrointestinal Tract. 2nd Ed. New York: Raven, 1987;383–422.)

Enteric Neurons Determine the Minute-to-Minute Strength of the Trailing Antral Contraction

The action potentials of the distal stomach are **myogenic** (i.e., an inherent property of the muscle) and occur in the absence of any neurotransmitters or other chemical messengers. The myogenic characteristics of the action potential are modulated by motor neurons in the gastric ENS. Neurotransmitters primarily affect the amplitude of the plateau phase of the action potential and, thereby, control the strength of the contractile event triggered by the plateau phase. Neurotransmitters, such as ACh from excitatory motor neurons, increase the amplitude of the plateau

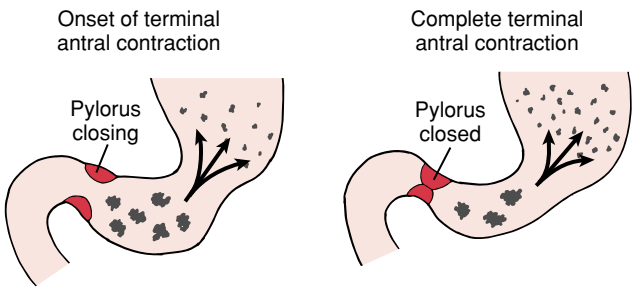

FIGURE 26.26 **Gastric retropulsion.** Jet-like retropulsion through the orifice of the antral contraction triturates solid particles in the stomach. The force for retropulsion is increased pressure in the terminal antrum as the trailing antral contraction approaches the closed pylorus.

phase and of the contraction initiated by the plateau. Inhibitory neurotransmitters, such as NE and VIP, decrease the amplitude of the plateau and the strength of the associated contraction.

The magnitude of the effects of neurotransmitters increases with increasing concentration of the transmitter substance at the gastric musculature. Higher frequencies of action potential discharged by motor neurons release greater amounts of neurotransmitter. In this way, motor neurons determine, through the actions of their neurotransmitters on the plateau phase, whether the trailing contraction of the propulsive complex of the distal stomach occurs. With sufficient release of transmitter, the plateau exceeds the threshold for contraction. Beyond threshold, the strength of contraction is determined by the amount of neurotransmitter released and present at receptors on the muscles.

The action potentials in the terminal antrum and pylorus differ somewhat in configuration from those in the more proximal regions. The principal difference is the occurrence of spike potentials on the plateau phase (see Fig. 26.25), which trigger short-duration phasic contractions superimposed on the phasic contraction associated with the plateau. These may contribute to the sphincteric function of the pylorus in preventing a reflux of duodenal contents back into the stomach.

Neural Control of Muscular Tone Determines Minute-to-Minute Volume and Pressure in the Gastric Reservoir

The gastric reservoir has two primary functions. One is to accommodate the arrival of a meal, without a significant increase in intragastric pressure and distension of the gastric wall. Failure of this mechanism can lead to the uncomfortable sensations of bloating, epigastric pain, and nausea. The second function is to maintain a constant compressive force on the contents of the reservoir. This pushes the contents into motor activity of 3 cycles/min for the antral pump. Drugs that relax the musculature of the gastric reservoir neutralize this function and suppress gastric emptying.

The musculature of the gastric reservoir is innervated by both excitatory and inhibitory motor neurons of the ENS. The motor neurons are controlled by the efferent vagus nerves and intramural microcircuits of the ENS. They function to adjust the volume and pressure of the reservoir to the amount of solid and/or liquid present while maintaining constant compressive forces on the contents. Continuous adjustments in the volume and pressure within the reservoir are required during both the ingestion and the emptying of a meal.

Increased activity of excitatory motor neurons, in coordination with decreased activity of inhibitory motor neurons, results in increased contractile tone in the reservoir, a decrease in its volume, and an increase in intraluminal pressure (Fig. 26.27). Increased activity of inhibitory motor neurons in coordination with decreased activity of excitatory motor neurons results in decreased contractile tone in the reservoir, expansion of its volume, and a decrease in intraluminal pressure.

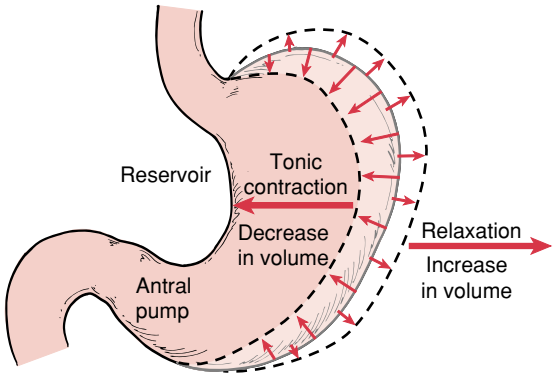

FIGURE 26.27 **Muscular tone in the gastric reservoir.** Tonic contraction of the musculature decreases the volume and exerts pressure on the contents. Tonic relaxation of the musculature expands the volume of the gastric reservoir. Neural mechanisms of feedback control determine intramural contractile tone in the reservoir.

Three Kinds of Relaxation Occur in the Gastric Reservoir

Neurally mediated decreases in tonic contracture of the musculature are responsible for relaxation in the gastric reservoir (i.e., increased volume). Three kinds of relaxation are recognized. **Receptive relaxation** is initiated by the act of swallowing. It is a reflex triggered by stimulation of mechanoreceptors in the pharynx followed by transmission over afferents to the dorsal vagal complex and activation of efferent vagal fibers to inhibitory motor neurons in the gastric ENS. **Adaptive relaxation** is triggered by distension of the gastric reservoir. It is a vago-vagal reflex triggered by stretch receptors in the gastric wall, transmission over vagal afferents to the dorsal vagal complex, and efferent vagal

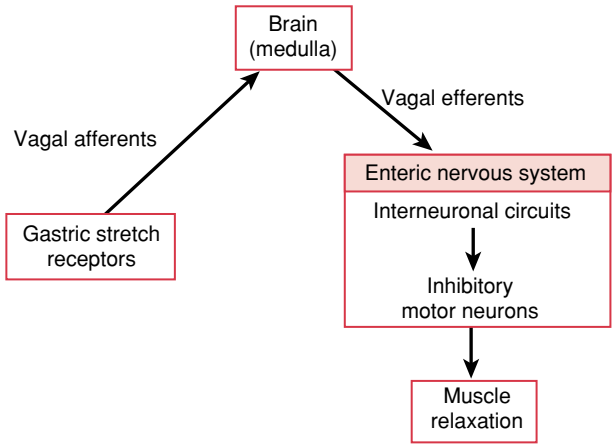

FIGURE 26.28 **Adaptive relaxation in the gastric reservoir.** Adaptive relaxation is a vago-vagal reflex in which information from gastric stretch receptors is the afferent component and outflow from the medullary region of the brain is the efferent component. Vagal efferents transmit to the ENS, which controls the activity of inhibitory motor neurons that relaxes contractile tone in the reservoir.

