Gastrointestinal Physiology and Function

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Contents

Abstract

The gastrointestinal (GI) system is responsible for the digestion and absorption of ingested food and liquids. Due to the complexity of the GI tract and the

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© Springer International Publishing AG 2017
Handbook of Experimental Pharmacology, DOI 10.1007/164_2016_118

substantial volume of material that could be covered under the scope of GI physiology, this chapter briefly reviews the overall function of the GI tract, and discusses the major factors affecting GI physiology and function, including the intestinal microbiota, chronic stress, inflammation, and aging with a focus on the neural regulation of the GI tract and an emphasis on basic brain-gut interactions that serve to modulate the GI tract. GI diseases refer to diseases of the esophagus, stomach, small intestine, colon, and rectum. The major symptoms of common GI disorders include recurrent abdominal pain and bloating, heartburn, indigestion/dyspepsia, nausea and vomiting, diarrhea, and constipation. GI disorders rank among the most prevalent disorders, with the most common including esophageal and swallowing disorders, gastric and peptic ulcer disease, gastroparesis or delayed gastric emptying, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD). Many GI disorders are difficult to diagnose and their symptoms are not effectively managed. Thus, basic research is required to drive the development of novel therapeutics which are urgently needed. One approach is to enhance our understanding of gut physiology and pathophysiology especially as it relates to gut-brain communications since they have clinical relevance to a number of GI complaints and represent a therapeutic target for the treatment of conditions including inflammatory diseases of the GI tract such as IBD and functional gut disorders such as IBS.

Keywords

Absorption • Barrier function • Central nervous system (CNS) • Colon • Constipation • Diarrhea • Digestion • Enteric nervous system (ENS) • Epithelial barrier • Gut microbiome • Inflammation • Inflammatory bowel disease (IBD) • Intestinal permeability • Irritable bowel syndrome (IBS) • Mucosa • Secretion • Small intestine • Smooth muscle • Stress • Visceral pain

1 Introduction

The overall function of the GI tract is to digest ingested nutrients through complex processes of digestive enzyme secretion and nutrient absorption. Luminal contents move along the GI tract via smooth muscle peristalsis, while smooth muscle segmentation ensures adequate contact time and exposure to the absorptive epithelial mucosal surface. The gut is capable of handling about 9 L of fluid per day, which is mainly absorbed by the small intestine. This fluid movement can occur through paracellular or transcellular routes. The former pathway involves water movements coupled to nutrient absorption via alterations in tight junction expression, while the transcellular route involves the passage of water through apical and basolateral membranes of epithelial cells by passive diffusion, cotransport with ions and nutrients, or through aquaporins. During intestinal absorption the epithelial barrier is specifically designed to protect against the movement of potentially

harmful antigenic, toxic, or infectious material across the GI mucosal surface (Camilleri et al. 2012).

To ensure effective digestion and proper GI tract health requires a complex series of coordinated neural events accomplished by the central nervous system (CNS), the nerve network within the gut itself known as the enteric nervous system (ENS), and a whole host of GI endocrine peptides that target specific cells and tissues that make up the GI tract. Specialized endoderm-derived epithelial cells termed enteroendocrine cells (EECs) form the largest endocrine organ in the body and are widely distributed throughout the GI tract. EECs play a key role in the control of GI function including secretion, motility, and regulation of food intake, postprandial glucose levels, and metabolism (Latorre et al. 2016). The gut also performs important immune functions and a vast array of inflammatory mediators can influence the recruitment of lymphocytes and other immune cells to the gut wall including mast cells, and at the same time modulate the activity of the gut neural networks (O'Malley 2015; Wouters et al. 2016). Additionally, the abundance of microbiota residing in the human intestine estimated at 10^{14} microorganisms plays a pivotal role in the development of the ENS, the overall health not only of the GI tract but also the entire human body via mechanisms that include activation of the immune system, and production of short-chain fatty acids (SCFAs) to promote colon cell health as well as brain-gut interactions (Patterson et al. 2014; Kabouridis and Pachnis 2015; Moloney et al. 2016; Obata and Pachnis 2016; Sandhu et al. 2016).

