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Fundamentals of Neurogastroenterology: Physiology/Motility – Sensation

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The fundamental gastrointestinal functions include motility, sensation, absorption, secretion, digestion, and intestinal barrier function. Digestion of food and absorption of nutrients normally occurs without conscious perception. Symptoms of functional gastrointestinal disorders often are triggered by meal intake, suggesting abnormalities in the physiological processes are involved in the generation of symptoms. In this article, normal physiology and pathophysiology of gastrointestinal function, and the processes underlying symptom generation, are critically reviewed. The functions of each anatomic region of the digestive tract are summarized. The pathophysiology of perception, motility, mucosal barrier, and secretion in functional gastrointestinal disorders as well as effects of food, meal intake, and microbiota on gastrointestinal motility and sensation are discussed. Genetic mechanisms associated with visceral pain and motor functions in health and functional gastrointestinal disorders are reviewed. Understanding the basis for digestive tract functions is essential to understand dysfunctions in functional gastrointestinal disorders.

Keywords: Gastrointestinal Motility; Sensation; Absorption; Secretion.

The complex process of digestion of food and absorption of nutrients normally occurs without conscious perception. Symptoms reported by patients with functional gastrointestinal disorders often are triggered by meal intake, suggesting that abnormalities in the physiological processes involved in digestion are involved. Evaluation of sensory function and gastrointestinal motility aims to identify abnormalities in neuromuscular function to ultimately guide therapeutic management. In this article, more general and region-specific aspects of normal physiology and pathophysiology, and the processes underlying symptom generation, are critically discussed.

Normal Physiology: Main Components

The fundamental gastrointestinal functions include sensation, motility, digestion, absorption, and secretion.

Perception

Peripheral nerves, afferent signaling. Human beings have the capability to consciously perceive a variety of highly differentiated sensations originating from the upper and lower sections of the gut. In the upper gastrointestinal (GI) tract, specific sensations amenable to conscious awareness range from temperature, taste, hunger, fullness, satiety, nausea, and pain. In the small and large bowel, distensions and contractions cause aversive sensations such as nausea, bloating, cramping, discomfort, and pain. Only a minority of the sensory information arising from the gastrointestinal tract is perceived consciously. The majority (estimated to be >90%) of afferent sensory information from the viscera serves homeostatic functions.

The gastrointestinal tract is densely innervated to provide information on its luminal contents, processes regulating digestion and absorption, and potential threats.[1] This information was collected by intrinsic and extrinsic afferent nerves and regulates physiological responses for homeostasis and health. In brief, sensory neurons of the enteric nervous system activate local responses. Extrinsic afferent nerves transmit sensory information to the spinal cord or brainstem for further processing and integration (for brain processing, see later). In general, the extrinsic afferent innervation of the gut is conducted through the vagus nerve and the spinal afferents. The cell bodies of the vagus afferents are in the nodose ganglion, and mainly project to the nucleus of the solitary tract. Vagovagal reflexes result in stimulation of vagal efferents in the dorsal motor nucleus of the vagus nerve. Two examples of vagovagal reflexes are transient lower esophageal sphincter relaxations and meal-induced gastric accommodation.

Abbreviations used in this paper: **FGID, functional gastrointestinal disorder; GI, gastrointestinal; GNb3, Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit β-3; IBS, irritable bowel syndrome; LES, lower esophageal sphincter; LM, longitudinal muscle; MMC, migrating motor complex.**

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The spinal afferents have cell bodies in dorsal root ganglia. These afferents are thoracolumbar (with neurons in thoracolumbar dorsal root ganglia and projections via splanchnic nerves and mesenteric/colonic/hypogastric nerves) or lumbosacral (with cell bodies in lumbosacral dorsal root ganglia and projections via pelvic nerves and rectal nerves to the distal bowel) nerves, which synapse in the spinal cord and send information to the brainstem. Of note, each region of the GI tract receives dual sensory innervation reflecting functional connectivity for the distribution of extrinsic primary afferents in these pathways.

Elucidating the afferent and central mechanisms mediating the specific sensation of visceral hyperalgesia or pain is relevant in the context of the functional gastrointestinal disorders (FGIDs), especially irritable bowel syndrome (IBS) and functional dyspepsia.[2,3] The sensation of pain appears to be mediated by different afferents depending on the location of the GI tract undergoing the noxious stimulus. Pain from the rectum primarily involves pelvic pathways; more proximal intestinal sensations are mediated by thoracolumbar spinal afferents. Inflammation (or inflammatory mediators) can change both the response properties of specific classes of sensory neurons and the involvement of specific ascending pathways, which is relevant in post-inflammatory hypersensitivity and postinfectious IBS.[4]

For the sensations of hunger, satiety, fullness, and nausea, which play a prominent role in functional gastroduodenal disorders, vagal afferent pathways play a primary role. Vagal mucosal afferent pathways are activated by enteroendocrine cell mediators including cholecystokinin, ghrelin, and glucagon-like peptide-1, which regulate food intake and satiety.[1] Ghrelin is released from gastric endocrine cells and inhibits intraganglionic laminar endings located in myenteric ganglia. Abdominal vagal afferents can contribute to nausea and vomiting, at least in part through effects of 5-hydroxytryptamine released by enterochromaffin cells.[1]

Multiple or multimodal ascending and descending pathways are involved in gastrointestinal sensation through bottom-up and top-down connections between the central nervous system and the GI tract along the brain–gut axis.

Brain processing. Within the brain, the multiple facets that define the conscious experience of pain or other sensations are shaped, involving sensory–discriminative as well as affective–motivational aspects, behavioral–motor responses, and cognitive components. Multiple brain regions and interconnected networks mediate normal and disturbed responses to visceral stimulation. From the spinal cord, nociceptive ascending signals from the gut reach the brain via the anterolateral and dorsal column pathways.[5] The spinothalamic tract projects to the ventral nuclei of the thalamus and the medial thalamus and then to the primary and secondary somatosensory cortices. These structures primarily mediate the sensory–discriminatory aspects of noxious stimulation, including information regarding intensity, duration, and location. Affective–motivational aspects of pain probably are shaped via connections between the medial thalamus and the limbic system, including the anterior cingulate cortex as well as the midbrain, including the periaqueductal gray.

The spinoreticular and spinomesencephalic tracts are additional anterolateral afferent systems that conduct sensory information to various loci within the brainstem, mediating reflexive, affective, and motivational consequences of noxious stimulation. Other cortical and subcortical brain regions in normal and abnormal visceral stimulus processing include the insula, the dorsolateral and ventrolateral prefrontal cortices, and the amygdala. These regions play a role in modulation of the response to pain by emotions such as stress and cognitions such as expectations in healthy human beings, as well as in patients with chronic pain or hyperalgesia. Descending corticolimbic pain modulation via inhibitory pathways involving the brainstem modulates afferent visceral signaling. Disturbed endogenous pain modulation probably plays a role in abnormal brain responsiveness to visceral pain stimuli in FGIDs.[6,7]

Motility

The major functions of human digestive tract motility are to accomplish propulsion along the gut, to mix gut contents with digestive secretions and expose them to the absorptive surface, to facilitate temporary storage in certain regions of the gut, to prevent retrograde movement of contents from one region to another, and to dispose of residues.

Anatomic and functional considerations. In each region of the gastrointestinal tract, the muscle layers of the gut wall and their innervation are adapted and organized to produce the specific motor patterns that serve the motor functions. The entire gastrointestinal tract interacts with the central nervous system and communication between various parts of the gut is facilitated by the longitudinal transmission of myogenic and neurogenic signals through the intrinsic neurons, as well as by reflex arcs through autonomic neurons. The aspects of gut motility that appear most relevant to the FGIDs are contractile activity and tone, compliance, and transit.