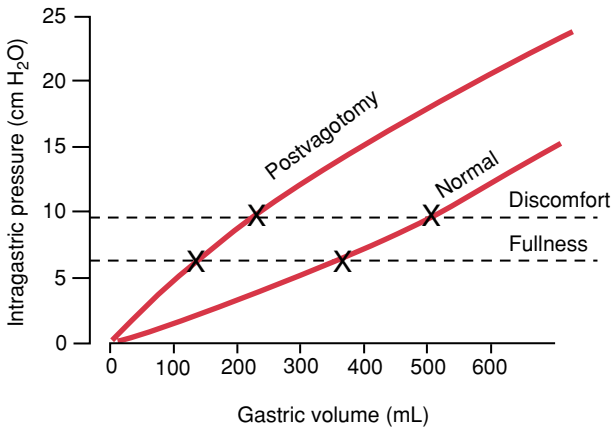

FIGURE 26.29 **Loss of adaptive relaxation following a vagotomy.** A loss of adaptive relaxation in the gastric reservoir is associated with a lowered threshold for sensations of fullness and epigastric pain.

fibers to inhibitory motor neurons in the gastric ENS (Fig. 26.28). **Feedback relaxation** is triggered by the presence of nutrients in the small intestine. It can involve both local reflex connections between receptors in the small intestine and the gastric ENS or hormones that are released from endocrine cells in the small intestine and transported by the blood to signal the gastric ENS.

Adaptive relaxation is lost in patients who have undergone a vagotomy as a treatment for gastric acid disease (e.g., peptic ulcer). Following a vagotomy, increased tone in the musculature of the reservoir decreases the wall compliance, which, in turn, affects the responses of gastric stretch receptors to distension of the reservoir. Pressure-volume curves before and after a vagotomy reflect the decrease in compliance of the gastric wall (Fig. 26.29). The loss of adaptive relaxation after a vagotomy is associated with a lowered threshold for sensations of fullness and pain. This response is explained by increased stimulation of the gastric mechanoreceptors that sense distension of the gastric wall. These effects of vagotomy may explain disordered gastric sensations in diseases with a component of vagus nerve pathology (e.g., autonomic neuropathy of diabetes mellitus) (see Clinical Focus Box 26.1).

The Rate of Gastric Emptying Is Determined by the Kind of Meal and Conditions in the Duodenum

In addition to storage in the reservoir and mixing and grinding by the antral pump, an important function of gastric motility is the orderly delivery of the gastric chyme to the duodenum at a rate that does not overload the digestive and absorptive functions of the small intestine (see Clinical Focus Box 26.1). The rate of gastric emptying is adjusted by neural control mechanisms to compensate for variations in the volume, composition, and physical state of the gastric contents.

The volume of liquid in the stomach is one of the important determinants of gastric emptying. The rate of emptying of isotonic noncaloric liquids (e.g., H_2O) is proportional to the initial volume in the reservoir. The larger the initial volume, the more rapid the emptying.

With a mixed meal in the stomach, liquids empty faster than solids. If an experimental meal consisting of solid particles of various sizes suspended in water is instilled in the stomach, emptying of the particles lags behind emptying of the liquid (Fig. 26.30). With digestible particles (e.g., studies with isotopically labeled chunks of liver), the **lag phase** is the time required for the grinding action of the antral pump to reduce the particle size. If the particles are plastic spheres of various sizes, the smallest spheres are emptied first; however, spheres up to 7 mm in diameter empty at a slow but steady rate when digestible food is in the stomach. The selective emptying of smaller particles first is referred to as the **sieving action** of the distal stomach. Inert spheres larger than 7 mm in diameter are not emptied while food is in the stomach; they empty at the start of the first migrating motor complex as the digestive tract enters the interdigestive state.

Osmolality, acidity, and caloric content of the gastric chyme are major determinants of the rate of gastric emptying. Hypotonic and hypertonic liquids empty more slowly than isotonic liquids. The rate of gastric emptying decreases as the acidity of the gastric contents increases. Meals with a high caloric content empty from the stomach at a slower rate than meals with a low caloric content. The mechanisms of control of gastric emptying keep the rate of delivery of calories to the small intestine within a narrow range, regardless of whether the calories are presented as carbohydrate, protein, fat, or a mixture. Of all of these, fat is emptied the most slowly, or stated conversely, fat is the most potent inhibitor of gastric emptying. Part of the inhibition of gastric emptying by fats may involve the release of the hormone cholecystokinin, which itself is a potent inhibitor of gastric emptying.

The intraluminal milieu of the small intestine is extremely different from that of the stomach (see Chapter

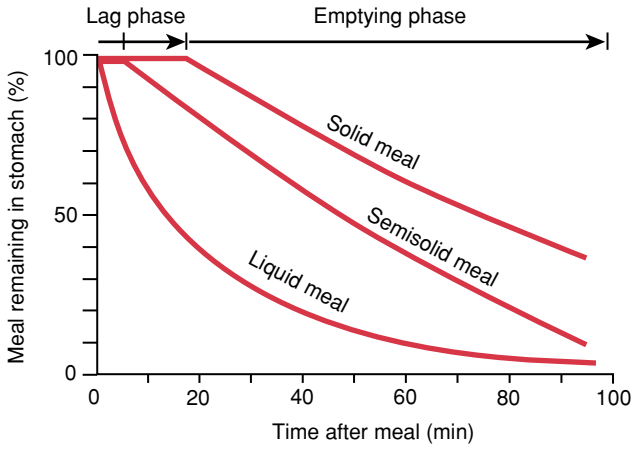

FIGURE 26.30 **Gastric emptying.** The rate of gastric emptying varies with the composition of the meal. Solid meals empty more slowly than semisolid or liquid meals. The emptying of a solid meal is preceded by a lag phase, the time required for particles to be reduced to sufficient size for emptying.

27). Undiluted stomach contents have a composition that is poorly tolerated by the duodenum. Mechanisms of control of gastric emptying automatically adjust the delivery of gastric chyme to an optimal rate for the small intestine. This guards against overloading the small intestinal mechanisms for the neutralization of acid, dilution to iso-osmolality, and enzymatic digestion of the foodstuff (see Clinical Focus Box 26.1).

MOTILITY IN THE SMALL INTESTINE

The time required for transit of experimentally labeled meals from the stomach to the small intestine to the large intestine is measured in hours (Fig. 26.31). Transit time in the stomach is most rapid of the three compartments; transit in the large intestine is the slowest. Three fundamental patterns of motility that influence the transit of material through the small intestine are the interdigestive pattern, the digestive pattern, and power propulsion. Each pattern is programmed by the small intestinal ENS.

The Migrating Motor Complex Is the Small Intestinal Motility Pattern of the Interdigestive State

The small intestine is in the **digestive state** when nutrients are present and the digestive processes are ongoing. It converts to the **interdigestive state** when the digestion and absorption of nutrients are complete, 2 to 3 hours after a meal. The pattern of motility in the interdigestive state is called the **migrating motor complex** (MMC). The MMC can be detected by placing pressure sensors in the lumen of the intestine or attaching electrodes to the intestinal surface (Fig. 26.32). Sensors in the stomach show the MMC starting as large-amplitude contractions at 3/min in the distal stomach. Elevated contraction of the lower esophageal sphincter coincides with the onset of the MMC in the stomach. Activity in the stomach appears to migrate into the duodenum and on through the small intestine to the ileum.

