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Colonic Physiology

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Key Concepts

- Colonic innervation is supplied by both extrinsic and intrinsic pathways. The extrinsic pathways are derived from the autonomic nervous system including parasympathetic and sympathetic routes. Parasympathetic input is excitatory while sympathetic input is inhibitory to colonic motor function. The intrinsic colonic nervous system consists of the myenteric plexus.
- Short chain fatty acids are produced by the colon as a result of the fermentation of complex carbohydrates by colonic flora. The SCFA, butyrate, is the primary energy source of the colon.
- The colon absorbs sodium and water and secretes bicarbonate and potassium. Aldosterone mediates the process of active sodium absorption in the colon.
- Colonic contractile events are divided into (1) segmental contractions and (2) propagated contractions (including low-amplitude and high-amplitude propagating contractions, LAPC and HAPC, respectively). The main function of HAPC is to propagate colonic contents towards the anus.
- The Interstitial cells of Cajal (ICC) are the primary pacemaker cells governing the function of the enteric nervous system.

Introduction

The colon plays a central role in gastrointestinal (GI) physiology. There are multiple functions that the colon and rectum serve. The primary role of the colon is one of absorption of excess water and electrolytes, serving to salvage valuable fluid and unabsorbed nutrients as well as to create solid stool. It also plays a central role in bacterial homeostasis, serving as a home to billions of commensal bacteria whose role is symbiotic in maintaining the health of the colonic epithelium. The rectum has evolved complicated and elegant mechanisms to store feces and accommodate it while allowing for the selective egress of stool or gas. Understanding the physiologic and histologic components of the colon and rectum are critical to understanding normal and pathologic states.

Embryology

Understanding the embryology of the colon and rectum provides essential information for understanding its function. During the third and fourth weeks of gestation, the primitive gut arises from the cephalic caudal and lateral foldings of the dorsal endoderm lined yolk sac. The mucosa arises from the endodermal layer, however the muscular wall, connective tissue and outer serosal surface arises from the mesodermal layer. By the fourth week of gestation, three distinct regions have differentiated based on their blood supply. The midgut, supplied by the superior mesenteric artery, begins distal to the confluence of the common bile duct in the third portion of the duodenum and includes the proximal two-thirds of the transverse colon. This portion of the intestine maintains a connection to the yolk sac via the vitelline duct. Absence of its obliteration results in a Meckel's diverticulum. The hindgut, which comprises the rest of the distal GI tract, includes the distal transverse colon, descending colon, sigmoid colon, and rectum. This is supplied by the inferior mesenteric artery (IMA). During the fifth week of gestation, the midgut undergoes a rapid elongation which exceeds the capacity of the abdominal cavity. This results in a physiologic herniation through the abdominal wall at the umbilicus. Through the sixth week, continued elongation results in a 90° counterclockwise rotation around the superior mesenteric artery (SMA). The small intestine continues its significant growth, forming loops, while the caudal end enlarges into the cecal bud. During the tenth week, herniated bowel returns to the abdominal cavity, completing an additional 180° counterclockwise loop which leaves the proximal small bowel on the left, and the colon on the right. The dorsal mesentery of

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the ascending and descending colon shortens and involutes resulting in secondary retroperitoneal fixation [1]. The embryology of the distal rectum is more complex. It initially begins as the cloaca which is a specialized area comprising endodermal and ectodermally derived tissue. The cloaca exists as a continuation between the urogenital and GI tracts, however, during the sixth week it begins to divide and differentiate into the anterior urogenital and posterior anorectal and sphincter components. At the same time, the urogenital and GI tracts become separated by caudal migration of the urogenital septum. During the tenth week, while the majority of the midgut is returning to the abdomen, the external anal sphincter is formed in the posterior cloaca as the descent of the urogenital septum becomes complete. The internal anal sphincter is formed during the 12th week by enlargement and specialization of the circular muscle layer of the rectum [1].

Colonic Anatomy

Introduction

The colonic epithelium has both absorptive and secretory functions. The colon is highly efficient at absorbing sodium chloride, water, and short chain fatty acids. In addition, the colonic epithelium secretes bicarbonate, potassium chloride, and mucus. The colonic epithelium is a typical electrolyte-transporting layer that is capable of moving large quantities of water and salt from the lumen towards the blood. Under normal circumstances, the colon is presented with between 1 and 2 l of electrolyte-rich fluid per day. Under normal physiologic conditions, nearly 90% of this fluid is absorbed. The end result is the excretion of feces that has a sodium concentration that approximates 30 mmol/l and a potassium concentration of approximately 75 mmol/l. Under normal circumstances, fecal and plasma osmolality are similar. Colonic epithelial cells are polarized and equipped with numerous ion channels, carriers, and pumps that are localized on both the luminal and basolateral membranes. Many transport proteins have been identified and their functions elucidated. While an in-depth discussion of these mechanisms is beyond the scope of this chapter, important aspects are highlighted below.

Colonic Wall Anatomy

The luminal surface of the colon is lined by epithelium. Deep to this is the submucosal layer, rich in vascular and lymphatic supply. This is surrounded by the continuous inner circular muscle layer and the outer longitudinal muscle layer which has three condensations known as taenia coli. The serosa, or outer layer of the colon, is surrounded by visceral peritoneum.