2 Basic Anatomy of the GI Tract

The human GI tract is composed of multiple different organs and can be divided into the upper and lower GI tract. The upper GI tract refers to the mouth, esophagus, stomach duodenum, jejunum, and ileum, while the colon, rectum, and anus make up the lower GI tract. The esophagus propels ingested food from the pharynx into the stomach via a wave of highly coordinated esophageal peristalsis. Once in the stomach, the food bolus is mixed with gastric acid and digestive enzymes and is broken down to allow digested material, now called chyme, to pass through the pyloric sphincter into the duodenum. Once in the small intestine (duodenum, jejunum, and finally ileum) the digestive process breaks down proteins, fats, and carbohydrates to smaller components to allow for nutrient absorption. Accessory organs that aid in the digestive process include the salivary glands, pancreas, liver, and gallbladder. Once the luminal contents reach the large intestine, the contents are now called feces, and are prepared for expulsion via the rectum and anal canal.

To accomplish the digestive processes in a coordinated manner, the GI tract has a functional anatomy that in general terms is composed of a series of layers including the inner mucosal layer of the GI tract composed of absorptive and secretory epithelial cells. The remaining layers of the GI tract include the submucosal layer containing nerves, lymphatics, and connective tissue; the smooth muscle layer composed of longitudinal and circular smooth muscle; and the

outer serosal layer. Specialized ECCs that are diffusely scattered in the GI mucosa possess the capability of sensing the luminal content and in turn release signaling molecules that enter the circulation to act as classic hormones on distant targets, and act locally in a paracrine fashion on neighboring cells and on distinct neuronal pathways including enteric and extrinsic neurons. Each type of EEC has a characteristic distribution along the GI tract. Among the mediators released, cholecystokinin (CCK) and glucagon-like peptide (GLP-1) play important roles in reflex control of GI function and in regulating food intake. EECs are divided into "*open type*" with a bottleneck shape and an apical prolongation with microvilli facing towards the intestinal lumen or "*closed type*" that are located close to the basal membrane, do not reach the lumen of the gut, and lack microvilli. The open-type EECs directly detect luminal contents through the microvilli reaching the lumen, whereas the closed types are thought to be activated by luminal content indirectly either through neural or humoral pathways (Gribble and Reimann 2016; Latorre et al. 2016). This EEC-sensory neuron connection has thus opened a new exciting prospective on EECs and their role in the communication with ENS and CNS and sheds new light on our understanding of the complexity of the bidirectional communication between the brain and the gut. The therapeutic potential of compounds working via EEC function is high. In support a GLP-1R agonist is used to treat diabetes mellitus type 2, based on its ability to stimulate insulin secretion from pancreatic β-cells (van Raalte et al. 2016). Furthermore, in patients that have a gastric bypass the beneficial role of GLP-1 and $PYY_{3\text{-}36}$ secretion in the reduction of food intake may have additional therapeutic potential to treat obesity (Svane et al. 2016). Drugs acting to alter EEC functions may also participate in the control of depression, anxiety, and visceral hypersensitivity, which are key components of functional GI disorders.

2.1 Basic Functions of the GI Tract: GI Motility

The major functions of the GI tract are motility, secretion, and absorption. Smooth muscle tone and contractility are modulated by interstitial cells of Cajal (ICC), which serve as the pacemaker creating spontaneous electrical slow waves that spread from the ICC to the smooth muscle in the presence of a stimulus such as a neurotransmitter leading to contraction of the GI smooth muscle. The reader is referred to excellent reviews of the topic (Ward and Sanders 2001; Sanders et al. 2016). Small and large intestinal motility is under multiple levels of control including the ENS and CNS, as well as GI hormones and paracrine agents. In general, there are two distinct patterns of small intestinal motility (1) following a meal when the intestinal lumen contains chyme and (2) during the inter-digestive period. During the digestive phase the longitudinal and circular smooth muscle of the GI tract generates coordinated patterns of contractility termed peristalsis and segmentation. Peristalsis occurs in waves of contraction behind and relaxation ahead of the luminal bolus, and travels down the GI tract over short distances. Segmentation is a mixing pattern of contractility that is more irregular and allows