Contractile activity and tone. Phasic (short-duration) contractions originate from electrical spikes on the plateau phase of the slow-wave activity, and thus the frequency of the phasic contractions in the stomach and small intestine is dictated by the slow wave frequency. The slow-wave frequency varies along the length of the gastrointestinal tract; the maximum contractile frequency varies similarly. The maximum contractile frequency in the stomach is approximately 3 per minute, whereas in the small intestine the frequency decreases gradually from approximately 12 per minute in the duodenum to 7 per minute in the terminal ileum. A mixture of slow-wave frequencies is found in the colon and ranges from 1 to 12 per minute where the correlation between electrical and contractile activities is less clear. Whether the gut phasic contractions accomplish mainly mixing or propulsion depends on their temporal (eg, frequency, duration) and spatial (eg, spread of propagation) characteristics.[8]

A more prolonged state of contraction, referred to as *tone*, is not regulated by slow waves and may be recognized clearly in the proximal stomach (accommodation response to a meal) and the colon (response to feeding), as well as in

some sphincteric regions. Tone is regulated by actin–myosin interaction mediated by cellular mechanisms that are modulated by neurogenic and mechanical stimuli. Phasic contractions, such as those regulating lumen occlusion, may be superimposed on tonic activity. Thus, tone can increase the efficiency of phasic contractions by diminishing the diameter of the lumen. Tone also modifies wall tension in response to gut filling, and is therefore one determinant of perception of distension.[9,10]

Compliance. Compliance refers to the capability of a region of the gut to adapt to intraluminal distension, expressed as the ratio of the change in volume to the change in pressure. Several factors contribute to compliance including the capacity (diameter) of the organ, the elastic properties of the gut wall (ie, thickness, fibrotic component, muscular activity), and the elasticity of surrounding organs (which can be influenced by fibrosis, ascites, abdominal masses). Although compliance sometimes has been expressed as the pressure/volume ratio at one distension step, it is expressed more accurately as the entire pressure/volume curve. Compliance can differ markedly in different regions of the gut, and even within an organ; for example, the descending colon is less compliant than the ascending colon, whereas the sigmoid colon is less compliant than the transverse colon. Compliance decreases during contraction and increases during relaxation, and in a given organ is determined by the muscular activity of its walls. Hence, short-term changes in compliance reflect the tone of the organ. In that respect, compliance measurements in vivo (volume/pressure relationship) reflect the elongation/tension relationship of the gut wall.

A distending intraluminal volume produces a stretch and tension (force) on the gut wall, which determines the intraluminal pressure increment. Perception of gut distension is in part determined by wall tension, rather than by intraluminal volume or pressure. Hence, assessment of wall tension may be important in assessing perception of visceral stimuli.[10–13]

Transit. Although flow reflects the local movements of intraluminal content, transit refers to the time taken for food or other material to traverse a specified region of the gastrointestinal tract. Transit represents the net interaction of a number of parameters and is a relevant and convenient index of organ function. Most measurements of transit are based on detecting intraluminal movements of an extrinsic marker labeling the luminal content. Transit depends on many factors, such as the physical (eg, solid, liquid, gas) and chemical (eg, pH, osmolality, and nutrient composition) nature of both gut contents and the administered marker. Transit measurement also is influenced by the state of gut motility at the time of marker administration (eg, fasted vs fed motility), and any preparation of the gut (eg, cleansing of the colon). The transit times have been shown to be abnormal in some FGIDs.

The relationship between transit and phasic activity or tone is incompletely understood, but studies examining the movement of radiolabeled colonic contents in healthy subjects have shown that only 28% are associated with propagating sequences, with the remainder associated with either nonpropagating activity (32%) or no pressure events (40%).[14] Moreover, patients with chronic constipation who have normal transit can show reduced fasting and/or postprandial colonic tone.[15]

Mucosal Barrier Integrity and Secretion

Interest in the role of abnormal barrier function in FGIDs has increased since the observation that postinfectious IBS is associated with increased permeability and increased rectal mucosal enteroendocrine cells and T lymphocytes.[16]

The intestinal barrier. A tightly regulated intestinal barrier is present to protect us against threats from the intestinal lumen.[16–18] At first, gastric acid and pancreatic juice degrade bacteria and antigens in the lumen. Next, the enterocytes are covered by an unstirred water layer, the glycocalyx, and, finally, a mucus layer secreted by goblet cells providing some kind of physical barrier against intraluminal bacteria. Together with secreted factors such as defensins secreted by Paneth cells and secretory immunoglobulins released by enterocytes, a subtle equilibrium with the external milieu is created within this layer covering the epithelium (Figure 1).

The epithelium is tightly sealed by 3 types of junctional complexes between the enterocytes: (1) tight junctions, (2) adherent junctions, and (3) desmosomes. Tight junctions are the most apical intercellular protein complex formed by transmembrane proteins such as claudins, occludin, and tricellulin, which are connected to the actin cytoskeleton via zona occludens. They are mainly responsible for the sealing of the intercellular space and regulate the passage of particles in a rather complicated manner with sometimes opposing functions.[16] Interaction with the strength of the tight junctions will increase permeability to large solutes with no charge discrimination, a pathway referred to as the leak pathway. Adherent junctions are located below the tight junctions and are linked to the actin cytoskeleton through multiprotein complexes consisting of the transmembrane protein E-cadherin and the intracellularly localized catenins.[17] Together with desmosomes, the third type of junctional complexes located at the basal pole of the intercellular space, they comprise strong adhesive bonds between epithelial cells, providing mechanical strength to the epithelial barrier. Stimuli modulating the strength of these bonds also thus will contribute to a more leaky barrier.

Factors leading to barrier dysfunction. Mainly from animal work, several factors have been proposed, such as genetic predisposition, alterations in the microbiome (including bacterial infection), and psychological stress (through mast cell activation). In human beings, the evidence is limited.

Genetics. Patients carrying a single-nucleotide polymorphism in the gene encoding for cadherin-1, one of the proteins of the adherent junctions, are at higher risk of developing postinfectious IBS.[19]

Glutamine. Glutamine synthase, a key enzyme in the synthesis of glutamine, is reduced in the intestinal mucosa of diarrhea-predominant IBS patients with increased