At a single recording site in the small intestine, the MMC consists of three consecutive phases:

- Phase I: a silent period having no contractile activity; corresponds to physiological ileus
- Phase II: irregularly occurring contractions
- Phase III: regularly occurring contractions

Phase I returns after phase III, and the cycle is repeated (Fig. 26.33). With multiple sensors positioned along the intestine, slow propagation of the phase II and phase III activity down the intestine becomes evident.

At a given time, the MMC occupies a limited length of intestine called the **activity front**, which has an upper and a lower boundary. The activity front slowly advances (migrates) along the intestine at a rate that progressively slows as it approaches the ileum. Peristaltic propulsion of luminal contents in the aboral direction occurs between the oral and aboral boundaries of the activity front. The frequency of the peristaltic waves within the activity front is the same as the frequency of electrical slow waves in that intestinal segment. Each peristaltic wave consists of propulsive and receiving segments, as described earlier (see Fig. 26.20). Successive peristaltic waves start, on average, slightly farther in the aboral direction and propagate, on average, slightly beyond the boundary where the previous one stopped. Thus, the entire activity front slowly migrates down the intestine, sweeping the lumen clean as it goes.

Phases II and III are commonly used descriptive terms of minimal value for understanding the MMC. Contractile activity described as phase II or phase III occurs because of the irregularity of the arrival of peristaltic waves at the aboral boundary of the activity front. On average, each consecutive peristaltic wave within the activity front propagates farther in the aboral direction than the previous wave. Nevertheless, at the lower boundary of the activity front, some waves terminate early and others travel farther (see Fig. 26.32). Therefore, as the lower boundary of the front passes the recording point, only the waves that reach the sensor are recorded, giving the appearance of irregular contractions. As propagation continues and the midpoint of the activity front reaches the recording point, the propulsive segment of every peristaltic wave is detected. Because the peristaltic waves occur with the same rhythmicity as the electrical slow waves, the contractions can be described as being "regular." The regular contractions that are seen

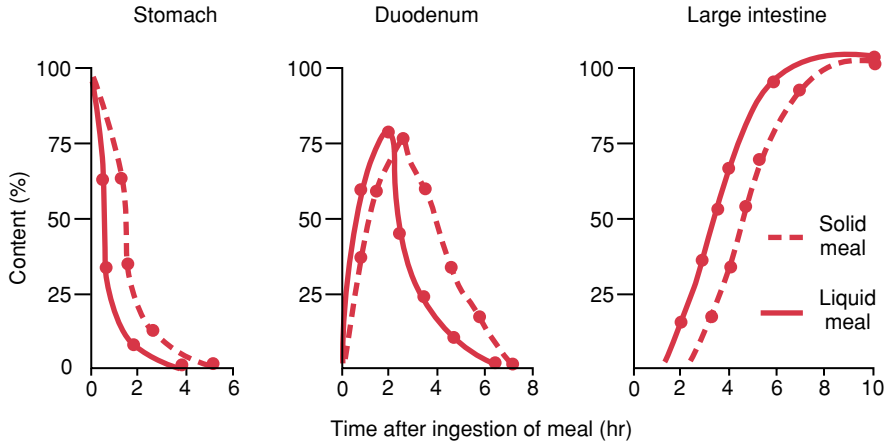

FIGURE 26.31 **GI transit times.** The time during which components of solid and liquid meals enter and leave the stomach, duodenum, and large intestine is measured in hours.

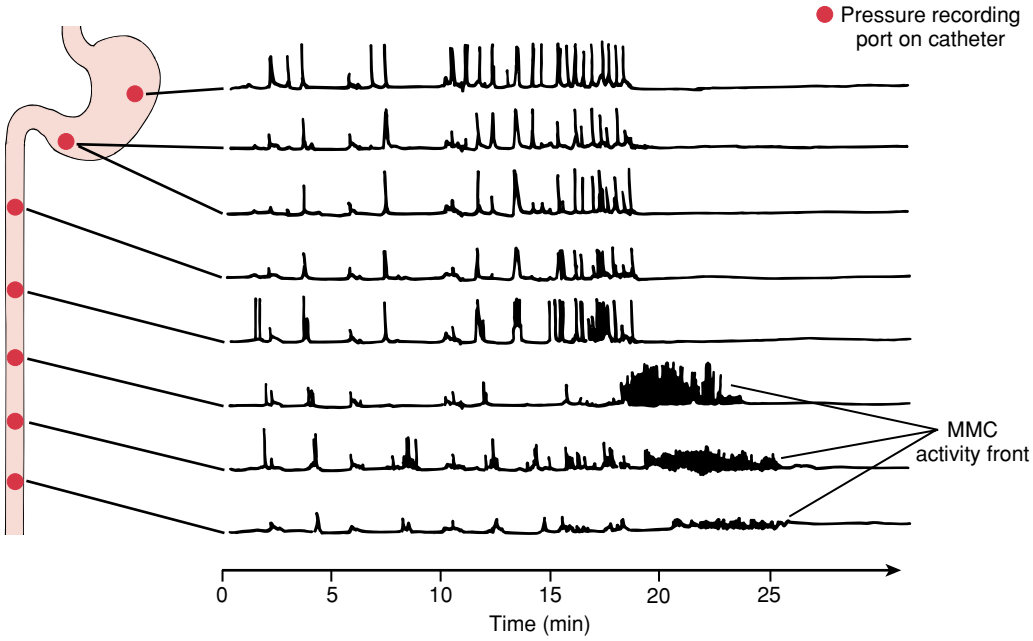

FIGURE 26.32 Migrating motor complex in the small intestine. The MMC consists of an activity front that starts in the gastric antrum and slowly migrates through the small intestine to the ileum. Repetitive peristaltic propulsion occurs within the activity front.

when the central region of the front passes a single recording site last for 8 to 15 minutes. This time is shortest in the duodenum and progressively increases as the MMC migrates toward the ileum.

The MMC is seen in most mammals, including humans, in conscious states and during sleep. It starts in the antrum of the stomach as an increase in the strength of the regularly occurring antral contractile complexes and accomplishes the emptying of indigestible particles (e.g., pills and capsules) greater than 7 mm. In humans, 80 to 120 minutes are required for the activity front of the MMC to travel from the antrum to the ileum. As one activity front terminates in the ileum, another begins in the antrum. In humans, the time between cycles is longer during the day than at night. The activity front travels at about 3 to 6 cm/min in the duodenum and progressively slows to about 1 to 2 cm/min in the ileum. It is important not to confuse the speed of travel of the activity front of the MMC with that of the electrical slow waves, action potentials, and peristaltic waves within the activity front. Slow waves with associated action potentials and associated contractions of circular muscle travel about 10 times faster.