Colonic Epithelial Cell Types

Three main cell types are present in the colonic epithelium including columnar epithelial cells, goblet cells, and enterochromaffin cells. Columnar epithelial and goblet cells comprise nearly 95% of the cells in the colonic epithelium. The surface and crypt epithelial cells can be differentiated from one another based on proliferative activity, degree of differentiation, and function. Crypt epithelium is highly proliferative, relatively undifferentiated, and secretes chloride. The surface epithelium in contrast has low proliferative activity, is well-differentiated, and is highly absorptive. In general, epithelial cells become increasingly differentiated the farther they are from the crypt base. Thus, the base of the crypts forms the source of continually regenerating epithelial cells. This polarization provides distinct histologic characteristics, which are easily identified on standard H and E staining (Figures 2-1 and 2-2). Recent evidence, however, indicates that ion absorption and secretion occurs at both the surface and crypt levels [2]. The role of the enterochromaffin cells is discussed below.

The cells responsible for the enteric nervous system, the enteric ganglia, are located in the submucosa, otherwise known as Meissner's plexus. An additional layer of ganglia are located between the inner circular and outer longitudinal muscle layers known as Auerbach's plexus. The interstitial cells of Cajal (ICC), are specialized, c-kit positive cells that are thought to primarily serve as the pacemaker cell of the enteric nervous system, linking the colonic submucosa electrochemically with the myenteric plexi. These are the cells of origin of GI stromal tumors (GISTs) which arise from the colonic wall rather than the mucosa [3].

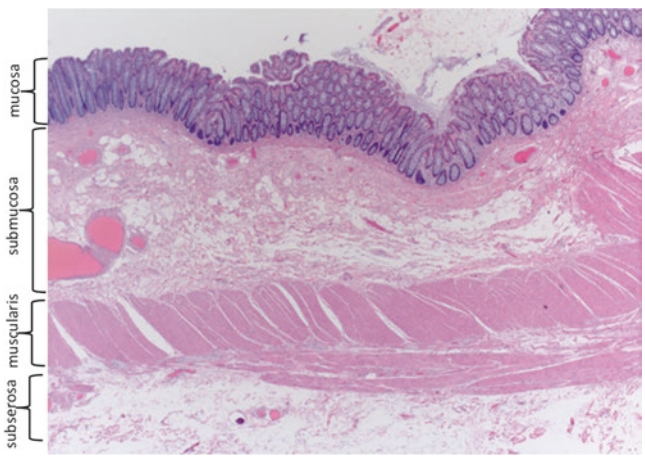

FIGURE 2-1. Normal colonic mucosa. H and E, 250×. The layers of the normal colonic wall are indicated by the *brackets. Courtesy of Julieta E. Barroeta, MD.*

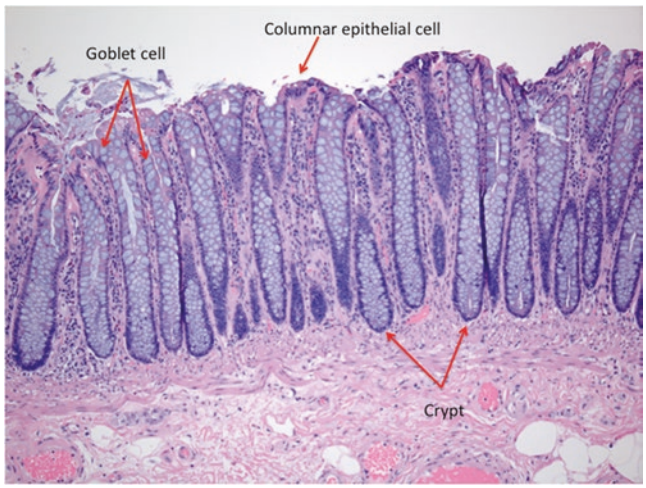

FIGURE 2-2. Normal colonic mucosa. H and E, 1000×. Epithelial cells types are clearly visible including goblet cells and columnar epithelial cells. The crypts are the source of the continually regenerating mucosal cells. *Courtesy of Julieta E. Barroeta, MD.*

Colonic Flora

By the time enteric contents reach the colon, the majority of nutrients have been digested and absorbed by the small intestine. This leaves a fluid rich in electrolytes, bile salts, and undigested starches. These are the primary substrates upon which the colon functions. The colon is home to an enormous quantity of autochthonous flora consisting of more than 400 species of bacteria. Feces contains as many as 10^{11}–10^{12} bacteria/gram of stool, and these bacteria contribute to approximately 50% of fecal mass. The majority of these bacteria are anaerobes which feed on residual proteins and undigested carbohydrates. This microflora contributes several important functions to the host including metabolic support of the colonocyte and gut-associated lymphoid tissue (GALT), which contributes significantly to both innate and adaptive immunity. *Bacteroides* species compose the predominant bacterial type throughout the colon, and they are responsible for almost 2/3 of the bacteria within the proximal colon and 70% of the bacteria in the rectum. The other predominant species are facultative aerobes and comprise *Escherichia*, *Klebsiella*, *Proteus*, *lactobacillus*, and *enterococci*. Unlike the majority of the proximal GI tract, the colonic mucosa does not receive its primary nutrition from blood-borne nutrients. In the colon and rectum, luminal contents provide the primary substrate. The main source of the substrate is undigested dietary fiber. This is metabolized by colonic bacteria through the process of *fermentation*. Cellulose is a partially fermented starch, which leaves behind bulk, whereas fruit pectins are completely metabolized (clarify). The primary end products of this process include short chain fatty acids, including butyrate, and gas. Several of the common dietary complex carbohydrates, including lignin and psyllium, are not metabolized at all, but remain as hydrophilic molecules in stool. These lead to water retention and stool bulking. Butyrate is the main source of energy for the colonocyte. This provides the substrate necessary to maintain epithelial integrity and developmental functions that stimulate epithelial cell differentiation and immune function. Protein fermentation, or *putrefaction*, may result in the formation of potentially toxic metabolites including phenols, indoles, and amines. These toxic end products of bacterial metabolism can lead to mucosal injury, reactive hyperproliferation, and possible promotion of carcinogenesis. Increased stool bulk is felt to provide enhanced colonic transit resulting in decreased time of exposure of the colonic lumen to these toxins, as well as a decreased need for higher intracolonic pressures necessary for segmental motility, a process which may retard the development of diverticular disease. Taken together, these aspects are the reason for many of the recommendations for dietary supplementation with indigestible fiber [4].