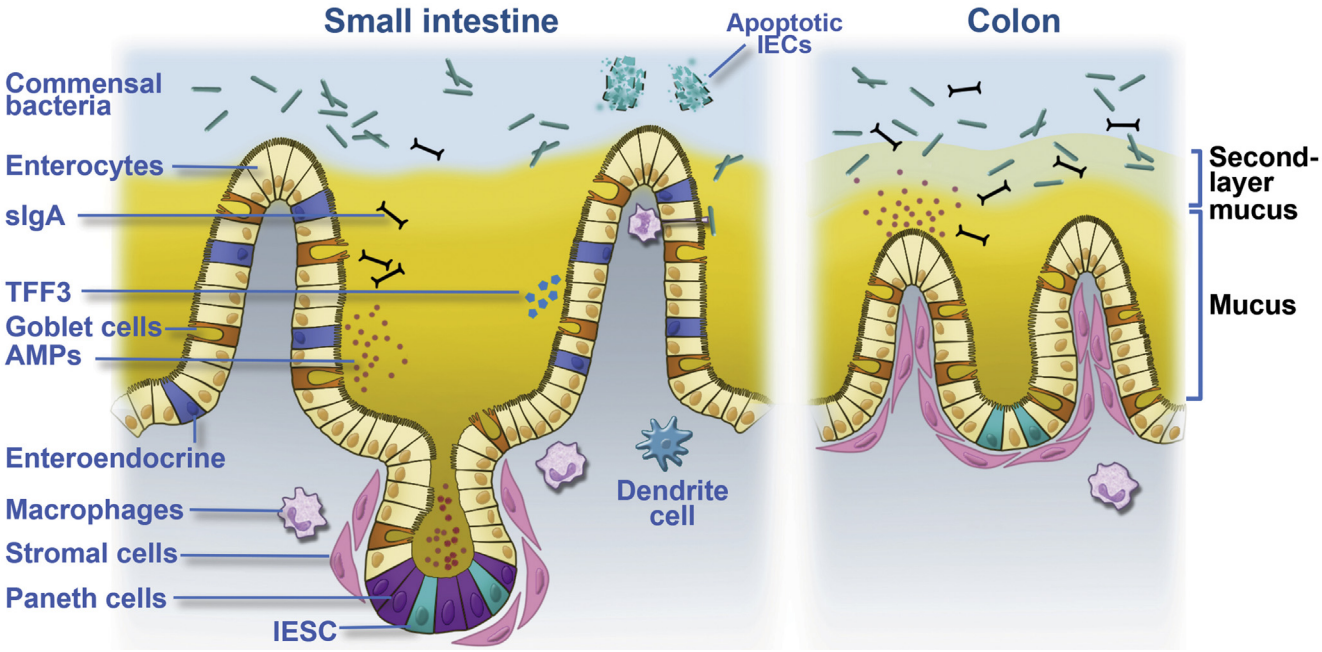

Figure 1. The intestinal mucosal barrier. A layer of unstirred water and mucus (secreted by goblet cells), together with secreted soluble immunoglobulin A (IgA), antimicrobial proteins (AMP), goblet cell–derived products (such as trefoil factor 3 [TFF3]) are the first line of defense against commensals and pathogens. Intestinal epithelial cells (IECs) form a biochemical and physical barrier that maintains segregation between luminal contents and the mucosal immune system. IESC, intestinal epithelial stem cell. Modified from Peterson and Artis.[117]

permeability.[20] Glutamine is a major energy source for rapidly dividing mucosal cells such as enterocytes, and thus important for the maintenance of intestinal barrier function.

Stress. In human beings, cold pain stress and psychological stress result in increased levels of mast cell mediators in jejunal fluid,[21,22] whereas psychological stress and infusion of corticotropin-releasing hormone induce increased permeability in healthy subjects. Mast cell activation induced by stress may be one of the mechanisms leading to barrier dysfunction in human beings (Figure 2).

Intraluminal proteolytic activity. Increased proteolytic activity in the intestinal lumen,[23,24] caused by either pancreatic enzymes or bacterial proteases, can lead to barrier dysfunction.[24] Application of diarrhea-predominant IBS fecal supernatant on colonic mucosa results in a rapid increase in phosphorylation of myosin light chain and delayed redistribution of zonula occludens-1 in colonocytes.

Secretion. Although abnormalities in secretion have not been studied in depth in FGIDs, interest in mechanisms triggering secretion has increased tremendously since the observation that compounds activating secretion are efficacious as treatment for functional constipation and constipation-predominant IBS.[25] Linaclotide, a 14–amino acid peptide homologous to bacterial heat-stable enterotoxins, activates receptor guanylyl cyclase C in the brush border of intestinal mucosa cells from the duodenum to rectum to open the cystic fibrosis transmembrane conductance regulator chloride channel, producing a net efflux of ions and water into the intestinal lumen.[26] Lubiprostone, an activator of chloride channels, is a member of a class of compounds called *prostones*,[27] and results in increased chloride secretion with associated passive transport of sodium and water across the epithelium, thereby enhancing fluid secretion.

Bile acids potently induce secretion and colonic motility.[28] Increased exposure of the colonic mucosa owing to reduced reabsorption in the distal small intestine (bile acid malabsorption) has been implicated in a subgroup of patients with diarrhea-predominant IBS.[29] Conversely, patients with constipation-predominant IBS or functional constipation have impaired bile acid synthesis,[30] indicating that alterations in bile acid metabolism may be implicated in the pathophysiology of functional gastrointestinal disorders.

Relevance of Motility, Secretion, and Barrier Functions to FGID

In the context of the FGIDs, gastrointestinal dysmotility can develop through several mechanisms involving the brain–gut axis. First, various inflammatory, immune, infiltrative, or degenerative processes may directly affect the muscle and/or other elements of the enteric nervous system effector system. Dysmotility also may be triggered indirectly in response to excess stimulation by visceral afferent (sensory) fibers that influence local gastrointestinal motor function via modulation of motor neurons in prevertebral ganglia. In addition, activation of visceral afferent fibers induces autonomic changes integrated in the brainstem, such as changes in heart rate, and alterations in colonic tone (eg, vagally mediated gastrocolonic motor response), which may be increased in certain FGIDs. Finally, psychosocial stressors can induce mast cell activation affecting motility, mucosal permeability, and visceral afferents (Figure 2).

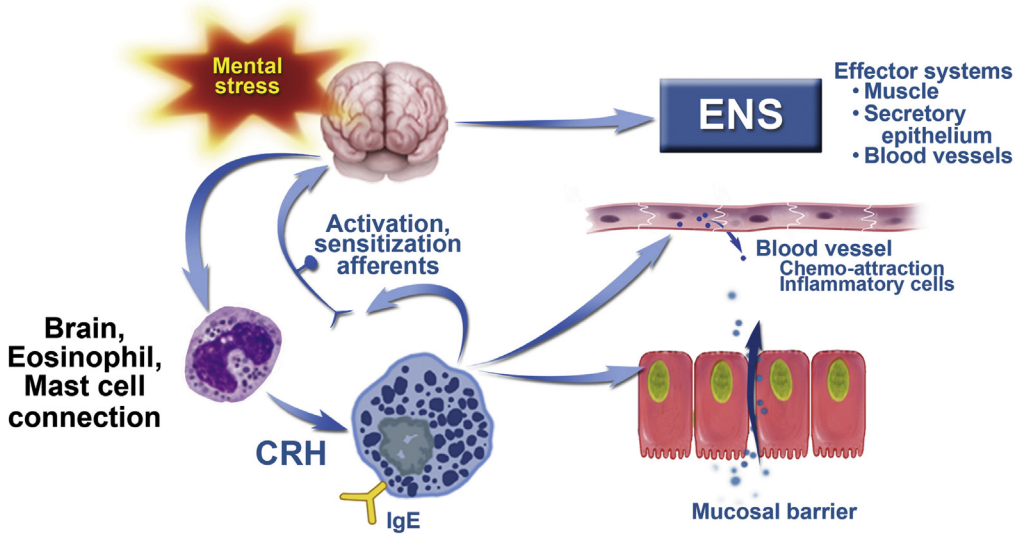

Figure 2. Psychological stress induces changes in motility, secretion, and barrier function via the brain–eosinophil–mast cell axis. Animal studies have indicated that stress indirectly activates mast cells via eosinophils. The latter cells release corticotropin-releasing hormone (CRH), inducing mast cell activation. Mast cell mediators subsequently act on afferent nerve fibers, barrier function, and blood vessels. Moreover, direct interaction between the brain and the enteric nervous system (ENS) further contributes to stress-induced changes in physiology due to stress.