for luminal contents and digestive enzymes to have adequate contact with the absorbing epithelium. During the inter-digestive phase, a complex pattern of motility called the migrating motor complex (MMC) sweeps along the entire small intestine to clear the GI tract of any remaining luminal debris. Large intestinal motility patterns serve to impede aboral movement of luminal contents, which facilitates water absorption. Contractility patterns of the colon are predominantly non-peristaltic and mix the colonic contents back and forth to enhance contact with the absorbing mucosa. A less frequent pattern of colonic motility which occurs 6–8 times/day is the high-amplitude propagating contractions (HAPC) which sweep the colon and often trigger the urge to defecate.

2.2 Basic Functions of the GI Tract: GI Secretion and Absorption

The GI tract secretes up to 9 L of fluid/day containing digestive enzymes, bile, ions, water, and mucus. Important for secretion and absorption of fluids, electrolytes, and solutes are the epithelial cells which differ in structure and function depending on their location in the GI tract. The stomach is a glandular organ. Gastric parietal cells in glands within the gastric body are important for the secretion of gastric acid and intrinsic factor, pepsinogen is secreted by the chief cells also within the gastric body, while hormones (gastrin, histamine, serotonin, and somatostatin) are released from EEC throughout the stomach. Most of the digestive process and intestinal absorption of food and electrolytes occur in the duodenum, jejunum, and ileum. Proteins, fats, and carbohydrates are broken down via the action of digestive enzymes into smaller units in preparation for absorption into the network of capillaries and lymphatic vessels (lacteals) by the small intestinal epithelial cells located on the small intestinal villi. Any remaining material that is not absorbed by the small intestine passes though the ileocecal valve into the colon. The large intestinal mucosa is responsible for the absorption of water, solidification of the colonic contents into feces, and then storage of the feces prior to expulsion.

2.3 Basic Functions of the GI Tract: GI Barrier Function

Solute and particulate matter moves across the intestinal epithelium in a regulated manner either between epithelial cells or across the apical membrane of epithelial cells. Routes of transport across the epithelium include passive permeability (relevant for the passage of larger hydrophilic compounds), transcellular transport of lipophilic and small hydrophilic compounds, transcellular route via aqueous pores of small hydrophilic compounds, and active carrier-mediated absorption of nutrients and electrolytes, and endocytosis, followed by transcytosis and exocytosis of larger peptides, proteins, and particles. Transport between epithelial cells occurs via the tight junction region. Far from being static, tight junctions are continually being monitored and regulated by both intra- and extracellular signals. Several types of proteins contribute to the development of tight junctions including

the claudin family of proteins that form the actual paracellular pore within the tight junction and are associated with other transmembrane proteins called occludins. Zonula occludens (ZO)-1 and other cytoplasmic proteins, such as ZO-2 and ZO-3, attach and serve as junctional complex proteins. Also relevant to the barrier properties are adherens, junctions that are defined as a cell junction where the cytoplasmic face is linked to the actin cytoskeleton. At the basal pole of the intercellular space, desmosomes are formed by interactions between desmoglein, desmocollin, desmoplakin, and keratin filaments (Camilleri et al. 2012; Volynets et al. 2016). An important function of the gut epithelium is its protective role, functioning as a barrier between the external environment and the internal milieu. Several components form the multilayered intestinal barrier that is region specific; in the upper GI tract, gastric acid, pancreatic juice, and production of antimicrobial substances serve as a first line of defense. Next, the microenvironment close to the epithelium consists of the unstirred water layer, glycocalyx, and mucus layer, and below are epithelial cells separated by tight junctions. Under pathophysiological conditions, increases in epithelial permeability allow products to translocate the epithelial barrier including luminal antigens, toxins, and microbial fermentation. These products are capable of activating afferent nerve endings leading to visceral afferent sensitization, which is important since several different human diseases, including IBD, celiac disease (CD), and IBS, have been associated with increases in gut permeability and abnormal barrier function (Camilleri et al. 2012; Ohman et al. 2015).