Electrolyte Regulation and Water Absorption

Sodium chloride absorption occurs by both electroneutral and electrogenic active transport mechanisms. While electroneutral absorption takes place in both the surface and crypt epithelium, electrogenic absorption appears to be confined to the surface epithelium. A majority of sodium chloride absorption occurs in the proximal colon and is driven primarily through electroneutral absorption by tightly coupled luminal Na^+/H^+ and Cl^-/HCO_3^- exchange. This process is driven by the basolateral Na^+-K^+-ATPase resulting in 1 mol of ATP being hydrolyzed for every 3 mol of NaCl absorbed. Three types of Na^+/H^+ exchangers (NHE) have been identified in colonic epithelium. Similarly, several Cl^- exchange mechanisms have been identified. The luminal Cl^-/HCO_3^- exchange is represented by the anion exchanger type 1 (AE1). A separate Cl^-/OH^- exchange is represented by a protein called DRA (downregulated in colonic adenomas). Human DRA mutations are responsible for congenital chloride diarrhea [2].

Epithelial cells in the distal colon participate in electrogenic absorption of sodium. The epithelial sodium channel (ENaC) mediates this absorption and is located on the luminal surface. Sodium is taken up by the ENaC on the luminal surface and is excreted on the basolateral side by the Na^+-K^+-ATPase. Potassium is secreted on the luminal side and is driven by the electrogenic uptake of sodium. Chloride is absorbed through luminal cystic fibrosis conductance regulator (CFTR) and other chloride channels. Chloride is then excreted on the basolateral side via multiple mechanisms including KCL cotransporter (KCC1), Cl^- channels, and Cl^-/HCO_3^- anion exchangers [2]. The net result is tight regulation of electrolyte secretion in excreted stool (Figure 2-3).

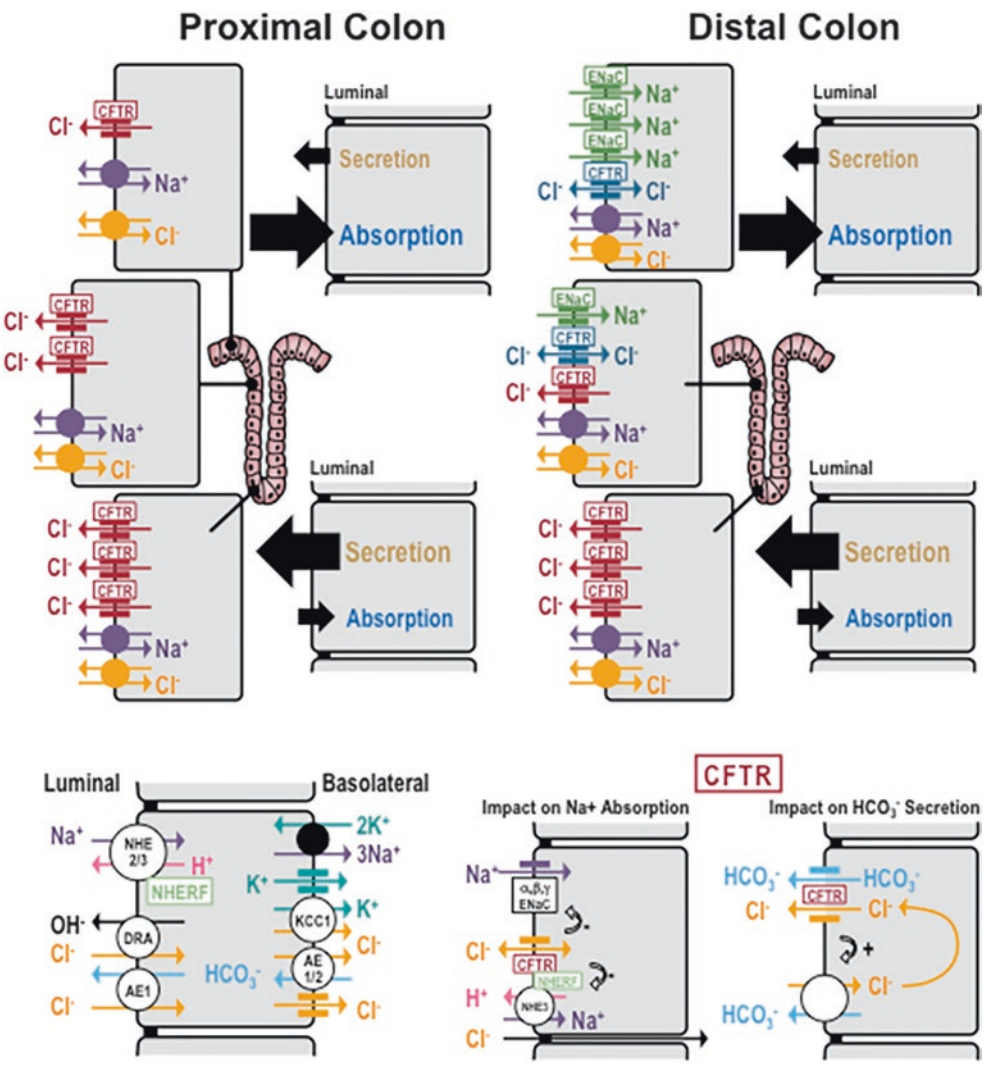

FIGURE 2-3. Schematic of ion-transport channels in proximal and distal colonocytes. *Courtesy of Robin Noel.*