Food, Meal Intake, and Microbiota

The meal ingested is transformed from the mouth to the ileum, first by digestion and then by absorption, so that only nonabsorbed residues pass into the colon. The whole digestive–absorptive process down to the terminal ileum is finely regulated depending on the composition of intraluminal content; nutrients in the stomach and small bowel have limited effects on colonic activity. Nonabsorbed meal residues entering the colon serve as substrate to feed microbiota and this interaction has several effects, including the modulation of the digestive system.

Effect of Food on Gastric and Small-Bowel Activity

During fasting, the gastrointestinal tract exerts cyclic activity with alternating periods of quiescence and periods of intense motor and secretory activity (Figure 3). This stereotyped pattern develops in the absence of extrinsic stimuli and its function seems to be the clearance of residues from the gut lumen. Ingestion of a meal stimulates the digestive system, suppresses the intrinsic interdigestive pattern, and activates reflexes that control the digestive process. The presence of nutrients in the gastrointestinal tract modulates gastrointestinal motility, barrier function (secretion, absorption), as well as sensitivity. Even before ingestion, the digestive system starts with a series of preparatory procedures, which include the cephalic phase of digestion and in normal conditions an anticipatory reward sensation. Food ingestion and swallowing activates oral and esophagogastric responses (salivation, esophageal peristalsis, and receptive relaxation). Meal arrival into the stomach induces an accommodative relaxation (gastric accommodation), as well as secretion, while solid particles activate the antral pump with peristaltic grinding activity. Intraluminal nutrients modulate the activity (motility, secretion, absorption) of the small bowel, adapting it to the local requirements of the digestive process. Meal ingestion exerts a profound influence down to the ileocecal junction, but it also has a relatively mild distal effect, inducing colonic contraction (gastrocolonic reflex).

The response to a meal is largely elicited by stimulation of gut receptors and activation of neurohumoral pathways. Some gut receptors are nutrient-specific. Meals are heterogeneous and their global effects depend on the nutrient composition. Food components elicit antegrade and retrograde responses, which also might be different (ie, retrograde stimulation and antegrade relaxation). Furthermore, the same component might elicit different effects when passing through different regions of the gut (ie, stimulation of gastric secretion in the proximal small bowel and inhibition in the distal). Fat is a very active component of food and has potent effects on motility, sensitivity, and barrier function, but other food components also play a role.

Normally, the digestive response to a meal also involves a cognitive–emotive component with a pleasant sensation of satiation, digestive well-being, even a positive influence on mood.[31] Patients with FGIDs show abnormal gut function and increased sensitivity owing to a mixed sensory–reflex dysfunction, so that physiological, normally unperceived stimuli induce symptoms.[32] The type of symptoms depends on the specific sensory–reflex pathways and region(s) affected. Nutrients modulate the responses of the gut to various stimuli and some of these modulatory mechanisms are abnormal in patients with FGIDs, which may explain the relationship between nutrients and functional GI symptoms. For instance, it consistently has been shown that FGID patients are much more sensitive to small intestinal lipid exposure than healthy controls. These effects seem to be specific for fat because isocaloric administration of other

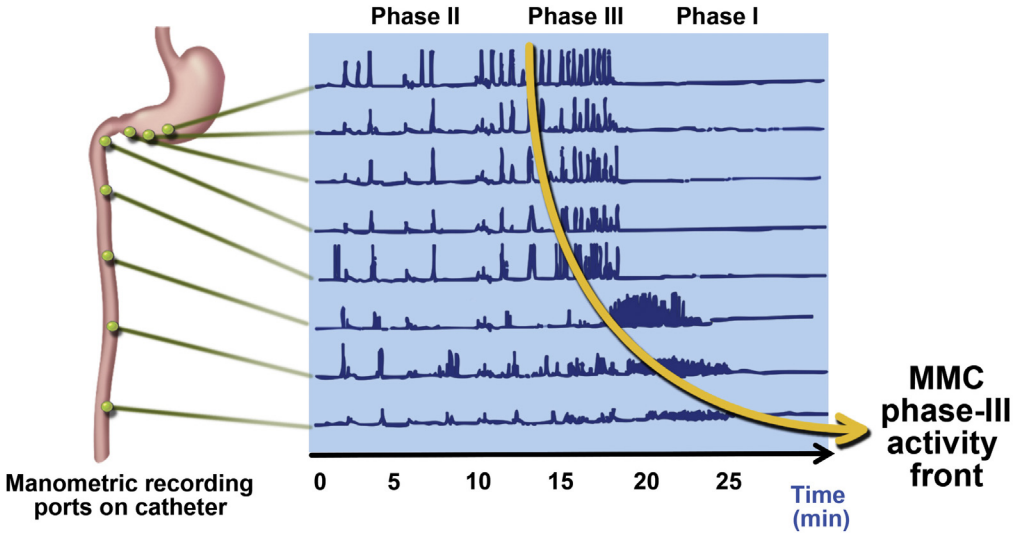

Figure 3. The MMC is the gastric and small intestinal motor pattern of the interdigestive state. The interdigestive pattern of small intestinal motility begins after digestion and absorption of nutrients are complete 2–3 hours after a meal and is called the *migrating motor complex*. Sensors in the stomach show that the MMC starts as large-amplitude contractions at 3 per minute in the distal stomach. Activity in the stomach appears to migrate into the duodenum and on through the small intestine to the ileum. At a given time, the MMC occupies a limited length of intestine called the *activity front*, which has an upper and lower boundary. The activity front slowly advances (migrates) along the intestine.

nutrients does not result in comparable symptomatic responses.[33,34]

Despite the general acceptance that functional gut symptoms are induced, or exacerbated, by food ingestion, few studies have been performed to evaluate the role of specific foods. Dyspeptic patients report several foods such as fried foods, pastry, or spices to be associated with their symptoms.[35] Cognitive factors also may contribute to functional digestive symptoms, especially because previous negative experiences might influence a patient's anticipation of symptoms. A study in patients with functional dyspepsia showed that information about the fat content of a test meal increased the symptoms induced by a low-fat yogurt when the patients were (mis)informed that the yogurt was high in fat.[36] Few studies have evaluated dietary habits in patients with FGID and the global outcome is not clear-cut. Furthermore, it is not clear whether the differences observed are the cause of symptoms, or whether the differences just reflect dietary modifications to prevent symptoms.

Food and Microbiota

The human organism hosts a large community of microorganisms. A large proportion of this resides in the colon, which provides a dedicated niche for this population of symbiotic organisms. Meal residues that have not been absorbed in the small bowel enter the colon and serve as feeding substrate for the microbiota.

Although the human organism feeds and hosts the microbiota, microbiota accomplish a series of important functions, operating as another organ of the host. Microbiota accomplish important biological functions for the host,[37–39] such as: (1) development of the immune system, particularly immune tolerance; (2) development of the central nervous system and behavior; (3) modulation of metabolic activity, energy balance, and growth; and (4) regulation of the digestive system. On the other hand, the host also influences the microbiome. Hence, there is dynamic cross-talk between the host and microbiota, but the messengers and circuits for communication still are poorly understood. The microbiota metabolize unabsorbed substrates delivered into the colon and release a vast amount of metabolites that could serve as messengers activating gut receptors or crossing the gut-blood barrier and acting at different sites. Some data indicate that microbiota may exert modulatory effects on gut function, both motility and barrier function. Prebiotic and probiotic treatment modify the microbiota and accelerate intestinal transit. The microbiota also may influence visceral sensitivity. Indeed, modulation of microbiota induces visceral hypersensitivity and visceral pain perception in animals.

