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Mechanisms of Diarrhea

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Abstract Diarrhea is a symptom common to a wide variety of gastrointestinal illnesses, and is an important public health challenge in underdeveloped regions of the world. Normal intestinal absorption is a complex process. Recent research offers new insights into normal physiology and pathophysiology. The role of the enteric nervous system and neurotransmitters in the pathogenesis of diarrhea in inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) is being actively investigated. In patients with IBD, ileal and sigmoid biopsies showed altered transepithelial sodium and fluid transport, specifically from decreased expression of the NHE3, NHERF-1, and NHE1 epithelial Na channel. This results in changes in normal intestinal electroneutral NaCl absorption and may be an additional factor contributing to the diarrhea in patients with IBD. Physiologic studies in humans suggest that primary bile acid malabsorption may be caused by an abnormal feedback system resulting in the increased bile salts, which may explain the watery diarrhea. Finally, the role of zinc in treatment of infectious diarrhea led to studies of its effect on intracellular human enterocyte ion secretion. Understanding such basic mechanisms may lead to better and novel therapies for treatment of diarrhea.

Keywords Serotonin (5-HT) · Sodium transporters · Irritable bowel syndrome (IBS) · Inflammatory bowel disease (IBD) · Primary bile salt malabsorption · Secondary bile salt malabsorption · Zinc

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Introduction

Nowhere in the gastrointestinal (GI) tract is the complexity of its systems better exemplified than in the absorption and excretion of fluid and nutrients. When these systems malfunction because of various conditions or diseases, diarrhea can result with dehydration, malabsorption, and malnutrition as a possible consequence. According to the World Health Organization, diarrhea accounts for 4% of all deaths and kills 2.2 million people every year, mostly children [1]. In the developed world, each person in the United States averages one episode of diarrhea per year. This article reviews normal mechanisms of absorption, aspects that can lead to diarrhea, and recent scientific developments in the past several years.

Normal Absorption

The gastrointestinal tract is remarkably effective in its capacity to absorb fluid and nutrients. The daily load of fluid to the small bowel is about 9 liters of water and 800 mg of sodium, comprised of 2 liters of dietary intake and 7 liters of secretions (saliva, gastric, pancreatic, biliary, and intestinal secretions). The small intestine absorbs 6 to 7 liters per day and the colon absorbs 1.5 to 1.9 liters daily, leaving just 0.5 to 0.1 liters typically excreted in the stool. Although normal colonic absorption is nearly 2 liters per day, its compensatory capacity can increase up to 4 to 6 liters per day over time, such as with short bowel syndrome.

Absorption of Electrolytes and Water

The absorption of electrolytes and water is well reviewed in recent papers [2•, 3, 4]. In the small intestine, there is active

absorption of sodium and active secretion of chloride. Water is not absorbed actively; it is passively absorbed with sodium and glucose. There are five known mechanisms of sodium absorption: the primary mechanism in the small bowel is stimulated by nutrients—glucose or amino acids. The four other mechanisms are Na–H exchange in the duodenum and proximal jejunum; parallel Na–H and chloride-HCO_3 exchange (without a parallel Cl–HCO_3 exchange) in the distal small bowel and proximal colon; short-chain fatty acid (SCFA) stimulation of sodium absorption in the colon; and an aldosterone-sensitive sodium absorption via the epithelial Na channel (ENaC; the apical membrane transport mechanism) in the distal colon (Table 1) [2•].

Significant recent research has been conducted on the sodium/hydrogen exchange genes, or *NHE*. The apically located Na–H transporters are called NHE1-3. The NHE3 isoform controls neutral sodium absorption, and is regulated during neutral absorption. It acts through the secondary messengers cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and intracellular calcium (Ca^{2+}), as well as neurohumoral substances. This results in inhibition of neutral NaCl absorption in the ileum and colon, with resultant inhibition of NHE3 activity. An excellent recent review of the role of intracellular calcium in the regulation of electroneutral sodium absorption and the brush border Na^+/H^+ exchanger points out that increased intracellular Ca^{2+} inhibits NHE3 and stimulates Cl^- secretion [4]. Both cAMP and cGMP also stimulate Cl^- secretion. In animal models, some bacterial pathogens increase intracellular Ca^{2+} concentration, resulting in inhibition of NaCl absorption. These include *Salmonella typhimurium, Shigella dysenteriae* type 1 toxin, and *Campylobacter jejuni*. [5–7]. Thus, diarrhea can result from inhibition of Na^+ absorption, and in some cases stimulation of Ca^{2+} secretion as well.