Regulation of sodium absorption is complex and multiple mechanisms are involved. One mechanism of sodium absorption regulation is by feedback inhibition. Namely, changes in intracellular sodium concentration during sodium chloride absorption downregulate ENaC activity. Blood pressure and potassium levels also regulate sodium absorption via angiotensin II. Aldosterone, a mineralocorticoid, is the final endocrine signal in the renin–angiotensin–aldosterone pathway that targets renal and colonic epithelium. Aldosterone is a steroid hormone that is synthesized in the *zona glomerulosa* of the adrenal cortex. Previously, it was thought that aldosterone regulated sodium absorption solely via luminal ENaC. However, aldosterone also increases activity of NHE3. Therefore, aldosterone plays a role in both electrogenic and electroneutral active sodium absorption. Early and late phase aldosterone genomic actions have been identified. In the first 1–6 h, aldosterone-induced proteins including serum and glucocorticoid-inducible kinase (Sgk), corticosteroid hormone-induced factor (CHIF), and K-Ras (KRAS) increase the posttranslational activation of existing ion channels and other proteins involved in ion transport such as ENAc. In the late phase (>6 h), aldosterone acts via the upregulation of nuclear transcription of these receptors. In addition, electroneutral absorption is known to be regulated in response to some G protein-linked receptors, tyrosine kinase-coupled receptors, and protein kinases. For example, activation of protein kinase C, Ca^{2+}/calmodulin-dependent kinase, and increases in cAMP inhibit NHE3 [2, 5].

Evidence also points towards the regulation of sodium absorption by CFTR. ENaC, NHE3, and CFTR are coexpressed in colonic epithelial cells and thus CFTR plays a role in both the electrogenic and electroneutral absorption of electrolytes. CFTR inhibits both electroneutral NaCl absorption as well as electrogenic Na^+ absorption. In the crypts, CFTR is a cAMP-mediated chloride channel that is essential for chloride secretion. In patients with cystic fibrosis, mutations in CFTR result in both impaired chloride secretion and enhanced sodium absorption [2, 6].

Along with the kidneys, the colon assists with potassium homeostasis through the absorption and secretion of potassium. Active potassium absorption is restricted to the distal colon and is mediated by H^+-K^+-ATPase [2].

Water is passively absorbed and can be transported by various pathways including through paracellular shunts and through transcellular flux potentially through aquaporin channels located on luminal and basolateral membrane surfaces [2].

Short Chain Fatty Acid Absorption

As indicated earlier, short chain fatty acids (SCFA) are produced during fermentation of dietary fibers by luminal bacteria. The most common short chain fatty acids include acetate, proprionate, and butyrate. Short chain fatty acids are absorbed by nonionic diffusion and paracellular absorption in the proximal colon. Butyrate is the main energy source for the colonocyte. Butyrate also plays a major role in the stimulation of sodium chloride absorption and inhibition of chloride secretion. Absorption of SCFA plays a significant role in NaCl absorption presumably by the acidification of colonocytes and activation of luminal Na^+/H^+ exchangers. Chloride absorption is also upregulated by increased HCO_3^- production and stimulation of the luminal Cl^-/HCO_3^- exchanger. This HCO_3^- luminal secretion is paramount in regulating luminal intestinal pH. It has been proposed that antibiotic associated diarrhea is secondary to decreased butyrate production resulting in net secretion of fluid [2, 7].

In addition to its role in ionic absorption, butyrate has several other important functions. Butyrate has a trophic effect and stimulates cell proliferation in the crypts. It also reduces the number and size of aberrant crypt foci. This is important as aberrant crypt foci are the earliest precursors of colonic neoplasms. In colon cancer cell lines, butyrate induces apoptosis and cell cycle arrest via inhibition of histone deacetylase. Butyrate also has an anti-inflammatory role primarily by inhibition of nuclear factor kB (NF-kB) in colonic epithelial cells. Some studies have implicated impaired butyrate metabolism in patients with ulcerative colitis. Butyrate stimulates the production of MUC2 mucin and thus may play a role in maintaining the colonic defense barrier. In addition, butyrate may play a role in intestinal motility by regulating gene expression in the enteric nervous system. Finally, butyrate may decrease visceral sensitivity [7, 8].

Despite, the benefits of butyrate discussed above, commercially available butyrate available for oral administration is limited by its short half-life, poor palatability, and side effects such as nausea and anorexia. Rectal formulations are most commonly utilized at this time. Prebiotics and probiotics which produce butyrate are alternative methods of delivery. Prebiotics are nutrients (typically carbohydrates) that support the growth of probiotics bacteria. Probiotics are live bacteria that when consumed in sufficient quantities confer positive health benefits [7, 8].

Secretory Role of the Colonic Epithelium

Another major function of the colonic epithelium is electrolyte secretion. Electrolyte secretion may help transport mucus from the crypts and mucus secretion may be activated by an increase in intracellular cAMP that parallels electrolyte secretion. Chloride secretion occurs predominantly in the crypt cells, but can occur from the surface epithelium as well. Chloride secretion is activated by cAMP-dependent stimulation of CFTR chloride channels. CFTR is the gene product that is affected by any of a number of mutations that cause cystic fibrosis. CFTR is the predominant Cl^- channel in the colon and is responsible for both cAMP- and Ca^{2+}-mediated chloride secretion. CFTR is primarily activated by protein kinase A; however, other second messenger pathways are involved including protein kinase C, cGMP, and calmodulin-dependent kinase [2, 6].