Genetics

Genetic mechanisms appear to be associated with visceral pain and motor functions in health and functional gastrointestinal disorders. Familial aggregation and twin studies support a genetic factor in IBS. In addition, gene variations have been described in association with the symptom phenotype of IBS, biomarkers of visceral pain, and motor function.

Familial aggregation and twin studies

Epidemiologic studies of familial aggregation[40,41] and twins[42–46] suggest that there is a genetic component of IBS. However, the data are conflicting, and the contribution of common environment to the association of IBS within studies presents a significant confounder that cannot be completely resolved.

Visceral pain

Genetic studies suggest that variation in the control of candidate genes involved in ion channel function, neurotransmitter synthesis, reuptake or receptor functions, and inflammatory disease susceptibility loci may impact variations in the prevalence of the symptom phenotype of abdominal pain or IBS, or quantitative traits (intermediate phenotypes) of rectal sensation. The candidate genes include *SLC6A4*, *CNR1*, and *TNFSF15* reflecting serotonin reuptake, cannabinoid receptors, and inflammatory–barrier functions. However, other than *TNFSF15*, the other candidate genes are only univariately associated with pain, IBS symptom complex, or quantitative traits of sensation.[47]

Motor and barrier functions

Genetic studies suggest that variation in the control of candidate genes involved in neurotransmitter (serotonergic, α2 adrenergic, and cannabinoid) mechanisms, inflammatory pathways (interleukin 10, tumor necrosis factor α, GNβ3, susceptibility loci involved in Crohn's disease), and bile acid metabolism are associated with symptoms and disturbances of motor function, particularly colonic transit.[48]

Region-Specific Physiology

The Esophagus

Physiology. *Esophageal motility and lower esophageal sphincter function.* The coordinated motor pattern of the esophagus initiated by the act of swallowing is called *primary peristalsis*. Primary peristalsis usually clears most contents of the esophagus into the stomach. Secondary peristalsis is provoked by residual food or reflux events, and it is not accompanied by pharyngeal contraction or upper esophageal sphincter relaxation. Peristalsis in the striated muscle part of the esophagus is dependent on central vagal pathways. It is mediated by sequential excitation of motor neurons in the nucleus ambiguous.[49] Peristalsis in the thoracic esophagus is mediated by both central and peripheral mechanisms.[50,51] The timing of peristalsis in the smooth muscle segment is based on the duration of the deglutitive inhibition that increases distally along the esophagus followed by deglutitive rebound excitation.[52] This deglutitive inhibition results from a near-simultaneous activation of short-latency inhibitory vagal fibers,[51] triggering a wave of inhibition that precedes the arrival of the peristaltic contraction.[53] This inhibitory wave, mediated by myenteric inhibitory neurons,[54] also results in relaxation of the lower esophageal sphincter, allowing passage of the bolus into the stomach. The rebound excitation occurs after the sequential termination of deglutitive inhibition. The balance of timing in inhibition and excitation is the fundamental mechanism that regulates esophageal peristalsis.

The esophageal peristaltic contractions are regulated by predominantly cholinergic excitatory input in the proximal but noncholinergic inhibitory (or nitrergic) in the distal esophagus. As a consequence, cholinergic antagonists such as atropine increase the latency and decrease the amplitude of contraction in the proximal but not the distal parts of the esophagus. In contrast, antagonists of nitric oxide synthase reduce the latency mainly in the distal segments and lead to simultaneous contractions. The fact that impaired deglutitive inhibition is reported in the esophageal body of patients with diffuse esophageal spasm[55] and nonspecific esophageal motility disorders suggest that decreased nitrergic input may be involved in the pathogenesis of these disorders.

Longitudinal muscle contraction may be important in esophageal bolus transport.[56] Synchrony between circular and longitudinal muscle (LM) contractions is important to create maximal increase in esophageal muscle thickness and efficiently show peak pressure contractility.[57] Esophageal shortening is important to produce lower esophageal sphincter (LES) axial movement and opening. This is true during swallowing and transient LES relaxation.[58] Finally, abnormal LM contraction and shortening may be associated with pathology and symptoms. Studies using high-frequency intraluminal ultrasound described long-lasting thickening of the esophageal wall (sustained esophageal contraction) associated with chest pain or heartburn.[59]

The junction between the esophagus and stomach is a highly specialized region, composed of the LES and crural diaphragm.[60] Because the 2 components are anatomically superimposed, contraction of the striated muscle of the crural diaphragm during inspiration or straining exerts a pressure on the LES, leading to a dynamic and powerful increase in esophagogastric junction pressure.[60] The esophagogastric junction has to be able to relax briefly upon swallowing to allow passage of ingested food toward the stomach. The postganglionic inhibitory myenteric neurons innervating the LES are nitrergic in nature, and act by releasing nitric oxide.[54]

Secretion and sensation. The esophageal submucosal glands secrete water, bicarbonate, mucins, epidermal growth factor, and prostaglandins. These substances are involved in mucosal clearance along with peristalsis and salivary secretion. The most important secreted substance is bicarbonate, which plays a protective role during gastroesophageal reflux.[61]

Vagal afferents merging from the esophageal smooth muscle layer and serosa are sensitive to muscle stretch, whereas vagal afferents in the mucosa are sensitive to various stimuli including chemical (acid), thermal (cold or hot), and mechanical intraluminal stimuli.[62] In general, vagal afferents do not play a direct role in visceral pain transmission to the brainstem but rather transmit physiological stimuli. In contrast, spinal afferents, which have their cell bodies in the dorsal root ganglia, are acting predominantly as nociceptors.[62] Spinal afferents terminate in the dorsal column nuclei and project stimuli to the brain.[63]

Esophageal symptoms and pathophysiology. The major esophageal symptoms are heartburn, chest pain, dysphagia, belching, and rumination.

Heartburn. Heartburn, the most frequently encountered symptom of esophageal origin, is characterized by discomfort or a burning sensation behind the sternum that arises from the epigastrium and may radiate toward the neck.[64] Heartburn is an intermittent symptom, most commonly experienced within 60 minutes of eating, during exercise,

and while lying recumbent. The most common cause of heartburn is esophageal acidification. Other stimuli such as esophageal distension also can provoke heartburn. In patients with esophagitis, luminal content easily can permeate the mucosa and stimulate sensory nerves to produce heartburn. In patients with nonerosive reflux disease, the mechanism of heartburn involves microscopic alterations of esophageal mucosa and esophageal hypersensitivity. In nonerosive reflux disease, the basal layer of the esophageal mucosal epithelium shows dilated intercellular spaces.[65] Dilated intercellular spaces in the basal layer of the esophageal epithelium may facilitate the passage of acid or other components in the refluxate into the mucosa, thereby triggering symptoms and inducing peripheral sensitization.[66,67]

Chest pain. Chest pain is a common esophageal symptom with characteristics similar to cardiac pain. Esophageal pain usually is experienced as a pressure-type sensation in the midchest, radiating to the midback, arms, or jaws. Esophageal distention or chemostimulation (eg, with acid) can be perceived as chest pain.[68] The most important mechanism for chest pain of esophageal origin is gastroesophageal reflux. Some patients perceive reflux as chest pain instead of heartburn. The reason for such difference is unknown, but higher reflux volume and esophageal distension have been proposed. Another mechanism associated with esophageal chest pain is severe esophageal motility disorders such as spastic achalasia (type 3) and severe hypermotility such as jackhammer esophagus.[69] Abnormal LM contraction and shortening may be associated with chest pain.[59] Finally, patients with noncardiac chest pain frequently have esophageal hypersensitivity and psychological comorbidity.[62]

Dysphagia. Esophageal dysphagia often is described as a feeling of food sticking on the way down or even lodging in the chest for a prolonged period. It can be caused by mechanical obstruction such as peptic stricture, absent esophagogastric junction relaxation (achalasia) or a Schatzki ring, by esophageal dysmotility either with significant hypomotility (ineffective motility), or by motility discoordination as very rapid contraction with short latency after swallows,[70] or a large gap between contractions at the transitional zone between the striated and smooth muscle.[71] Mucosal inflammation associated with esophagitis also can be responsible for dysphagia in gastroesophageal reflux disease. Finally, dysphagia can occur in the absence of any identifiable abnormality, in which case it is likely the result of hypersensitivity to bolus movement during peristalsis.