Cycling of the MMC continues until it is ended by the ingestion of food. A sufficient nutrient load terminates the MMC simultaneously at all levels of the intestine. Termination requires the physical presence of a meal in the upper digestive tract; intravenous feeding does not end the fasting pattern. The speed with which the MMC is terminated at all levels of the intestine suggests a neural or hormonal mechanism. Gastrin and cholecystokinin, both of which are released during a meal, terminate the MMC in the stomach and upper small intestine but not in the ileum, when injected intravenously.

The MMC is organized by the microcircuits in the ENS. It continues in the small intestine after a vagotomy or sympathectomy but stops when it reaches a region of the intestine where the ENS has been interrupted. Presumably, command signals to the enteric neural circuits are necessary for initiating the MMC, but whether the commands are neural, hormonal, or both is unknown. Although levels of the hormone **motilin** increase in the blood at the onset of the MMC, it is unclear whether motilin is the trigger or is released as a consequence of its occurrence.

Adaptive Significance of the MMC. Gallbladder contraction and delivery of bile to the duodenum is coordinated with the onset of the MMC in the intraduodenal region. After entering the duodenum, the activity front of the MMC propels the bile to the terminal ileum, where it is reabsorbed into the hepatic portal circulation. This mechanism minimizes the accumulation of concentrated bile in the gallbladder and increases the movement of bile acids in the enterohepatic circulation during the interdigestive state (see Chapter 27).

The adaptive significance of the MMC appears also to be a mechanism for clearing indigestible debris from the intestinal lumen during the fasting state. Large indigestible particles are emptied from the stomach only during the interdigestive state.

Bacterial overgrowth in the small intestine is associated with an absence of the MMC. This condition suggests that the MMC may play a housekeeper role in preventing the overgrowth of microorganisms that might occur in the small intestine if the contents were allowed to stagnate in the lumen.

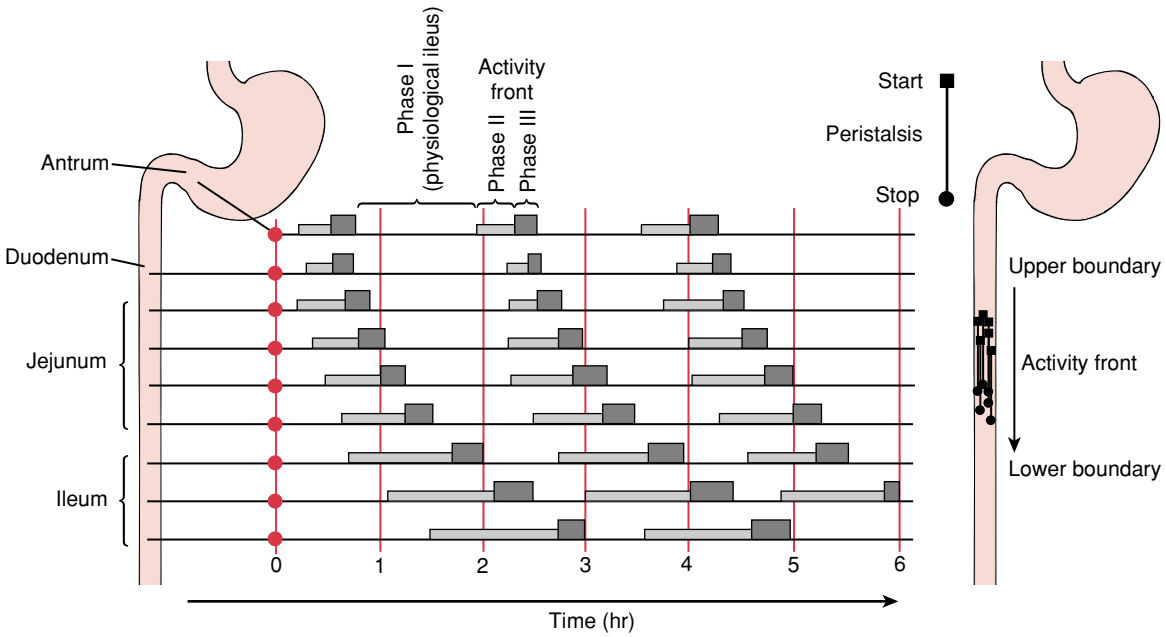

FIGURE 26.33 **The three phases of the MMC.** (See text for details.)

Mixing Movements Characterize the Digestive State

A mixing pattern of motility replaces the MMC when the small intestine is in the digestive state following ingestion of a meal. The mixing movements are sometimes called **segmenting movements** or **segmentation**, as a result of their appearance on X-ray films of the small intestine. Peristaltic contractions, which propagate for only short distances, account for the segmentation appearance. Circular muscle contractions in short propulsive segments are separated on either end by relaxed receiving segments (Fig. 26.34). Each propulsive segment jets the chyme in both directions into the relaxed receiving segments where stirring and mixing occur. This happens continuously at closely spaced sites along the entire length of the small intestine. The intervals of time between mixing contractions are the same as for electrical slow waves or are multiples of the shortest slow-wave interval in the particular region of intestine. A higher frequency of electrical slow waves and associated contractions in more proximal regions and the peristaltic nature of the mixing movements result in a net aboral propulsion of the luminal contents over time.

The Role of the Vagus Nerves and ENS. The mixing pattern of small intestinal motility is programmed by the ENS. Signals transmitted by vagal efferent nerves to the ENS interrupt the MMC and initiate mixing motility during ingestion of a meal. After the vagus nerves are cut, a larger quantity of ingested food is necessary to interrupt the interdigestive motor pattern, and interruption of the MMCs is often incomplete. Evidence of vagal commands for the mixing pattern has been obtained in animals with cooling cuffs placed surgically around each vagus nerve. During the digestive state, cooling and blockade of impulse transmission in the nerves result in an interruption of the pattern of mixing movements. When the vagus nerves are blocked during the digestive state, MMCs reappear in the intestine but not in the stomach. With warming of the nerves and release of the neural blockade, the mixing motility pattern returns.

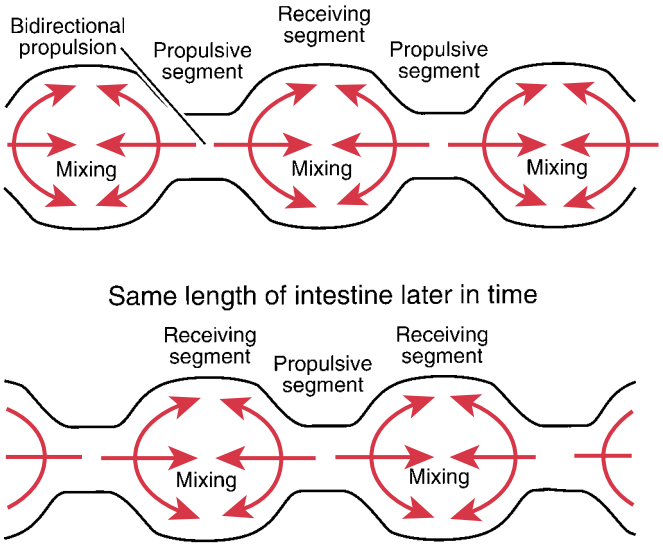

FIGURE 26.34 **Mixing movements.** The segmentation pattern of motility is characteristic of the digestive state. Propulsive segments separated by receiving segments occur randomly at many sites along the small intestine. Mixing of the luminal contents occurs in the receiving segments. Receiving segments convert to propulsive segments, while propulsive segments become receiving segments.