Additional Cl^- channels have been identified in the colonic mucosa that belong to a family of ClC Cl^- channels. The ClC-2 channel is found in colonic epithelium and is regulated by changes in intracellular pH as well as cell volume. They have been localized at tight junction complexes in the crypts [2]. Lubiprostone accelerates colonic transport through the activation of ClC-2 channels on the apical membrane of epithelial cells [9, 10].

As mentioned above, bicarbonate is also secreted to the luminal side of the epithelium and is responsible for the slightly alkaline pH of the colonic lumen [2].

Secretion of electrolytes is often accompanied by secretion of macromolecules. Mucus is probably the most important of these macromolecules and this mucus creates a barrier between the colonic luminal contents and the epithelium [2]. Secreted mucus in the colon forms two distinct layers. The outer loose layer contains bacteria and lubricates feces and protects epithelial cells from abrasion and chemical insult. An inner layer is essentially sterile and is a dense gel that contains antimicrobial peptides, enzymes, and secretory immunoglobulin A (IgA) amongst other substances [3]. Mucus is secreted from goblet cells as well as crypt epithelial cells. Cholinergic stimulation releases preformed mucus. Increased intracellular cAMP induces mucus synthesis. Prostaglandins stimulate mucus secretion from columnar epithelial cells [2].

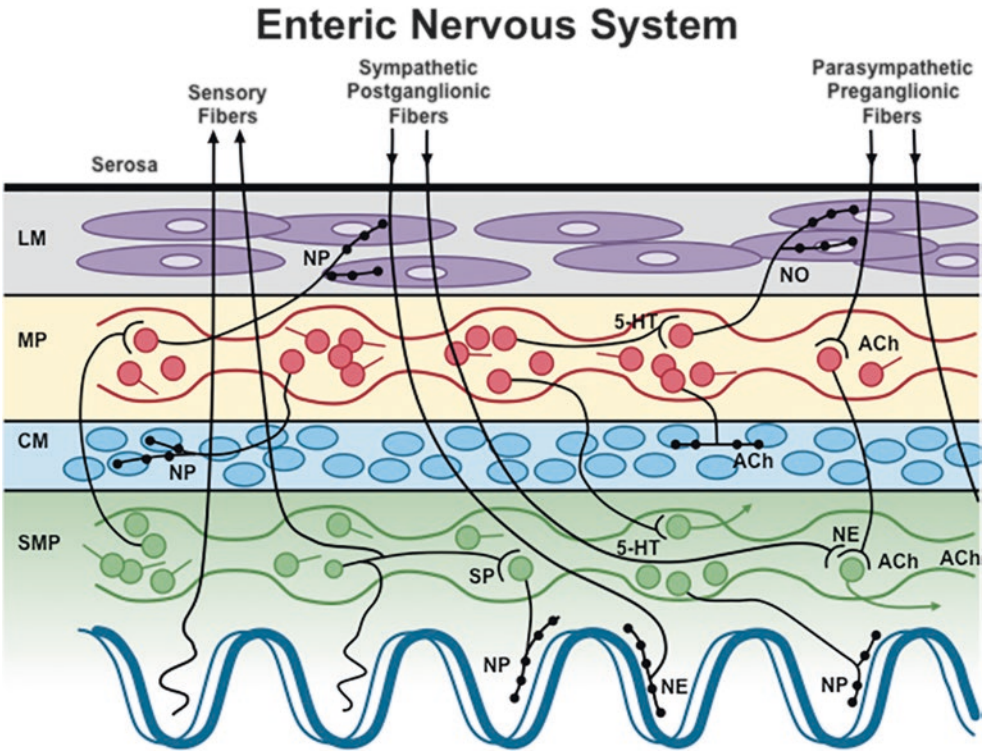

FIGURE 2-4. Schematic representation of the components of the enteric nervous system. *Courtesy of Robin Noel.*

Regulation of Electrolyte and Water Absorption and Secretion

Under normal physiologic conditions, there is a net absorption of sodium chloride and water. Under pathologic conditions, active Cl^- secretion predisposes to the development of diarrhea. Secretion and absorption are mediated by endocrine, paracrine, autocrine, immunologic, and neuronal input [2, 6]. The major neuronal input is via the myenteric (Auerbach's) plexus and the submucosal (Meissner's) plexus. These plexi innervate epithelial as well as vascular smooth muscle cells and regulate colonic blood flow, absorption, and secretion. Food substances, bile acids, and bacterial or viral toxins may act as secretagogues. Secretory hormones and neurotransmitters include vasoactive intestinal polypeptide (VIP), acetylcholine (ACh), histamine, secretin, and serotonin. Substances that inhibit secretion include growth hormone, neuropeptide Y, somatostatin, opiates, and norepinephrine [2]. There is also evidence to suggest that small gaseous molecules, gasotransmitters, also play a role in regulating colonic ion transport. Examples of gasotransmitters include nitric oxide, carbon monoxide, and hydrogen sulfide [6].

Colonic Innervation

Nerves supplying the colon serve to control and modulate colonic motor function. These nerves have a multitude of functions including the following: (1) afferent input via chemoreceptors and mechanoreceptors, (2) efferent output to smooth muscles cells that either stimulate or inhibit contraction by the release of neurotransmitters, (3) modulate the release of neurotransmitters through the release of neuromodulators, (4) control colonic sphincter activity for functions including defecation, and (5) generate signals for the initiation of propagating and nonpropagating motor complexes (see below) [11].