Belching. Gastric belching is a physiological mechanism that enables venting of gas from the stomach to the esophagus. In another type of belching, supragastric belching (identified with impedance), air is sucked rapidly into the esophagus and is followed immediately by a rapid expulsion of air without ever reaching the stomach. Both gastric and supragastric belching are common symptoms in gastroesophageal reflux disease patients. Supragastric belches can induce reflux episodes.[72]

Rumination. Rumination is clinically suspected when chronic, effortless regurgitation of recently ingested food occurs, followed by re-mastication, re-swallowing, or expulsion.[73] The absence of nausea, discontinuation of symptoms when the contents become acidic, and the impression of pleasant taste of clearly recognizable food in the regurgitate are supportive criteria to diagnose rumination clinically. The characteristic high-resolution manometric pattern of rumination shows an abrupt increase in intragastric pressure (strain), followed by an increase in intraesophageal pressure in all channels (common cavity), followed by primary or secondary peristalsis. In some patients, however, it is difficult to distinguish rumination from postprandial belching–regurgitation. Esophageal impedance combined with manometry allows recognition of liquid retrograde flow in rumination and a better time definition between increased abdominal pressure and regurgitation events.[74]

Stomach

Physiology. Gastric physiology often is described by the different functions of the proximal and distal stomach. During fasting, the stomach participates in the cyclic interdigestive motor pattern (migrating motor complex) with alternating periods of quiescence and periods of activity (Figure 3). During the periods of phase III activity, the proximal stomach generates a high-level tonic contraction with superimposed prolonged phasic contractions at a 1-minute rhythm, whereas the antrum produces shorter 3 per minute phasic contractions.[75] The antral phasic contractions are timed by the gastric pacemaker in the body of the stomach, emanating from the interstitial cells of Cajal.[76]

Ingestion of food suppresses interdigestive motility, and the gut switches to a fed pattern. The stomach accommodates an ingested heterogeneous meal, and delivers homogenized chyme into the small bowel at a rate adapted to the intestinal processing capability. In response to ingestion, the proximal stomach partially relaxes to accommodate the meal. Later during this postprandial period, the proximal stomach progressively regains tone, and this tonic contraction gently forces intragastric food distally. Solid particles are retained and ground in the antrum by phasic contractions, whereas liquid chyme is squeezed through the pyloric gate, which determines the final gastric outflow.

The motor responses of the proximal stomach during the postprandial period are modulated by several mechanisms. The motor response induced by swallowing produces a transient and brief receptive relaxation not only of the esophagogastric sphincter, but also of the fundus.[77] Antral filling releases antrofundal relaxatory reflexes, which may play a major role in the early accommodation phase.[78] Nutrients entering the intestine induce a variety of reflexes depending on the type of nutrients and the region of the intestine stimulated, which probably constitute a fine feedback control to adapt the nutrient delivered rate to the intestinal processing capability. Other chyme parameters, such as pH and osmolality, also play a role. Gastric accommodation is modulated by vagovagal reflexes involving the release of 5-hydroxytryptamine, probably at the level of the enteric nervous system, and subsequent activation of inhibitory nitrergic motor neurons to produce fundic relaxation[79] (Figure 4).

The stomach has a rich sensory innervation, and in normal conditions, meal ingestion not only induces digestive, but also cognitive and emotive, responses involving satiation and a pleasant sensation of digestive well-being.[31]

Symptoms and pathophysiology. The stomach has a reservoir function. Symptoms may originate by 4 types of pathophysiological mechanisms: delayed gastric emptying, impaired accommodation, increased perception, or accelerated gastric emptying. Of note, the symptomatic expression of the stomach is limited and the manifestations may be similar regardless of the underlying pathophysiological mechanisms involved.

Delayed gastric emptying. Gastric emptying is the net output of the stomach, which is governed by 3 areas of the stomach: proximal fundus, distal antrum, and the pyloric sphincter. Neural and hormonal pathways from the small intestine also influence gastric emptying. Because phasic antral contractions produce the grinding of solid particles required for passage through the pylorus into the intestine, impaired antral contractions results in the delayed emptying of solids.[80] On the other hand, the tonic contraction of the proximal stomach pushes gastric content distally and feeds the antral pump. Hence, impaired tonic contraction of the proximal stomach results in impaired grinding of solids and also may produce an overall delay in the emptying of both solids and liquids. During the phases of activity of the interdigestive period (phase III), gastric contractions propagating from the proximal to the distal stomach coincide with pyloric opening and duodenal quiescence, have a very propulsive effect and produce the evacuation of indigestible particles retained into the stomach after the digestive period. The absence of gastric phase III activity may promote gastric bezoar formation.

Delayed gastric emptying produces symptoms if the disturbance is relatively severe, resulting in chyme retention into the stomach. The symptoms vary from mild symptoms (early satiety, epigastric fullness, vague nausea) to severe manifestation of gastric stasis with retention-type emesis (ie, vomiting of food ingested many hours or even days earlier) and nutritional compromise. Nausea and vomiting may occur in some patients during fasting rather than postprandially. In some patients, this may lead to an inability to eat because of symptoms and resultant weight loss. In severe cases, even endogenous fasting secretions cannot be emptied.[81] Delayed gastric emptying in the absence of mechanical obstruction is called *gastroparesis*.[82,83] Chronic idiopathic gastroparesis constitutes a relatively uncommon but important entity. The diagnosis of gastroparesis should be restricted to patients with objective demonstration of grossly abnormal gastric emptying of solids and liquids. Some patients with functional dyspepsia show a delay of solid emptying with normal emptying of liquids.

Impaired accommodation. Impaired accommodation of the proximal stomach in response to food ingestion increases gastric wall tension, which might activate sensory endings in the gastric wall and produce symptoms. Inappropriate relaxation might be related to impaired enterogastric and antrofundic reflexes that normally modulate the gastric accommodation/emptying process.[78,84] Reduced proximal gastric relaxation in response to a meal can be seen in some patients with functional dyspepsia and this may be associated with more prevalent early satiety and weight loss.[85] Impaired accommodation is associated with abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach or antral overload.[86] The latter may explain the impression of postprandial antral hypomotility in dyspepsia because only occlusive contractions are recorded by manometry. A distended antrum may produce a slower grinding of solids, and lead to prolonged gastric retention and delayed emptying of solids observed in a subpopulation of these patients.

Increased gastric sensitivity. Distending the stomach can produce conscious sensations similar to the symptoms reported by patients with gastric functional disorders.