3 Neural Control of the GI Tract

The neural innervation of the GI tract allows for the movement of contents along the GI tract, secretion of digestive enzymes, and absorption of luminal contents and makes certain that information from GI tract is carefully integrated and that the appropriate reflex responses are generated to ensure that all parts of the digestive system function in concert.

3.1 Enteric Nervous System

Contained within the gut wall is the ENS that is a subdivision of the autonomic nervous system (ANS) and is capable of autonomous activity. The ENS contains many of the transmitters and neuromodulators found in the CNS and is organized into specific circuits that control smooth muscle and mucosal function. These circuits within the ENS allow for the routine mechanisms of digestion to proceed without the involvement of the CNS. The ENS contains sensory neurons, motor neurons, and a complex number of interneurons that enable the information from the GI tract to be carefully integrated. Within the ENS, intrinsic primary afferent neurons are synaptically connected to interneurons that control the activity of

motor neurons regulating the GI musculature and secretomotor neurons innervating secretory cells.

3.2 Extrinsic Innervation of the GI Tract

The gut also has a dense extrinsic afferent innervation that transmits sensory information to the brain and spinal cord and is used as a basis of reflexes through parasympathetic and sympathetic nerves. Sensory information is conveyed from the GI tract to the brain stem and spinal cord via vagal and spinal (splanchnic and pelvic) afferents, respectively. Gut afferents are also involved in nausea and vomiting, feeding, and satiety, and in addition generate sensations particularly under pathophysiological circumstances when the bowel can become hypersensitive leading to visceral pain. Within the GI tract, extrinsic nociceptors can respond to multimodal stimuli, depending on receptor expression, including stretch, pH, bacterial products, substances released from immune cells, and neurotransmitters released from the ENS or ECCs. The nociceptors have nerve endings throughout the layers of the GI tract (mucosal, submucosal, muscular) and their cell bodies are located in the dorsal root ganglion (DRG). The first synapse is in the superficial layers of the dorsal horn of the spinal cord. The nociceptive signal is then transmitted to the spinal cord and pain signals reach the brain via the spinothalamic tract and dorsal column. Within the brain, the signal is then relayed to cortical areas for localization and to limbic areas for the emotional component of the pain response. Output from the cortical and limbic regions in response to the pain of GI origin activates descending inhibitory circuitry within the brain stem that causes release of inhibitory neurotransmitters within the dorsal horn of the spinal cord. Although vagal afferents were not previously thought to be involved in the mediation of visceral pain, evidence suggests a role for vagal transmission of anti/pronociceptive signals, which bypasses the spinal cord.

3.3 Visceral Afferent Sensitization

Peripheral sensitization normally develops rapidly and is relatively short-lived. Visceral afferent sensitization can occur in response to increases in epithelial permeability which allows luminal antigens, toxins, and microbial fermentation products to translocate the epithelial barrier to activate afferent nerve endings. Furthermore, intestinal inflammation and release of immune mediators at the site of injury can produce long-term alterations in the physiology of the afferent terminals. Mediators such as cytokines, prostaglandins, histamine, proteases, and/or low pH at the site of an acute injury activate receptors on the afferent terminals to increase intracellular second messengers causing the release of neurotransmitters, such as substance P, calcitonin gene-related peptide, and/or nitric oxide, which can further sensitize visceral afferents. The second messenger systems (protein kinase A, protein kinase C) also lead to changes in gene expression that induces

neuronal plasticity to alter the expression of receptors (neurokinin receptor 1, tyrosine receptor kinase A, prostaglandin receptor, protease-activated receptors, etc.) that leads to persistent changes in the excitability of the neuron, through modifying the expression or function of ion channels (sodium, calcium, and potassium).