The nerves that control these functions are of both extrinsic and intrinsic origin. The extrinsic pathways originate from the central and autonomic (sympathetic and parasympathetic) nervous systems. Intrinsic innervation consists of the enteric nervous system [11, 12].

It is speculated that central control contributes minimally to baseline colonic tone except as it relates to defecation when voluntary relaxation of the external anal sphincter and contraction of abdominal musculature is required. It is unknown whether the central nervous system provides continuous input to colonic motor control [11].

Autonomic pathways run along parasympathetic and sympathetic chains. Each of these pathways include afferent (sensory) and efferent (motor) innervation. Vagal and pelvic nerves provide parasympathetic input to the colon. Vagal fibers reach the proximal colon along the posterior vagal trunk that follows the arterial blood supply along superior mesenteric arterial branches. The rectum and distal colon receives parasympathetic input from the sacral nerves (S2–S4) through the pelvic plexus. Parasympathetic stimulation stimulates motor activity of the circular and longitudinal muscle throughout the colon. Unlike vagal afferents, the pelvic afferents contain pain fibers and thus convey visceral sensory input (Figure 2-4). Acetylcholine is the major cholinergic parasympathetic neurotransmitter. Noncholinergic neurotransmitters may also play a role [11, 12].

Sympathetic fibers originate from several sources including the lumbar ventral roots (L2–L5), postganglionic hypogastric nerves, and the splanchnic nerves (T5–T12). The lumbar ventral nerve roots provide the main sympathetic supply to the colon. These nerves synapse on the inferior mesenteric ganglia. From there, the post-ganglionic nerves course along the inferior mesenteric artery to synapse on the enteric ganglia. The postganglionic hypogastric nerves also originate from the inferior mesenteric ganglia and then join the pelvic plexus. The hypogastric nerves primarily innervate the anal sphincters. The splanchnic nerves reach the proximal colon as they course along the blood supply. It is speculated that the lumbar nerves innervate the entire colon while the splanchnic nerves likely only innervate the proximal colon. The primary targets of the sympathetic efferent pathways include myenteric ganglia, submucosal ganglia, blood vessels, and sphincters. Sympathetic innervation is inhibitory to the myenteric ganglia and thus inhibits colonic contractions. However, sympathetic input to sphincter muscle is excitatory. Taken together, sympathetic input decreases peristalsis. Amongst numerous other substances, norepinephrine is a neurotransmitter that is known to exert inhibitory effects via a-2 adrenergic receptors in the myenteric plexus [13, 14].

While central and autonomic innervation is important, the intrinsic (enteric) nervous system is unique in that colon can continue to function even when these circuits have been interrupted. Specifically, the colon exhibits reflexes in the absence of extrinsic neural input. This is due to the complex system of 200–600 million ganglia that comprise the enteric nervous system. These ganglia arise from neural crest cells that colonize the gut during embryological development. The enteric nervous system consists of full reflex circuits comprising sensory neurons, interneurons, and motor neurons. This complex system is regulated by a multitude of neurotransmitters and neuromodulators and is responsible not only for controlling colonic motor activity, but also mucosal ion absorption and secretion and intestinal blood flow [3, 11, 12, 15].

Two major sets of ganglia are found in the colon. The myenteric or Auerbach's plexus is located between the longitudinal and circular smooth muscle layers and plays a crucial role in colonic smooth muscle function. The submucosal or Meissner's plexus regulates ion transport [3, 13–15]. The extreme importance of these two plexuses is clear in children with Hirschsprung's disease in which the ganglia of the myenteric and submucosal plexuses are congenitally absent. The aganglionic segments do not relax and peristalsis is disturbed resulting in severe constipation [14]. There is also a mucosal abnormality predisposing to enterocolitis. Nearly 20 types of enteric neurons have been identified and every class of CNS neurotransmitters has been identified in the enteric nervous system. Besides neurotransmitters, other chemicals act in an endocrine or paracrine function to influence the enteric nervous system. While not totally inclusive, substances identified as playing a role in the enteric nervous system include acetylcholine, norepinephrine, 5-hydroxytryptamine (serotonin), dopamine, substance P, neurotensin, vasoactive intestinal peptide, somatostatin, prostaglandins, and neuropeptide Y [11, 12, 16].

Intrinsic primary afferent neurons (IPANs) are the neurons through which enteric reflexes are initiated. These were initially described as Type II neurons with long axonal processes extending to the mucosa and other neurons. However, it has become clear that other non-Type II neurons also play a crucial role in enteric sensation. Nonetheless, these IPANs function to sense changes in luminal chemistry and pressure as well as colonic muscular tone. IPANs are present in the myenteric and submucosal plexi [12, 14, 15]. While the IPANs monitor luminal stimuli, they need to do this transepithelially, since nerve fibers do not directly have contact with the colonic lumen. Therefore, sensory transducer cells in the epithelium are present to respond to mucosal changes. Enterochromaffin (EC) cells represent a type of this sensory transducer cell. EC cells contain large quantities of serotonin. Nearly 95% of serotonin is found in the gut and most of that is stored in the EC cells. When EC cells are stimulated, serotonin is secreted from the basolateral surface of the EC cells of the lamina propria. This is where the serotonin has access to nerve fibers. Serotonin can be excitatory or inhibitory depending on which type of serotonin receptor with which it interacts. Serotonin is not catabolized by enzymes, but is taken up by specific serotonin reuptake transporters (SERT) present in serotonergic neurons. While beyond the scope of this chapter, it is worth mentioning that in patients with irritable bowel syndrome, mucosal expression of SERT is reduced. The importance of serotonin in the enteric nervous system and the role it plays in irritable bowel syndrome has allowed the development of medications to reduce the symptoms of IBS [3, 12, 15]. The 5-HT3 antagonist, alosetron, has been approved for treatment of IBS-associated diarrhea in women [10, 15]. On the other hand, the 5-HT4 agonist, tegaserod, was initially approved for the treatment of IBS-associated constipation. Tegaserod was withdrawn from the market by the FDA in 2007 because of concerns of potential adverse cardiac events [9, 12, 15].