Power Propulsion Is a Defensive Response Against Harmful Agents

Power propulsion involves strong, long-lasting contractions of the circular muscle that propagate for extended distances along the small and large intestines. The giant migrating contractions are considerably stronger than the phasic contractions during the MMC or mixing pattern. Giant migrating contractions last 18 to 20 seconds and span several cycles of the electrical slow waves. They are a component of a highly efficient propulsive mechanism that rapidly strips the lumen clean as it travels at about 1 cm/sec over long lengths of intestine.

Intestinal power propulsion differs from peristaltic propulsion during the MMC and mixing movements, in that circular contractions in the propulsive segment are stronger and more open gates permit propagation over longer reaches of intestine. The circular muscle contractions are not time-locked to the electrical slow waves and probably reflect strong activation of the muscle by excitatory motor neurons.

Power propulsion occurs in the retrograde direction during emesis in the small intestine and in the orthograde direction in response to noxious stimulation in both the small and the large intestines. Abdominal cramping sensations and, sometimes, diarrhea are associated with this motor behavior. Application of irritants to the mucosa, the introduction of luminal parasites, enterotoxins from pathogenic bacteria, allergic reactions, and exposure to ionizing radiation all trigger the propulsive response. This suggests that power propulsion is a defensive adaptation for the rapid clearance of undesirable contents from the intestinal lumen. It may also accomplish mass movement of intraluminal material in normal states, especially in the large intestine.

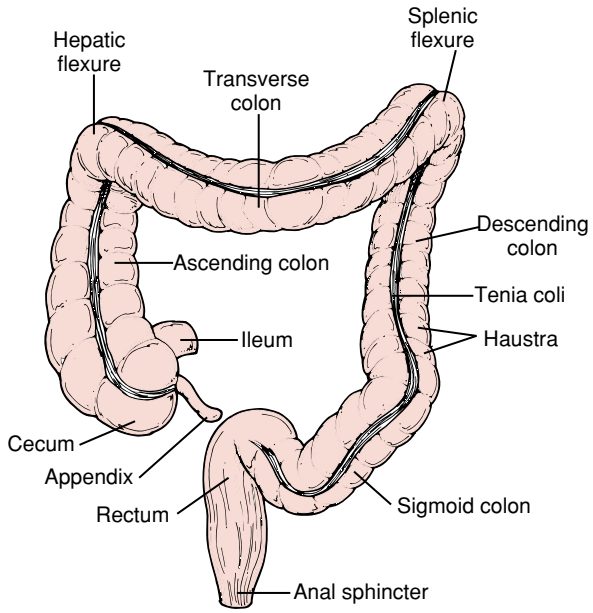

FIGURE 26.35 **Anatomy of the large intestine.** The main anatomic regions of the large intestine are the ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The hepatic flexure is the boundary between the ascending and the transverse colon; the splenic flexure is the boundary between the transverse and the descending colon. The sigmoid colon is so defined by its shape. The rectum is the most distal region. The cecum is the blind ending of the colon at the ileocecal junction. The appendix is an evolutionary vestige. Internal and external anal sphincters close the terminus of the large intestine. The longitudinal muscle layer is restricted to bundles of fibers called tenia coli.

MOTILITY IN THE LARGE INTESTINE

In the large intestine, contractile activity occurs almost continuously. Whereas the contents of the small intestine move through sequentially with no mixing of individual meals, the large bowel contains a mixture of the remnants of several meals ingested over 3 to 4 days. The arrival of undigested residue from the ileum does not predict the time of its elimination in the stool.

The large intestine is subdivided into functionally distinct regions corresponding approximately to the ascending colon, transverse colon, descending colon, rectosigmoid region, and internal anal sphincter (Fig. 26.35). The transit of small radiopaque markers through the large intestine occurs, on average, in 36 to 48 hours.

The Ascending Colon Is Specialized for Processing Chyme Delivered From the Terminal Ileum

Power propulsion in the terminal length of ileum may deliver relatively large volumes of chyme into the **ascending colon**, especially in the digestive state. Neuromuscular mechanisms analogous to adaptive relaxation in the stomach permit filling without large increases in intraluminal pressure. Chemoreceptors and mechanoreceptors in the cecum and ascending colon provide feedback information for controlling delivery from the ileum, analogous to the feedback control of gastric emptying from the small intestine.

Dwell-time of material in the ascending colon is found to be short when studied with gamma scintigraphic imaging of radiolabeled markers. When radiolabeled chyme is instilled into the human cecum, half of the instilled volume empties, on average, in 87 minutes. This period is long in comparison with an equivalent length of small intestine, but it is short in comparison with the transverse colon. It suggests that the ascending colon is not the primary site for the large intestinal functions of storage, mixing, and removal of water from the feces.

The motor pattern of the ascending colon consists of orthograde or retrograde peristaltic propulsion. The significance of backward propulsion in this region is uncertain; it may be a mechanism for temporary retention of the chyme in the ascending colon. Forward propulsion in this region is probably controlled by feedback signals on the fullness of the transverse colon.

The Transverse Colon Is Specialized for the Storage and Dehydration of Feces

Radioscintigraphy shows that the labeled material is moved relatively quickly into the **transverse colon** (Fig. 26.36),