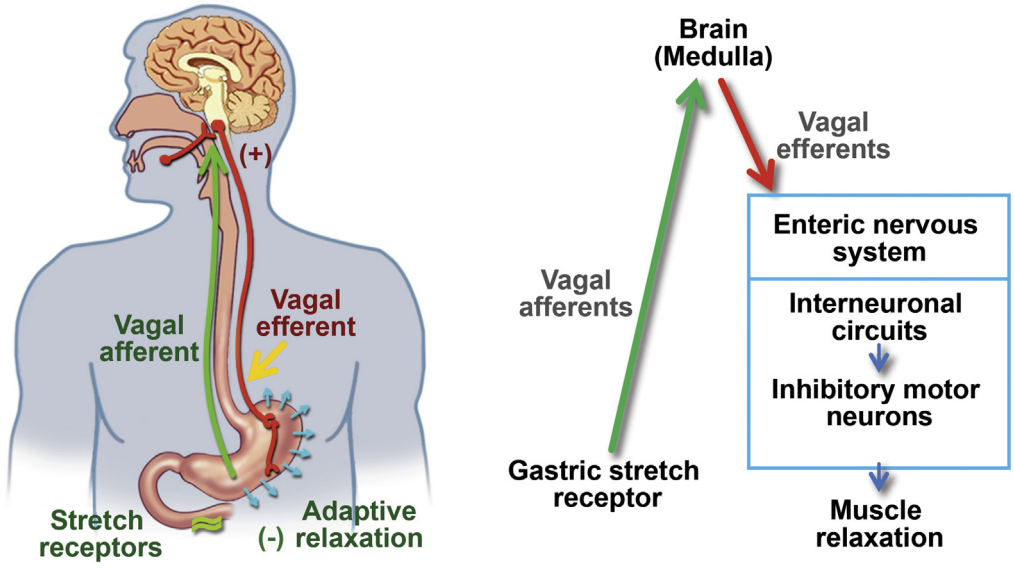

Figure 4. Adaptive relaxation in the gastric reservoir is a vagovagal reflex. The adaptive relaxation is triggered by filling and distension of the gastric reservoir. It is a vagovagal reflex that is triggered by stretch receptors in the gastric wall, transmission over vagal afferents to the dorsal vagal complex, and efferent vagal transmission to inhibitory motor neurons in the gastric enteric nervous system.

Perception of gastric distension depends on activation of tension rather than elongation or volume receptors in the gastric wall.[87] Some patients with functional dyspepsia show increased perception of gastric distension or hypersensitivity of the stomach, but not of the duodenum. Moreover, somatic sensitivity in these patients is normal or even decreased, with enhanced tolerance of aversive somatic stimuli characteristic of chronic pain conditions.[78,88] Gastric hypersensitivity is more prevalent in patients with predominant epigastric pain[89] and may coexist with impaired gastric accommodation to meal ingestion and/or delayed gastric emptying.

The cause and mechanism of gastric hypersensitivity has not been elucidated. In normal conditions, gastric sensitivity is modulated by several mechanisms. For instance, lipids in the small intestine increase perception of gastric distension. This modulatory mechanism is up-regulated in patients with functional dyspepsia, and, hence, contributes to the genesis of symptoms. Some data indicate that altered perception in a subset of patients with dyspepsia occurs as a consequence of an acute (possibly viral) gastroenteritis, which leads to impaired nitrergic nerve function in the proximal stomach.[90] Central mechanisms also may play a role. Anxiety is correlated negatively with pain and discomfort threshold in hypersensitive functional dyspeptic patients.[91]

Accelerated gastric emptying. In some patients, mainly after partial or complete gastrectomy, rapid gastric emptying is accompanied by vasomotor and gastrointestinal symptoms. Dumping Syndrome also may be observed after vagotomy, intentional or unintentional, at the time of surgery at the gastroesophageal junction.

Symptoms typically occur after ingestion of liquids and meals rich in carbohydrates, and usually occur within the first weeks after surgery, when patients resume their normal diet. Dumping symptoms can be subdivided into early dumping and late dumping. Early dumping occurs in the first hour after meal ingestion and is associated with both abdominal and systemic symptoms owing to the rapid passage of hyperosmolar contents into the small bowel, leading to a shift of fluids from the intravascular compartment to the gut lumen. This induces intestinal distension and gastrointestinal symptoms such as bloating, abdominal pain, and diarrhea.[92] Enhanced release of several gastrointestinal hormones, including enteroglucagon, vasoactive intestinal polypeptide, peptide YY, pancreatic polypeptide, and neurotensin are thought to cause a systemic and splanchnic vasodilation, most likely explaining the vasomotor symptoms. Late dumping occurs 1–2 hours postprandially and results from reactive hypoglycemia. Rapid gastric emptying induces high glycemic levels, which lead to increased insulin secretion. Because of the long half-life of insulin and the often very transient character of the initial increase in glycemia, reactive hypoglycemia occurs when all sugars have been absorbed.

Small Intestine

Small intestinal physiology. *Motility and secretion.* The small intestine is where most of the digestion of food to absorbable nutrients takes place. Digestion and absorption require a combination of motor activity and secretion of water, electrolytes, bile, and enzymes. The pancreas delivers most of the enzymes needed for digestion of lipids and proteins. It also delivers amylase for the digestion of starch and glycogen, whereas the final digestion of carbohydrates takes place at the microvilli of enterocytes using brush-border enzymes. Little is known about the role of small intestinal motility in digestion.

Phase III of the migrating motor complex (MMC) is coordinated with intestinal, biliary, and pancreatic secretion,[93,94] and probably serves a housekeeper function in the small intestine. The MMC is a program that resides in the enteric nervous system but can be influenced by extrinsic control systems, such as the vagus nerve, and a number of gut hormones and neurotransmitters.[95] Motilin, which is secreted from enteroendocrine M cells in the upper small intestine, can induce premature activity complexes in the stomach. Of note, the occurrence of the phase III portion of the migrating motor complex in the antrum is associated with a peak in plasma motilin level.[96] However, phase IIIs that originate in the upper small intestine are not associated with changes in plasma motilin levels.[97] Ghrelin is secreted by P/D_1-cells in the gastric fundus. Similar to motilin, ghrelin induces premature activity complexes in the stomach when given exogenously.[98] Both motilin-induced and ghrelin-induced activity complexes behave similar to phase IIIs and are propagated to the small intestine.[96,99] Premature activity complexes in the small intestine without activation of the stomach can be elicited using somatostatin[100] or octreotide.[101] Somatostatin is secreted from neuroendocrine neurons of the periventricular nucleus of hypothalamus but also from enteroendocrine cells in the small bowel and the stomach and from ∂-cells of the pancreas. It is as yet unclear if somatostatin has a direct effect on small intestinal motility or if the effect is mediated by inhibition of pancreatic polypeptide.[100] An intact vagus nerve is required for inhibition of MMC and conversion to fed motor activity in the small intestine.

Sensation. In healthy people, the functions of the small intestine are hardly perceived. Borborygmus sometimes can be noticed after a meal and the audible noise is caused by movement of swallowed air and fluids in the bowel, but it also can arise during fasting in association with the migration of an activity complex. The gut usually is effective at handling gas.[102] Bloating is a feeling of being puffed up in the abdomen and can be felt after eating.

Small intestinal symptoms and pathophysiology. In pathologic conditions, dysfunction in the small intestine can give rise to abdominal pain, bloating, abdominal distension, and diarrhea. The mechanisms that lead to pain and discomfort are somewhat unclear but distension of the intestines is one such mechanism. Pain caused by distension is mediated by stretch receptors in muscle layers and serosa that project through splanchnic and vagal nerves to the brain.[103] Abnormal sensitivity seems to involve other mechanisms including mast cells.[104,105] Bloating and abdominal distension are symptoms that recent research have ascribed to abnormal viscerosomatic reflexes.[106,107] Patients with enteric

dysmotility as well as patients with IBS show a greater retention of infused gas compared with healthy controls, indicating impaired gas clearance as a mechanism for distension in these patient groups.[108] Diarrhea can be caused by increased intestinal secretion (eg, from stimulation of guanylate- or adenylate-cyclase receptors on the enterocytes). Diarrhea also can follow from impaired digestion of foods in the small intestine, resulting in an osmotic increase in luminal water. Diarrhea caused by maldigestion or malabsorption in the small intestine can be enhanced further by colonic bacterial fermentation.