Colonic Motility

Basic colonic motility requirements include slow net caudal propulsion, extensive mixing of semisolid stool, and uniform exposure of luminal contents to the mucosal surface. The colon also needs to rapidly move stool caudally during mass movements. In addition, the colon must be able to store fecal material in the colon until defecation. As reviewed above, most colonic motility is involuntary and is primarily mediated by the enteric nervous system in association with autonomic parasympathetic and sympathetic input.

Cellular Basis of Motility

The muscular apparatus of the colon consists of two distinctive layers of smooth muscle cells including the circular and longitudinal layers. These smooth muscle cells are interconnected by gap junctions that allow electrical signals to spread in coordinated fashion. Very important to this function are the colonic pacemaker cells, also called the interstitial cells of Cajal. The ICC are cells of mesenchymal origin. The ICC generates electrical pacemaker activity that provides the smooth muscle with the mechanism to produce propulsive rhythmic activity. They also appear to serve as conduits for muscle innervation and may transmit sensory information. In colon biopsy specimens, ICC density is able to be measured by c-Kit immunohistochemistry. ICC occur in the submucosa and myenteric borders [3, 17–20]. ICC of the submucosa (ICC-SM) generate electrical stimuli with an oscillatory pattern of 2–4 Hz. Coupling of the ICC-SM to smooth muscle cells triggers large, slow repetitive depolarizations of the smooth muscle referred to as slow waves. Higher frequency oscillations (17–18 Hz) are generated in the ICC of the myenteric border (ICC-MP), but the slow waves from the ICC-SM seem to predominate [17–19].

Motility Patterns and Measurement

Intraluminal colonic motility measurements (manometry and barostat studies) have provided an understanding of colonic motility patterns. Colonic motor activity is not rhythmic, but is characterized by brief (phasic) and sustained (tonic) contractions. At least seven different patterns of human colonic phasic pressure activity have been identified. These include non-propagating and propagating pressure waves and contractions. Non-propagating pressure waves occur randomly for at least 30 s. Simultaneous pressure waves occur simultaneously at least 10 cm apart with an onset time of <1 s. Periodic colonic motor activity also manifests as discrete random bursts of phasic and tonic pressure waves with a frequency of ≥3 per minute and a cycle duration of ≥3 per minute. Similar discrete bursts of phasic and tonic pressure waves also occur in the rectosigmoid and occur predominantly at night and are referred to as periodic rectal motor activity (PRMA). The function of these non-propagating waves is not well delineated, but they may serve as a means for local mixing of luminal contents and may allow for adequate mucosal sampling [19–22].

Propagating pressure waves and contractions serve to propel the colonic contents in aborad and orad directions. Aborad pressure waves include propagating pressure waves that migrate aborad across ≥10 cm at a velocity of 0.5 cm/s and high amplitude propagated contractions (HAPC) of pressures ≥75 mmHg and that migrate aborad ≥15 cm. HAPCs occur approximately six times a day and serve to move stool *en masse* across the colon. Frequently, but not always, these occur prior to defecation. There are also retrograde waves that migrate orad ≥15 cm with a velocity of >0.5 cm/s [19, 21, 22].

Clear physiologic patterns of colonic motor activity are recognized. Phasic activity demonstrates diurnal variation with activity decreasing during sleep and increasing upon awakening. Phasic activity also increases within a few minutes after a meal and continues for up to 2.5 h depending on the nutrient composition and caloric content of the meal. High fat meals elicit more of a response than carbohydrate rich meals. At least 500 kcal needs to be ingested to predictably cause a colonic response to the meal. Finally, colonic instillation of bisacodyl or intravenous neostigmine induces HAPCs. Colonic tone can be measured with a barostat. In physiologic states, colonic tone increases in response to a meal [17, 21–23].

Altered colonic motility may be manifest as constipation. Patients with constipation can be evaluated with several modalities including radiopaque marker studies, radionuclide scintigraphy, magnetic resonance imaging, dynamic defecography, wireless motility capsule (smart pill®, Given Imaging) evaluation, and colonic manometry/barostat studies [17, 18, 22, 23]. While the details of these modalities are discussed in subsequent chapters, it is worth mentioning several common findings in patients with slow transit constipation. Patients with slow transit constipation have a reduced frequency of HAPCs. These patients also lack the normal phasic response that is elicited by the intake of a meal. The diurnal variation of colonic motor activity also may be abnormal in patients with slow transit constipation. Colonic bisacodyl administration also produces a blunted HAPC response in patients with slow transit constipation. A diminished increase in colonic tone following a meal has also been observed in slow transit constipation [21–24]. Loss and injury to the ICC has also been observed in patients with constipation [20]. Taken together, slow transit constipation may be associated with both myopathic and neuropathic etiologies.