Enteric Nervous System

The enteric nervous system (ENS) also plays a role in intestinal absorption and secretion. Enteric neurons are phenotypically diverse, and act via many types of neurotransmitters, most of which are the same as those in the central nervous system (CNS). Sensory neurons have their cell bodies in the spinal dorsal roots or nodose ganglia and terminate in the intestinal wall and spinal cord. They detect thermal, chemical, and mechanical stimulus energy, resulting in action potentials that are processed in the ENS and CNS. They innervate muscle, epithelial, and secretory cells, among others cells of the GI tract. The nerves do not go into the lumen, yet information about luminal contents is transmitted transepithelially via endocrine cells (eg, enterochromaffin [EC] cells). The EC cells are mucosal sensory cells that release mediators (serotonin, among others) following mechanical or chemical stimulation. These mediators activate intrinsic primary afferent neurons in the submucosal plexus, signaling via interneurons or secromotor neurons, and resulting in fluid and chloride secretion. The EC cells are activated by nutrients, changes in pH, changes in solute concentrations, luminal irritants, mechanical stimuli, and invading microorganisms, with secretion of Cl^-, HCO_3, K, mucin, and fluid. EC cells store serotonin in granules; in fact, the largest stores of serotonin in the human body are found in the GI tract. Serotonin is secreted into the lamina propria, where it accesses nerve fibers. Serotonin is secreted into the portal circulation and intestinal lumen and increases after a meal. In an excellent review, Gershon [8•] describes the large amount of serotonin secreted necessary for sufficient concentrations to reach neural receptors, comparing it to a Niagara Falls that wets all boats in the area. This topic is well reviewed in recent papers [8•, 9].

Regulation of serotonin is an area of great interest, especially in theories about its role in the pathophysiology of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). This has led to the development of serotonin-modulating drugs used to treat IBS. Because serotonin is not catabolized, it must be removed via reuptake by a specific serotonin receptor transport (SERT) in the plasma membranes of serotonergic neurons and mucosal cells. Compounds that inhibit SERT include tricyclic antidepressants, selective serotonin reuptake inhibitor drugs, and cocaine.

Intrinsic primary afferent neurons (IPANs) transmit information from EC cells to processing neurons. IPANs are present in the submucosal and myenteric plexuses. The submucosal IPANs affect mucosal peristalsis and secretory reflexes. They secrete acetylcholine (ACH) and calcitonin gene-related peptide; their effects are potentiated by serotonin. The myenteric plexus IPANs may initiate stretch-driven reflexes and giant migratory contractions. The submucosal IPANs are activated by a receptor 5-HT1p that is unique to enteric mucosa.

Much work was published on the neurotransmitters that result in contraction of smooth muscle and mucosal gland

Table 1 Role of sodium transporters in sodium homeostasis

Transport process	Location
Na–H exchange	Duodenum/jejunum
Nutrient-stimulated Na absorption	Small bowel
Coupled Na–Cl absorption	Ileum/colon
SCFA-stimulated Na absorption	Colon
Na channel	Distal colon

SCFA short-chain fatty acid.
(*Adapted from* Binder [2•].)

secretion. Of the many peptides that have been identified, the main transmitter inducers of smooth muscle contraction are ACH and substance P, and the main transmitters for secretion are ACH, vasoactive intestinal peptide (VIP), and adenosine triphosphate (ATP). There are also enteric neurons that suppress muscle contraction; VIP, nitrous oxide, and ATP appear to play this role. Many motility experts have become very interested in the interstitial cells of Cajal, which serve as pacemaker cells for the stomach and intestinal circular muscle. These are nonneural cells that are vital for small intestine function because they generate electrical slow waves. They also mediate excitatory and inhibitory motor neurotransmission, and serve as nonneural stretch receptors in intestinal muscles. They are associated with vagal afferents, so they may have a role in signaling [10]. They are thought to be important in some disorders of GI tract motility [11].

The mechanisms of neurogenic secretion involve secromotor neurons that release ACH and VIP. Because innervations of blood vessels are linked to secromotor glands, release of these products results in dilation of blood vessels, increased blood flow, and stimulation of release of water, NaCl, bicarbonate, and mucus from the intestinal glands into the lumen. If this normal system is stimulated, watery diarrhea can result. The best example of this is the rare VIP-secreting islet cell tumor.