3.4 Central Sensitization

In the presence of maintained injury or inflammation, visceral afferent sensitization can be prolonged by changes in gene expression. These genes may alter the expression of channels, receptors, or mediators in the sensory neuron. They may also modify the amount and pattern of neurotransmitters released by central nerve terminals in the brain and spinal cord. This alters the way that sensory signals are processed within the CNS and contributes to "central sensitization" which involves neuronal remodeling within the dorsal horn of the spinal cord and brain. Such spinal and supraspinal neuroplastic changes likely contribute to chronic pain. Within the dorsal horn of the spinal cord, there are two mechanisms that increase pain signals reaching the brain: (1) increased synaptic transmission and/or (2) decreased descending inhibitory modulation. Thus, a combination of increased excitation and disinhibition can produce a persistent hyperexcitable state in the second-order neuron and chronic nociceptive signaling. The increased synaptic transmission occurs via glutamate to activate a second-order neuron, causing activation of sodium-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors followed by the subsequent activation of sodium and calcium-permeable *N*-methyl-D-aspartate (NMDA) receptors. Primary afferents also release algesic mediators, such as substance P, which activates second messenger signaling that initiates remodeling of the second-order neuron by the primary nociceptor leading to changes in the properties of the receptors present in the dendritic structure of the second-order neuron (Woolf and Salter 2000). Decreased descending inhibitory modulation at the level of the spinal interneurons leads to hypersensitivity within the dorsal horn of the spinal cord via the release of neurotransmitters from the primary nociceptive afferent activating presynaptic receptors on the inhibitory interneuron, causing hyperpolarization of the inhibitory interneuron and a decreased release of gamma-aminobutyric acid (GABA) and/or glycine onto the second-order neuron. In the brain a similar mechanism to produce chronic visceral pain can be invoked within the central pain matrix in the brain by which ascending afferent information from the second-order spinal neurons leads to hyperexcitability within the central pain matrix by increasing the sensory signals reaching the tertiary neurons within the thalamus, raphe, or parabrachial nucleus, which then enhances signaling to secondary cortical and limbic structures. Remodeling of integration nuclei (amygdala, ACC/MCC, insula) can make the perception of the noxious stimulus more unpleasant, producing an enhanced negative emotional response (Staud 2012). Imaging studies have demonstrated that in patients with chronic visceral pain, there is increased activation of brain regions that

integrate pain signals and produce negative affect, such as the amygdala and insula, along with a decreased activity in pain inhibitory/positive affect nuclei, such as the prefrontal cortex (PFC) and cingulate. In particular, the amygdala is a key nucleus that integrates noxious visceral signals with anxiety/fear behaviors and hyperactivation could influence not only multiple nuclei in the central pain matrix, but also descending brainstem nuclei that modulate GI function. Additionally, the altered signaling within the central pain matrix disrupts the descending dorsal column inhibitory pathway by modulating the activity in the periaqueductal gray (PAG) and rostroventral medulla (RVM). Recently, a significant amount of attention has been given to a subgroup of EECs secreting 5-HT and their role in visceral perception. 5-HT is a key neurotransmitter in the control of nociceptive responses and mood, with receptors located in both the periphery and CNS. Much evidence suggests that activation of 5-HT receptors, specifically 5-HT_3 and 5-HT_4, sends signals from the gut to the CNS through vagal afferent fibers, which activate multiple pathways including those involved in nociception (Chen et al. 2009; Zhang et al. 2011; Browning 2015).