Clinical Aspects of Colon Physiology

Ultimately, the main goal of understanding the concepts behind colonic physiology is to be able to translate these into effective therapy for the problems that plague our patients. Subsequent chapters in the text deal more specifically with these issues, but to illustrate this concept, we can consider the use of sacral neuromodulation (SNM). This is not a new therapy; however, its FDA approval for the treatment of fecal incontinence has brought it into the spotlight more recently. In addition to its efficacy for fecal incontinence and its complex interaction with the pelvic floor, European data has also shown its efficacy for the treatment of colonic motility disorders, specifically chronic constipation as well as low anterior resection syndrome. The postulated effectors for its success are based on the known principles of colonic motility

illustrated in this chapter. Dinning et al. performed an elegant study in which patients with slow-transit constipation were treated with SNM. A manometry catheter was positioned colonoscopically, with its tip fixed in the cecum. Electrodes were then placed in both the S2 and S3 foramina and stimulated. They found that stimulation to the S3 nerve root significantly increased pan-colonic antegrade propagating sequences (PS), while stimulation at S2 significantly increased retrograde PSs. During a 3-week trial 75% of patients reported increase frequency of bowel movements and decreased laxative use [25]. The true mechanism of SNM on the enteric nervous system is not known; however, it is hypothesized to affect autonomic innervation, largely through CNS-mediated effects.

The colorectum is a complex organ with multiple roles in human homeostasis. By increasing understanding of its anatomy and complex physiologic components, the colorectal surgeon can gain not only a better understanding of its normal role, but the etiology of derangement in pathophysiologic conditions, as well as an opportunity to develop new therapies based on its known functions. These examples are demonstrated with much greater detail throughout other sections of the text.

References

1. Szmulowicz U, Hull T. Colonic physiology. In: Beck DE, Roberts P, Saclarides T, Senagore A, Stamos M, Wexner SD, editors. The ASCRS textbook of colon and rectal surgery. 2nd ed. New York: Springer Science+Business media LLC; 2011. p. 23.
2. Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: mechanisms and implications for disease. Physiol Rev. 2002;82(1):245–89.
3. Sellers RS, Morton D. The colon: from banal to brilliant. Toxicol Pathol. 2014;42(1):67–81.
4. Fry R, Mahmoud N, Maron D, Bleier J. Chapter 52: Colon and rectum. In: Townsend C, Beauchamp R, Evers B, Mattox K, editors. Sabiston textbook of surgery. 19th ed. Philadelphia: Elsevier Saunders; 2012. p. 1294.
5. Booth RE, Johnson JP, Stockand JD. Aldosterone. Adv Physiol Educ. 2002;26(1–4):8–20.
6. Pouokam E, Steidle J, Diener M. Regulation of colonic ion transport by gasotransmitters. Biol Pharm Bull. 2011;34(6):789–93.
7. Canani RB, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol. 2011;17(12):1519–28.
8. Leonel AJ, Alvarez-Leite JI. Butyrate: implications for intestinal function. Curr Opin Clin Nutr Metab Care. 2012;15(5):474–9.
9. Hussain ZH, Everhart K, Lacy BE. Treatment of chronic constipation: prescription medications and surgical therapies. Gastroenterol Hepatol. 2015;11(2):104.
10. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. JAMA. 2015;313(9):949–58.
11. Sarna SK. Colonic motor activity. Surg Clin North Am. 1993;73(6):1201–23.
12. Furness JB, Callaghan BP, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. Adv Exp Med Biol. 2014;817:39–71.
13. Sarna SK. Physiology and pathophysiology of colonic motor activity (2). Dig Dis Sci. 1991;36(7):998–1018.
14. Furness JB. The enteric nervous system: normal functions and enteric neuropathies. Neurogastroenterol Motil. 2008;20 Suppl 1:32–8.
15. Gershon MD. Nerves, reflexes, and the enteric nervous system: pathogenesis of the irritable bowel syndrome. J Clin Gastroenterol. 2005;39(5 Suppl 3):S184–93.
16. Straub RH, Wiest R, Strauch UG, Harle P, Scholmerich J. The role of the sympathetic nervous system in intestinal inflammation. Gut. 2006;55(11):1640–9.
17. Gudsoorkar VS, Quigley EM. Colorectal sensation and motility. Curr Opin Gastroenterol. 2014;30(1):75–83.
18. Quigley EM. What we have learned about colonic motility: normal and disturbed. Curr Opin Gastroenterol. 2010;26(1):53–60.
19. Brookes SJ, Dinning PG, Gladman MA. Neuroanatomy and physiology of colorectal function and defaecation: from basic science to human clinical studies. Neurogastroenterol Motil. 2009;21 Suppl 2:9–19.
20. Huizinga JD, Chen JH. Interstitial cells of Cajal: update on basic and clinical science. Curr Gastroenterol Rep. 2014;16(1):363.
21. Bassotti G, de Roberto G, Castellani D, Sediari L, Morelli A. Normal aspects of colorectal motility and abnormalities in slow transit constipation. World J Gastroenterol. 2005;11(18):2691–6.
22. Camilleri M, Bharucha AE, di Lorenzo C, Hasler WL, Prather CM, Rao SS, et al. American Neurogastroenterology and Motility Society consensus statement on intraluminal measurement of gastrointestinal and colonic motility in clinical practice. Neurogastroenterol Motil. 2008;20(12):1269–82.
23. Dinning PG, Smith TK, Scott SM. Pathophysiology of colonic causes of chronic constipation. Neurogastroenterol Motil. 2009;21 Suppl 2:20–30.
24. Bassotti G, Crowell MD, Whitehead WE. Contractile activity of the human colon: lessons from 24 hour studies. Gut. 1993;34(1):129–33.
25. Dinning PG, Fuentealba SE, Kennedy ML, Lubowski DZ, Cook IJ. Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow-transit constipation. Colorectal Dis. 2007;9(2):123–32.