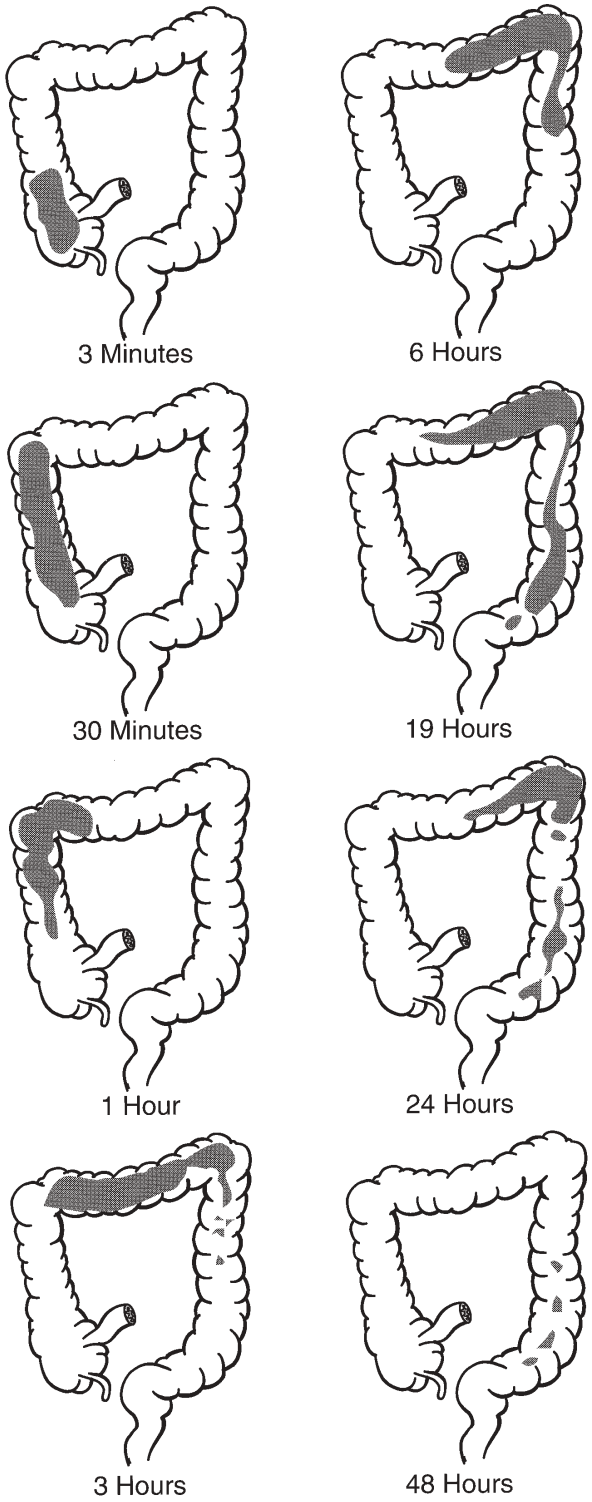

FIGURE 26.36 **Colonic transit revealed by radioscintigraphy.** Successive scintigrams reveal that the longest dwell-time for intraluminal markers injected initially into the cecum is in the transverse colon. The image is faint after 48 hours, indicating that most of the marker has been excreted with the feces.

where it is retained for about 24 hours. This suggests that the transverse colon is the primary location for the removal of water and electrolytes and the storage of solid feces in the large intestine.

A segmental pattern of motility programmed by the ENS accounts for the ultraslow forward movement of feces in the transverse colon. Ring-like contractions of the circular muscle divide the colon into pockets called **haustra** (Fig. 26.37). The motility pattern, called **haustration**, differs from segmental motility in the small intestine, in that the contracting segment and the receiving segments on either side remain in their respective states for longer periods. In addition, there is uniform repetition of the haustra along the colon. The contracting segments in some places appear to be fixed and are marked by a thickening of the circular muscle.

Haustrations are dynamic, in that they form and reform at different sites. The most common pattern in the fasting individual is for the contracting segment to propel the contents in both directions into receiving segments. This mechanism mixes and compresses the semiliquid feces in the haustral pockets and probably facilitates the absorption of water without any net forward propulsion.

Net forward propulsion occurs when sequential migration of the haustra occurs along the length of the bowel. The con-

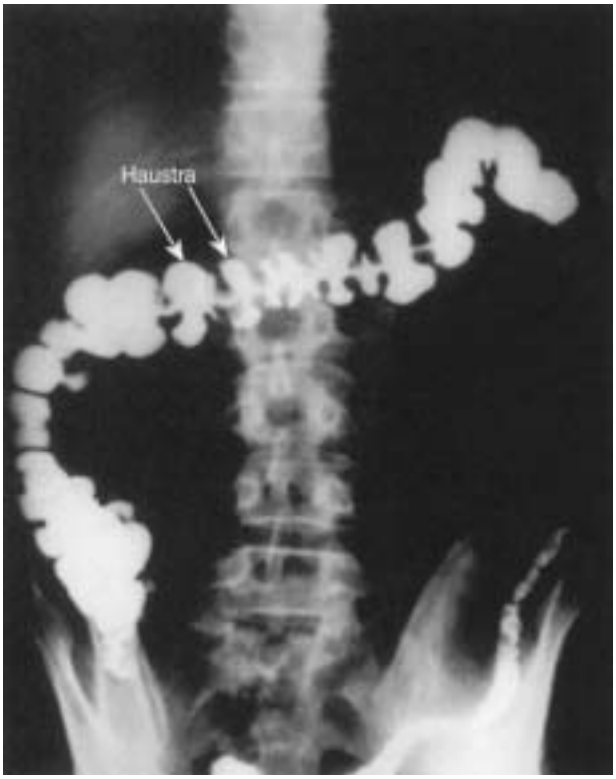

FIGURE 26.37 **Haustra in the large intestine.** This X-ray film shows haustral contractions in the ascending and the transverse colon. Between the haustral pockets are segments of contracted circular muscle. Ongoing activity of inhibitory motor neurons maintains the relaxed state of the circular muscle in the pockets. Inactivity of inhibitory motor neurons permits the contractions between the pockets.

tents of one haustral pocket are propelled into the next region, where a second pocket is formed, and from there to the next segment, where the same events occur. This pattern results in slow forward progression and is believed to be a mechanism for compacting the feces in storage.

Power propulsion is another programmed motor event in the transverse and the descending colon. This motor behavior fits the general pattern of neurally coordinated peristaltic propulsion and results in the mass movement of feces over long distances. Mass movements may be triggered by increased delivery of ileal chyme into the ascending colon following a meal. The increased incidence of mass movements and generalized increase in segmental movements following a meal is called the **gastrocolic reflex**. Irritant laxatives, such as castor oil, act to initiate the motor program for power propulsion in the colon. The presence of threatening agents in the colonic lumen, such as parasites, enterotoxins, and food antigens, can also initiate power propulsion.

Mass movement of feces (power propulsion) in the healthy bowel usually starts in the middle of the transverse colon and is preceded by relaxation of the circular muscle and the downstream disappearance of haustral contractions. A large portion of the colon may be emptied as the contents are propelled at rates up to 5 cm/min as far as the rectosigmoid region. Haustration returns after the passage of the power contractions.

The Descending Colon Is a Conduit Between the Transverse and Sigmoid Colon

Radioscintigraphic studies in humans show that feces do not have long dwell-times in the **descending colon**. Labeled feces begin to accumulate in the sigmoid colon and rectum about 24 hours after the label is instilled in the cecum. The descending colon functions as a conduit without long-term retention of the feces. This region has the neural program for power propulsion. Activation of the program is responsible for mass movements of feces into the sigmoid colon and rectum.

The Physiology of the Rectosigmoid Region, Anal Canal, and Pelvic Floor Musculature Maintains Fecal Continence

The **sigmoid colon** and **rectum** are reservoirs with a capacity of up to 500 mL in humans. Distensibility in this region is an adaptation for temporarily accommodating the mass movements of feces. The rectum begins at the level of the third sacral vertebra and follows the curvature of the sacrum and coccyx for its entire length. It connects to the anal canal surrounded by the internal and external anal sphincters. The pelvic floor is formed by overlapping sheets of striated fibers called **levator ani** muscles. This muscle group, which includes the **puborectalis muscle** and the striated external anal sphincter, comprise a functional unit that maintains continence. These skeletal muscles behave in many respects like the somatic muscles that maintain posture elsewhere in the body (see Chapter 5).