4 GI Pathophysiology

Proper functioning of the GI tract is essential for supporting life; however disorders of the GI tract are common, unpleasant, and complex affecting the mucosa, musculature, and neural innervation from the esophagus to the colon, and manifested as ulceration, inflammation, obstruction, diarrhea, constipation, and abdominal pain. A growing body of evidence suggests that defects in intestinal barrier function are associated with diseases of the GI tract. Abnormalities in GI function can lead to life-threatening diseases such as IBD or conditions that severely affect quality of life such as gastroesophageal reflux disease (GERD) and IBS. The symptoms of common GI disorders are worsened during periods of stress and negative emotions. Stress has profound effects on the GI tract with both chronic adult stress and early-life stress being capable of modifying central pain circuitry, as well as causing changes in motility and permeability throughout the GI tract. A generally accepted hypothesis is that dysfunction of the bidirectional communication between the brain and the gut in response to chronic stress activates the hypothalamic pituitary (HPA) axis and autonomic nervous system and plays a role in the symptomatology of functional GI disorders such as IBS. Inflammation of the gut mucosal surface has substantial effects on enteric and extrinsic afferent neuronal function though complex changes in neuroimmune interaction. In rodent models, acute colitis alters enteric neuronal function and evidence suggests that these changes are persistent despite recovery from the gut inflammation. Although the effects of an intestinal inflammation on the CNS are less clearly understood, patients with IBD exhibit centrally mediated comorbidities including anxiety, depression, and fatigue, which strongly suggests altered brain function in response to peripheral inflammation perhaps through alterations in central immune-mediated mechanisms. Evidence supporting this concept has been derived from experimental

models of acute colitis in which transient inflammation leads to long-term visceral pain as well as long-term altered expression of CRF in the paraventricular nucleus of the hypothalamus (PVN) (Greenwood-Van Meerveld et al. 2006). Recent evidence points to changes in the gut microbiota playing a key role in GI disorders. Specifically, disorders directly affecting the GI tract such as IBS and CD have been shown to exhibit microbial dysbiosis. Gut inflammation causes marked alterations in the gut microbiota populations and may play a role in gut-brain miscommunication. Another important factor altering the physiology of the GI tract is age. The normal functioning of the gut is compromised as we age, with the elderly often complaining of constipation, hemorrhoids, heartburn, decreased energy, and food allergies. In nonhuman primate models, aging was shown to have profound effects on the intestinal epithelial barrier and the neural control of smooth muscle contractility (Tran and Greenwood-Van Meerveld 2013, 2014). The impact of aging on the intestinal barrier and immune system was recently reviewed (Man et al. 2014). There are also numerous animal studies showing that aging has significant effects on the enteric and extrinsic neural innervation of the GI tract (reviewed by Bitar et al. 2011). Understanding the effects of aging on the gut is of growing and profound importance in light of demographic data demonstrating a steady increase in the aging population.

4.1 Stress and the GI Tract

There is a substantial amount of compelling evidence that psychological and physical stressors play an important role in the onset and modulation of GI disorders. It is a generally accepted hypothesis that dysfunction of the bidirectional communication between the brain and the gut, in part through activation of the principal neuroendocrine stress system, namely the HPA axis, plays a role in the symptomatology of IBS. The HPA axis is activated by stress causing the release of CRF from the paraventricular nucleus of the hypothalamus (PVN) into the hypophyseal portal circulation to bind in the anterior pituitary. Adrenocorticotropic hormone (ACTH) is then released from the pituitary into the systemic circulation to cause the synthesis and release of the glucocorticoid cortisol (*corticosterone in rats*) from the adrenal cortex. Multiple lines of evidence have shown that activation of central mechanism(s) by stress results in colorectal hypersensitivity, and involves descending facilitation from the brain to induce remodeling of colorectal responsiveness via sensitization of spinal dorsal horn neurons. Brainstem regions responsible for the modulation of descending inhibitory pain signals are modulated by both pain and stress. The periaqueductal gray (PAG) receives excitatory signaling from the prefrontal cortex (PFC) and inhibitory signaling from the amygdala. The rostroventral medulla (RVM) receives not only direct nociceptive information from the spinoreticular pathway but also integrated pain and stress signals from the amygdala and PAG. Additionally, the locus coeruleus (LC) and amygdala form a circuit that can potentiate both endocrine and autonomic stress responses. Central structures regulating affective and sensory processes including the amygdala, insula, cingulate, and prefrontal cortex show enhanced activation in IBS patients.