Large Intestine and Anorectum

Physiology. *Colon.* Motor functions of the colon include propulsion, accommodation, or storage, and rapid emptying of a variable portion of the colon during defecation. Propulsion is achieved by a number of motor events including individual contractions, contractile bursts, high-amplitude propagated contractions, and possibly changes in tone. High-amplitude propagated contractions have been correlated with large-volume movements of the intraluminal content of the colon that initially were recognized on barium studies as mass movements.

High-amplitude propagated contractions occur more often in the morning, during the postprandial period, and preceding defecation.[109,110] Other colonic motor events propel contents over short distances in either an orad or an aborad direction, and their primary function appears to be to facilitate mixing. It is likely that regular contractile bursts—colonic motor complexes—do occur, each burst occurring once or twice per hour and lasting approximately 6 minutes. Periodic or cyclic motor activity is evident more clearly in the rectum, the so-called *rectal motor complexes*. They do not appear to be synchronized with the small intestinal MMC and their precise function and regulation remain unclear. In terms of sensitivity of the colon, experimental distension of the descending or sigmoid colon is perceived as a sensation of cramping, gas, or pressure in the lower abdomen, lower back, or perineum.[111]

Accommodation and storage are essential functions of the colon so that fluids, electrolytes, and some products of carbohydrate and fat digestion can be salvaged by bacterial metabolism. Accommodation, storage, and distribution of material within the colon are mediated by colonic tone (Figure 5). Tone and phasic activity in the colon show considerable diurnal variation, increasing slowly after a meal, reducing during sleep, and increasing dramatically upon waking.[112,113] The colonic motor response to eating consists of an increase in phasic and tonic contractile activity that begins within several minutes of ingestion of a meal and continues for a period of up to 3 hours. This response is influenced by both the caloric content and composition of the meal with fat and carbohydrate stimulating colonic motor activity, while amino acids and protein inhibit motor activity. The response of the proximal colon is less than that of the distal colon.[114]

Anorectum. The anorectum functions in defecation and continence. Defecation is achieved through the integration of a series of motor events and involves both striated and smooth muscle.[115,116] A sensation of rectal fullness is generated by rectal afferents when colonic contents reach the rectum.[13] Rectal filling also induces the rectoanal inhibitory or rectosphincteric reflex that leads to internal anal sphincter relaxation and external sphincter contractions. At this stage, the individual can decide to postpone or proceed with defecation. To facilitate defecation, the puborectalis muscle and external anal sphincter relax, thereby straightening the rectoanal angle and opening the anal canal. The propulsive force enabling defecation then is generated by contractions of the rectosigmoid, diaphragm, and the muscles of the abdominal wall to propel the rectal contents through the open sphincter. The internal anal sphincter is a continuation of the smooth muscle of the rectum and is under sympathetic control and provides approximately 80% of normal resting anal tone, whereas the external anal sphincter and pelvic floor muscles are striated muscles innervated by sacral roots and the pudendal nerve. Somatic and autonomic nervous system convergence within the anorectum means that it is

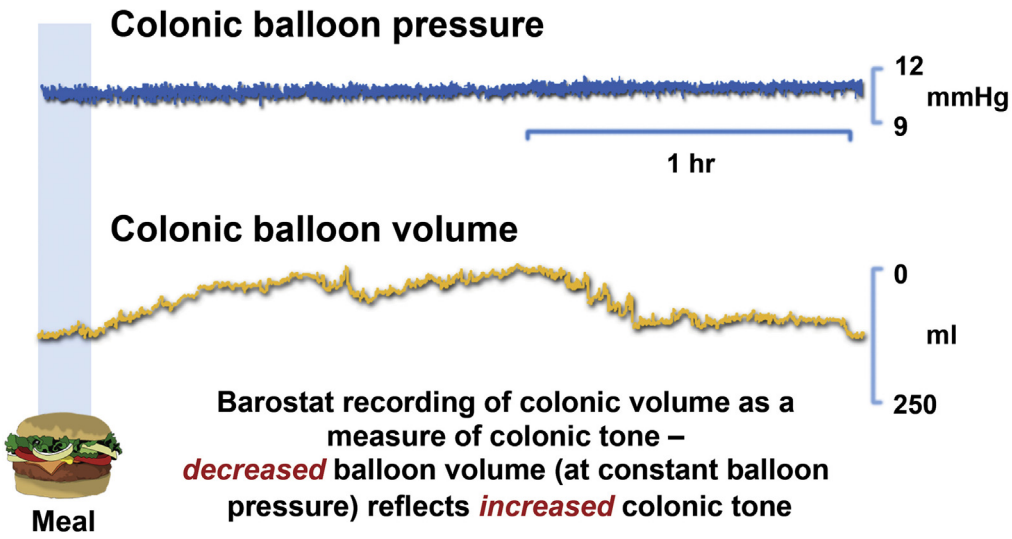

Figure 5. Colonic motility: normal tonic response of sigmoid colon to a meal. An example of the normal postprandial increase in tone in the descending colon measured using the electronic barostat is shown. Note the reduction in volume of the colonic balloon (*lower tracing*) at constant balloon pressure (*upper tracing*) after the meal, which represents an increase in colonic tone.

susceptible to disorders of both striated and smooth muscle, as well as to diseases of the central, peripheral, and autonomic nervous systems.

Main symptoms and pathophysiology. Main symptoms of dysfunction include constipation, diarrhea, urgency, straining to defecate, sense of incomplete rectal evacuation, and incontinence. Bloating and abdominal pain also are features that often coexist, especially in patients with dysfunction of the large intestine, but they also may arise as a result of dysfunctions of the anorectum and pelvic floor. Abdominal pain in the right and left lower quadrants of the abdomen may suggest origin in the large intestine. Right subcostal and epigastric pain may be symptoms of stasis in the transverse colon. The pain also may become aggravated postprandially, which often is mistaken for gastric origin of the pain. In patients with constipation, the presence of postprandial epigastric pain may arise from stimulation of colonic contraction in the face of inadequate onward propulsion of colonic content as a result of fecal obstruction in the left colon or rectosigmoid (eg, caused by rectal evacuation disorders).

Concluding Remarks

Understanding the basis for digestive tract functions is essential to understand dysfunctions in the functional gastrointestinal disorders. This article has discussed and critically assessed the normal physiology and pathophysiology, and the processes underlying symptom generation. From this careful review, the following recommendations for future research in this area emerge.

- Define new characteristics of wall function other than phasic and tonic contractions (eg, longitudinal muscle contractions, elasticity, connective tissue).
- Improve differentiation of health from disease using standardized stimuli when basal conditions are not discriminatory.
- Conduct physiological measurements during times of symptoms.
- Investigate luminal content (eg, microbiota, metabolomic factors), and contrast with the content juxtaposed to the mucosa.
- Further characterization of peripheral and central mechanisms of normal and abnormal sensory function.
- Apply physiological measurements as biomarkers in epidemiology, phenotyping, and therapeutics.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.02.030.

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Conflicts of interest
The authors disclose no conflicts.

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