The pelvic floor musculature can be imagined as an inverted funnel consisting of the levator ani and external sphincter muscles in a continuous sheet from the bottom margins of the pelvis to the anal verge (the transition zone between mucosal epithelium and stratified squamous epithelium of the skin). After defecation, the levator ani contract to restore the perineum to its normal position. Fibers of the puborectalis join behind the anorectum and pass around it on both sides to insert on the pubis. This forms a U-shaped sling that pulls the anorectal tube anteriorly, such that the long axis of the anal canal lies at nearly a right angle to that of the rectum (Fig. 26.38). Tonic pull of the puborectalis narrows the anorectal tube from side to side at the bend of the angle, resulting in a physiological valve that is important in the mechanisms that control continence.

The puborectalis sling and the upper margins of the internal and external sphincters form the anorectal ring, which marks the boundary of the anal canal and rectum. Surrounding the anal canal for a length of about 2 cm are the internal and external anal sphincters. The **external anal sphincter** is skeletal muscle attached to the coccyx posteriorly and the perineum anteriorly. When contracted, it compresses the anus into a slit, closing the orifice. The **internal anal sphincter** is a modified extension of the circular muscle layer of the rectum. It is comprised of smooth muscle that, like other sphincteric muscles in the digestive tract, contracts tonically to sustain closure of the anal canal.

Sensory Innervation and Continence. Mechanoreceptors in the rectum detect distension and supply the enteric neural circuits with sensory information, similar to the innervation of the upper portions of the GI tract. Unlike the rectum, the anal canal in the region of skin at the anal verge is innervated by somatosensory nerves that transmit signals to the CNS. This region has sensory receptors that detect touch, pain, and temperature with high sensitivity. Processing of information from these receptors allows the in-

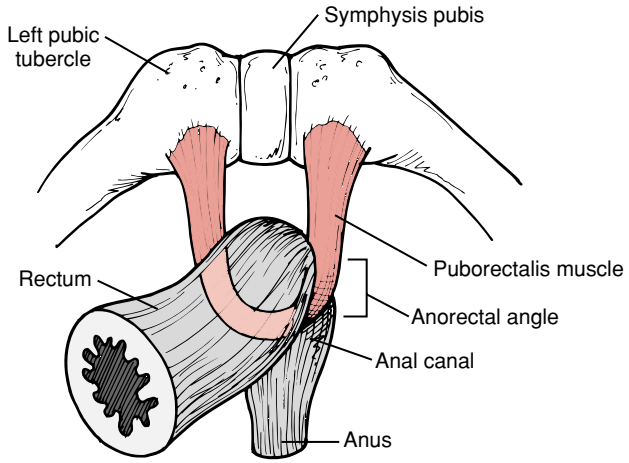

FIGURE 26.38 Structural relationship of the anorectum and puborectalis muscle. One end of the puborectalis muscle inserts on the left pubic tubercle, and the other inserts on the right pubic tubercle, forming a loop around the junction of the rectum and anal canal. Contraction of the puborectalis muscle helps form the anorectal angle, believed to be important in the maintenance of fecal continence.

dividual to discriminate consciously between the presence of gas, liquid, and solids in the anal canal. In addition, stretch receptors in the muscles of the pelvic floor detect changes in the orientation of the anorectum as feces are propelled into the region.

Contraction of the internal anal sphincter and the puborectalis muscles blocks the passage of feces and maintains continence with small volumes in the rectum (see Clinical Focus Box 26.3). When the rectum is distended, the **rectoanal reflex** or **rectosphincteric reflex** is activated to relax the internal sphincter. Like other enteric reflexes, this one involves a stretch receptor, enteric interneurons, and excitation of inhibitory motor neurons to the smooth muscle sphincter. Distension also results in the sensation of rectal fullness, mediated by the central processing of information from mechanoreceptors in the pelvic floor musculature.

Relaxation of the internal sphincter allows contact of the rectal contents with the sensory receptors in the lining of the anal canal, providing an early warning of the possibility of a breakdown of the continence mechanisms. When this occurs, continence is maintained by voluntary contraction of the external anal sphincter and the puborectalis muscle. The external sphincter closes the anal canal, and the puborectalis sharpens the anorectal angle. An increase in the anorectal angle works in concert with increases in intra-abdominal pressure to create a "flap" valve. The flap valve is formed by the collapse of the anterior rectal wall onto the upper end of the anal canal, occluding the lumen.

Whereas the rectoanal reflex is mediated by the ENS, synaptic circuits for the neural reflexes of the external anal sphincter and other pelvic floor muscles reside in the sacral portion of the spinal cord. The mechanosensory receptors are muscle spindles and Golgi tendon organs similar to those found in skeletal muscles elsewhere in the body. Sensory input from the anorectum and pelvic floor is transmitted over dorsal roots to the sacral cord, and motor outflow to these areas is in sacral root motor nerve fibers. The spinal circuits account for the reflex increases in contraction of the external sphincter and pelvic floor muscles by behaviors that raise intra-abdominal pressure, such as coughing, sneezing, and lifting weights.

Defecation Involves the Neural Coordination of Muscles in the Large Intestine and Pelvic Floor

Distension of the rectum by the mass movement of feces or gas results in an urge to defecate or release flatus. CNS processing of mechanosensory information from the rectum is the underlying mechanism for this sensation. Local processing of the mechanosensory information in the enteric neural circuits activates the motor program for relaxation of the internal anal sphincter. At this stage of rectal distension, voluntary contraction of the external anal sphincter and the puborectalis muscle prevents leakage. The decision to defecate at this stage is voluntary. When the decision is made, commands from the brain to the sacral cord shut off the excitatory input to the external sphincter and levator ani muscles. Additional skeletal motor commands contract the abdominal muscles and diaphragm to increase intra-abdominal pressure. Coordination of the skeletal muscle components of defecation results in a straightening of the anorectal angle, descent of the pelvic floor, and opening of the anus.

Programmed behavior of the smooth muscle during defecation includes shortening of the longitudinal muscle layer in the sigmoid colon and rectum, followed by strong contraction of the circular muscle layer. This behavior corresponds to the basic stereotyped pattern of peristaltic propulsion. It represents **terminal intestinal peristalsis**, in that the circular muscle of the distal colon and rectum becomes the final propulsive segment while the outside environment receives the forwardly propelled luminal contents.