In animal models with visceral hypersensitivity and in IBS patients, imaging studies have shown that limbic regions regulating sensory processing and emotion, including the amygdala, show greater responsiveness in response to visceral stimulation. The amygdala is an important limbic structure involved in the potentiation of the HPA axis with diffuse connections to pain-modulatory networks, and has been implicated to influence visceral sensitivity and may contribute to the aberrant HPA activity observed in IBS patients. The amygdala is sensitive to corticosteroids but in contrast to the hippocampus and prefrontal cortex, the amygdala *facilitates* behavioral, neuroendocrine, and autonomic responses to stress. Thus, this altered balance in stress modulation induced by amygdala hyperactivity may represent an essential aspect of alterations in GI motor function, colonic permeability, and colorectal sensitivity apparent in IBS. In support, elevating amygdala corticosterone in rats by stereotaxically implanting corticosterone micropellets onto the CeA causes a persistent increase in the sensitivity to visceral stimuli as well as induces anxiety-like behavior (Greenwood-Van Meerveld et al. 2001). These findings suggest that in IBS patients exposed to chronic stress increased amygdala activation dysregulates the HPA axis and may be particularly relevant to the etiology and pathophysiology of IBS. Evidence also suggests that remodeling of the epigenome by chronic stress may result in long-term changes in gene expression. Recent studies have also demonstrated the importance of histone acetylation in stress-induced pain of GI origin by showing that direct administration into the brain of a histone deacetylase (HDAC) inhibitor reversed visceral hypersensitivity induced by stress or activation of the amygdala with corticosterone (Tran et al. 2013, 2015). In another study exposure to early-life stress (ELS) was associated with CRF promoter hypomethylation and an increase in CRF transcriptional responses to stress in adulthood suggesting that neonatal stress is capable of causing long-lasting epigenetic changes in the CRF expression within the HPA axis (Chen et al. 2012). During stress and inflammation mast cell mediators such as TNF-α, tryptase [via protease-activated receptor type 2 (PAR-2)], nerve growth factor (NGF), and interleukins may affect paracellular permeability (by altering expression of claudins in the tight junctions) or transcellular uptake route (by increasing macro-pinocytosis), thereby disrupting the barrier to antigens and bacteria. The release of serine proteases from mast cells results in the activation of PAR-2 on epithelial cells; further, activation of PAR-2 has been linked with tight junction disassembly and increased permeability. It is thought that this increase in permeability in response to stress activates and sensitizes sensory nerves within the gut and this barrage of afferent information leads to peripheral and central sensitization to produce visceral hypersensitivity.

4.2 Gut Immune System

The GI tract has a complex innate and adaptive mucosal immune system that is capable of monitoring the luminal content for a diverse array of innocuous antigens including commensal microbiota and food antigens (oral tolerance) versus invasion of the host by potentially toxic pathogens. The immune cells that reside in the intestine mucosa, mesenteric lymph nodes, and Peyer's patches make up the

gut-associated lymphoid tissue (GALT). Cells of the GALT, dendritic cell, macrophages and B-cells make up the antigen-presenting cells and shape the responses of a heterogeneous population of T cells. Such response can be tolerogenic against commensal bacterial antigens or immunogenic against invading pathogens. Together, the cells of the GALT play a role in both innate and adaptive immunity and are pivotal for maintaining immune homeostasis in the gut. The maintenance of a delicate balance between tolerance and immune system activation is key for overall gut health with abnormalities in this equilibrium leading to pathologies of the gut including IBD, CD, and food intolerances. The complexity of the gut immune system is beyond the scope of this chapter; however, the reader is referred to excellent reviews by Mann and Li (2014); Reboldi and Cyster (2016); and Vitale et al. (2016).