The neuropeptide Y family includes the gut hormones PYY [1–36] and the truncated form PYY [3–36]. This peptide inhibits intestinal secretion and can decrease diarrhea in experimental animal models. In humans, PYY inhibited prostaglandin E_2 (PGE_2) and VIP stimulated intestinal water secretion [12]. Other peptides and neurotransmitters besides serotonin include γ-aminobutyric acid, neuropeptide Y, substance P, corticotropin-releasing hormone, and neurotensin. An excellent recent review explores the possible role of neuropeptides in IBD [13].

Pathogenesis of Diarrhea

Insights in Infectious Diarrhea

The pathophysiology of diarrhea has numerous mechanisms. Infectious diarrhea is an area that has been studied extensively. As noted earlier, bacterial enterotoxins interact with receptors that transport, and thus can cause an increase in secretion, or can block absorptive pathways, or both. The most common interaction is inhibition of NaH exchange in the small intestine and colon. Peptides that stimulate secretion include ACH, serotonin, histamine, and inflammatory cytotoxins, which act via changes in intracellular cAMP, cGMP, and calcium that control specific pathways of sodium transport. Drugs and toxins can disrupt normal mechanisms and cause diarrhea. Toxins or secretogogues can drive chloride secretion into the lumen, with obligate flow of water, which may have a role in diarrhea in infection and IBD.

New evidence suggests that serotonin may be a target for enteric pathogens. For example, enteropathogenic *Escherichia coli* (EPEC) is a pathogen known to cause diarrhea. It attaches and effaces the mucosal cells, disrupts barrier function, and causes decreased absorption of Na^+, Cl^-, and butyrate. A recent study in animal models using a Caco-2 cell line showed that EPEC inhibits intestinal serotonin transporter function and expression [14]. EPEC infection decreased SERT function very quickly, which would result in an increased serotonin concentration and lead to increased diarrhea. Thus, this SERT function data may be another example of epithelial-microbe interactions.

Dysregulated Electrolyte Transporters in IBD

Inflammation results in diarrhea by many different mechanisms. Inflammation results in mononuclear cells releasing proinflammatory cytokines and eicosanoids, which probably result in decreased absorption but no increase in secretion. Many inflammatory cytokines inhibit Na transport, including tumor necrosis factor-α, interferon-γ, and interleukins (IL-4, -6, -8, -12, -13).

Recent studies in patients with IBD elucidate changes in sodium absorption that may be a result of inflammation. Early evidence of dysregulated electrolyte transporters was found in studies showing that patients with Crohn's colitis had increased Na^+ and CL^- in their stools, although the pH was lower [15, 16].

To test the hypothesis that intestinal Na^+-related transporter channels and proteins that downregulate them could possibly contribute to IBD-associated diarrhea, Sullivan et al. [17•] obtained ileal and sigmoid biopsies from patients with IBD—from areas of active inflammation and uninflamed mucosa—and examined expression of N^+/H^+ exchangers 1–3 (NHE1-3), ENaC, Na^+/K^+-ATPase, the intracellular Cl channel 5 (ClC5), and NHE3 regulatory factors (NHER F1,2). They also studied colon biopsies taken at colonoscopy from individuals with no intestinal inflammation [17•]. They found downregulation of multiple Na^+ transporter proteins, including apical transporters NHE1,3, ENaC, and basolateral Na^+/K^+-ATPase, and downregulation of NHE3 and NHER F1, 2 in mucosa from the sigmoid biopsies of active disease sites in IBD patients compared to biopsies from controls. Moreover, NHE3 was also decreased in half of the sigmoid biopsies from sites of inactive ulcerative colitis and Crohn's disease as well as in ileal biopsies from active Crohn's disease. They observed similar downregulation in inflamed mouse colon using two different chemical-induced models of colitis. Sullivan et al.

[17•] concluded that there is a coordinated downregulation of Na^+-related transporter proteins, and suggest that a common regulating mechanism may exist to systematically downregulate multiple Na^+ transporters and functionally related proteins involved in intestinal Na^+ absorption [17•].