A voluntary decision to resist the urge to defecate is eventually accompanied by relaxation of the circular muscle of the rectum. This form of adaptive relaxation accommodates the increased volume in the rectum. As wall tension relaxes, the stimulus for the rectal mechanoreceptors is removed, and the urge to defecate subsides. Receptive relaxation of the rectum is accompanied by a return of contractile tension in the internal anal sphincter, relaxation of tone in the external sphincter, and increased pull by the puborectalis muscle sling. When this occurs, the feces remain in the rectum until the next mass movement further increases the rectal volume and stimulation of mechanoreceptors again signals the neural mechanisms for defecation.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A surgeon makes an incision in the jejunum starting at the serosal surface and ending in the lumen. What is the sequential order of bisected structures as the scalpel passes through the intestinal wall?
   (A) Circular muscle → longitudinal muscle → submucous plexus
   (B) Longitudinal muscle → myenteric plexus → circular muscle
   (C) Myenteric plexus → circular muscle → longitudinal muscle
   (D) Network of interstitial cells of Cajal → longitudinal muscle → circular muscle
   (E) Longitudinal muscle → network of interstitial cells of Cajal → submucous plexus
2. A mouse with a new genetic mutation is discovered not to have electrical slow waves in the small intestine. What cell type is most likely affected by the mutation?
   (A) Enteric neurons
   (B) Inhibitory motor neurons
   (C) Enterochromaffin cells
   (D) Interstitial cells of Cajal
   (E) Enteroendocrine cells
3. A patient with chronic intestinal pseudoobstruction has action potentials and large- amplitude contractions of the circular muscle associated with every electrical slow wave at all levels of the intestine in the interdigestive state. Dysplasia of which cell type most likely explains this patient's condition?
   (A) Unitary-type smooth muscle

(continued)

(B) Interstitial cells of Cajal
(C) Inhibitory motor neurons
(D) Sympathetic postganglionic neurons
(E) Vagal efferent neurons

4. A neural tracer technique labels the axon and cell body when it is applied to any part of a neuron. Where are labeled cell bodies most likely to be found after the tracer substance is injected into the wall of the stomach?
(A) Prefrontal cortex
(B) Intermediolateral horn of spinal cord
(C) Dorsal vagal complex
(D) Hypothalamus
(E) Gray matter of sacral spinal cord

5. An electrophysiological study of a neuron in the ENS detects a fast EPSP. Which is the most likely property associated with the EPSP?
(A) Acetylcholine (ACh) receptors
(B) Suppression of hyperpolarizing after-potentials
(C) Receptor activation of adenylyl cyclase
(D) Hyperpolarization of the membrane potential
(E) Mediation by a metabotropic receptor

6. The application of norepinephrine (NE) to the ENS suppresses cholinergically mediated EPSPs but has no effect on depolarizing responses to applied acetylcholine (ACh). This finding is best interpreted as
(A) Postsynaptic excitation
(B) Slow synaptic inhibition
(C) Presynaptic inhibition
(D) Postsynaptic facilitation
(E) Inhibitory junction potential

7. A 10-cm segment of small intestine is removed surgically and placed in a 37°C physiological solution containing tetrodotoxin. A stimulus at one end of the segment evokes an action potential and an accompanying contraction that travels to the opposite end of the segment. This finding is best explained by
(A) Electrical slow waves
(B) Varicose motor nerve fibers
(C) Interstitial cells of Cajal
(D) Functional electrical syncytial properties
(E) Release of neurotransmitters

8. A disease that results in the loss of enteric inhibitory motor neurons to the musculature of the digestive tract will most likely be expressed as
(A) Rapid intestinal transit
(B) Accelerated gastric emptying
(C) Gastroesophageal reflux
(D) Diarrhea
(E) Achalasia of the lower esophageal sphincter

9. The viewing of intestinal peristaltic propulsion in real time with magnetic resonance imaging shows the stereotyped formation of propulsive and receiving segments. What is the normal sequence of events in enteric neural programming of the propulsive and receiving segments?
(A) Relaxation of the longitudinal and circular muscles in the propulsive segment
(B) Relaxation of the circular and longitudinal muscles in the receiving segment
(C) Contraction of the longitudinal and circular muscles in the receiving segment
(D) Relaxation of the circular muscle and contraction of the longitudinal muscle in the receiving segment
(E) Contraction of the longitudinal muscle and relaxation of the circular muscle in the propulsive segment

10. Examination of the properties of a normal sphincter in the digestive tract will show that
(A) Primary flow across the sphincter is unidirectional
(B) The lower esophageal sphincter is relaxed at the onset of a migrating motor complex in the stomach
(C) Blockade of the sphincteric innervation by a local anesthetic causes the sphincter to relax
(D) The manometric pressure in the lumen of the sphincter is less than the pressure detected in the lumen on either side of the sphincter
(E) The inhibitory motor neurons to the sphincter muscle stop firing during a swallow

11. The absence of intestinal motility in the normal small intestine is best described as
(A) A migrating motor complex
(B) An interdigestive state
(C) Segmentation
(D) Physiological ileus
(E) Power propulsion

12. The best description of the lag phase of gastric emptying is the time required for
(A) Conversion from the interdigestive to the digestive enteric motor program
(B) Maximal stimulation of gastric secretion
(C) Return of the emptying curve to baseline
(D) Reduction of particle size to occur
(E) Emptying of half of a liquid meal

13. Increased strength of the trailing component of the contractile complex in the gastric antral pump is most likely to occur when
(A) Excitatory motor neurons are activated to release ACh at the antral musculature
(B) Sympathetic postganglionic neurons decrease the amplitude of the plateau phase of the gastric action potential
(C) Frequency of the gastric action potential increases beyond 3/min
(D) The pyloric sphincter opens
(E) Excitatory motor neurons to the musculature of the gastric reservoir are activated

14. When elevated in an ingested meal, the factor with the greatest effect in slowing gastric emptying is
(A) pH
(B) Carbohydrate
(C) Protein
(D) Lipid
(E) H_2O

15. On a return visit after receiving a diagnosis of functional dyspepsia, a 35-year-old woman reports sensations of early satiety and discomfort in the epigastric region after a meal. These symptoms are most likely a result of
(A) Malfunction of adaptive relaxation in the gastric reservoir
(B) Elevated frequency of contractions in the antral pump
(C) An incompetent lower esophageal sphincter
(D) Premature onset of the interdigestive phase of gastric motility
(E) Bile reflux from the duodenum

16. A 46-year-old university professor with an allergy to shellfish must be cautious when eating in restaurants because a trace of shrimp in any form of food triggers an allergic reaction, including abdominal cramping and diarrhea. Which kind of contractile behavior is the most likely intestinal motility pattern during the professor's allergic reaction to shellfish?
(A) Physiological ileus
(B) Migrating motor complex
(C) Retrograde peristaltic propulsion
(D) Segmentation
(E) Power propulsion

17. The instillation of markers in the large intestine is used to evaluate transit time in the large intestine and diagnose motility disorders. In healthy subjects, dwell-times for instilled markers in the large intestine are greatest in the
(A) Ascending colon
(B) Sigmoid colon
(C) Descending colon
(D) Transverse colon
(E) Anorectum

18. An 86-year-old woman has complaints of a compromised lifestyle because of fecal incontinence. Examination of this patient will most likely reveal the underlying cause of the incontinence to be
(A) Absence of the rectoanal reflex
(B) Elevated sensitivity to the presence of feces in the rectum

(continued)

(C) Loss of the ENS in the distal large intestine (adult Hirschsprung's disease)
(D) Weakness in the puborectalis and external anal sphincter muscles
(E) A myopathic form of chronic pseudoobstruction in the large intestine

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