4.3 Effect of Aging on the GI Tract

Disorders of the GI tract are common in the elderly; however the precise trait(s) of aging that contribute to the vulnerability of the GI tract are poorly understood. Despite the need to further understand age-associated factors that increase the susceptibility to GI dysfunction, there is a paucity of studies investigating the key factors in aging that affect the GI tract. Thus far studies in rodents have demonstrated that aging alters intestinal smooth muscle contractility (O'Mahony et al. 2002), as well as the neural innervations of the GI tract musculature (Phillips and Powley 2007) and sensory signaling (Keating et al. 2016). Several studies in rodents have also reported an increase in intestinal permeability to macromolecules with age (Hollander and Tarnawski 1985; Katz et al. 1987; Ma et al. 1992; Annaert et al. 2010). Specifically, advancing age was shown to correlate with an enhanced transepithelial permeability of D-mannitol, indicating that there may be an age-associated decline in barrier function (Mullin et al. 2002). Our latest findings showed that a pivotal contributing factor to geriatric vulnerability to GI dysfunction may be increased colonic permeability via age-associated remodeling of intestinal epithelial tight junction proteins. We found that epithelial permeability was greater in colonic biopsies isolated from older baboons (Tran and Greenwood-Van Meerveld 2013). Supporting this observation, we discovered that there is significant tight junction remodeling including a decrease in ZO-1, occludin, and JAM-A proteins, and an increase in claudin-2 expression in old baboon colon compared to young. Upon investigation of the potential mechanisms that may be responsible for age-associated changes in tight junction protein expression, we found an increase in miR-29a, but no observable differences in GLUL expression. We also measured an elevated level of pro-inflammatory cytokines, in the absence of overt inflammation as assessed via routine histology and MPO activity, supporting the claim that inflammatory cytokines modulate intestinal permeability through regulation of tight junction protein expression and trafficking. Advanced age is associated with reduced neurotransmitter content and expression. It has been shown that spinal levels of calcitonin gene-related peptide (CGRP) and substance P (SP) are decreased in aged rats compared to younger animals, as is the expression of dopamine and serotonin receptors. Available data suggests that

advanced age likely has differential effects on subpopulations of neurons in the ENS which demonstrate regional- and species-specific differences. In summary, aging has profound effects on the GI tract and future research is required in relevant animal models to delineate the mechanisms responsible for age-related pathologies of the GI tract.

5 Summary and Conclusion

The GI tract is a complex organ and is responsible for the effective digestion and nutrient absorption. To accomplish this undertaking the GI tract has specialized and region-specific anatomical, histological, and functional diversities that are controlled by a complex interaction between neuronal, hormonal, and paracrine elements. Under pathophysiological conditions, disorders may involve pathological damage to the GI tract as apparent in IBD where the GI tract becomes inflamed and damaged, leading to abdominal pain, diarrhea, and even rectal bleeding. In contrast, other GI disorders, such as IBS, lack a structural or biochemically defined abnormality and are termed "functional" disorders. Currently, there are a limited number of medications available to treat GI disorders in part due to a lack of knowledge of the exact mechanisms underlying the complex physiology of GI motility, absorption, secretion, inflammation, and sensation. Although these significant gaps in the understanding of GI disorders exist today, it is likely that new therapies will emerge from current basic and translational research. Since alterations in the bidirectional communication between the brain and the gut are likely associated with an impairment of gut functions, approaches that have emerged to treat GI dysmotility, abdominal pain, and IBS include mechanisms linking the nervous system in the GI tract to the CNS. Another area of active research is the gut microbiome, and although our understanding of the microbiota within the gut remains in its infancy, major advances linking the intestinal microbiome to the brain-gut axis will likely offer new therapeutic targets for the development of novel drugs to treat GI disorders. Another approach will be to focus on intestinal barrier dysfunction which has been associated with many GI disorders. EEC receptors on the luminal side could also be a potential target of new drugs to activate hormonal and neuronal pathways providing a novel approach to treat diseases such as diabetes and obesity.

Acknowledgements BGVM would like to thank the Departments of Veterans Affairs for their support of her Senior VA Career Scientist and for funding to support the study from her VA Merit grant. The VA had no influence over the preparation, review, or approval of this chapter.

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