Serotonin in IBS

Serotonin (5-HT) affects absorption or secretion of fluid and electrolytes via interactions with 5-HT receptor subtypes. Rapid intake of 5-HT occurs through a selective SERT transporter that regulates 5-HT in the gut. It is postulated that overactive release of serotonin from EC cells may contribute to diarrhea in IBS. Impairment of SERT function was described [18]. Decreases in SERT can alter motility, and thus could contribute to diarrhea and/or constipation. Studies have documented decreased SERT in biopsies from patients with IBS [19]. The intestinal mucosa in patients with IBS was shown to have increased numbers of EC cells [20]; other studies detected changes in serotonin metabolism [21, 22]. Kerckhoffs et al. [22] documented increased serotonin and serotonin transporter transcript levels in the small intestine of IBS patients. Further evidence for mediators released from the mucosa contributing to the pathogenesis of diarrhea in patients with IBS comes from a recent study of supernatants from biopsies from patients with IBS and from control patients [23]. Supernatants were tested on cell bodies of human submucosal neurons, and found to increase the rate of spike discharges in 58% of these neurons. This activation was inhibited by H1–H3 histamine antagonists, $5HT_3$ receptor antagonists, and protease inhibition. Mast cell density was increased. Although the results were not correlated with IBS subtypes, these findings suggest that serotonin and the ENS may be involved in the pathophysiology of IBS and possibly in diarrhea.

Research in this area has led to development of drugs that affect serotonin metabolism. Alosetron, an antagonist of the 5HT3 receptor, decreased severe diarrhea in patients with diarrhea-predominant IBS [24]. Its prescribing is now restricted by the FDA due to some concern of ischemic colitis. The 5HT4 agonist tegaserod, now off the market, is a prokinetic that was prescribed for constipation-predominant IBS.

Primary Bile Acid Malabsorption

Bile acids are synthesized from cholesterol, with a negative feedback system. Bile acids are synthesized in the liver, transported into bile ducts, stored in the gall bladder, and released into the duodenum, with significant amounts (95%) reabsorbed by distal ileum and returned to the liver. Two pathways exist for bile acid synthesis: a neural (classic) pathway that occurs only in the liver and an acidic (alternative) pathway. Bile acid synthesis is regulated by a negative feedback mechanism. There are several genes that involve intake of conjugated bile acids by enterocytes. The expression of these genes is regulated by transcription factors.

The role of decreased bile acid absorption in the pathophysiology of diarrhea is well established, especially in the setting of ileal disease or intestinal resection, in which it is termed "secondary bile acid malabsorption." Resections of less than 100 cm of terminal ileum interrupt the normal feedback, resulting in increased bile acid synthesis and increased amounts of unabsorbed bile acids reaching the colon, where they stimulate salt and water secretion, causing a watery diarrhea (ie, choleretic diarrhea). When more than 100 cm of distal ileum is resected,

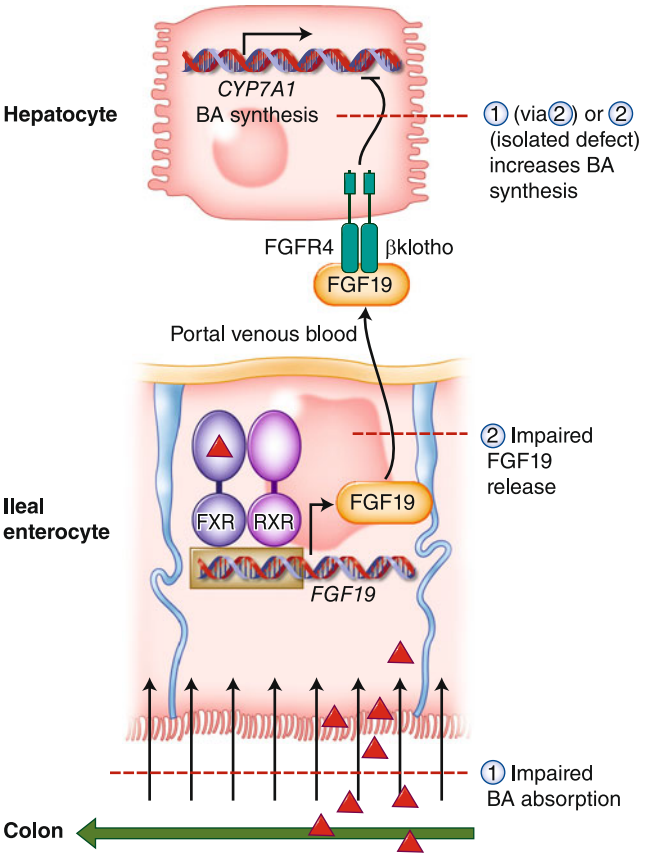

Fig. 1 Diagram of the pathway of enterohepatic circulation of bile acid. Bile acids traverse the ileal enterocyte and activate FXR, the nuclear receptor (shown as a heterodimer FXR, RXR). This promotes synthesis of fibroblast growth factor (FGF) 19, a protein that then travels via the portal circulation to interact with a receptor on the hepatocyte (FGFR4/βklotho), which inhibits CYP 7A1, the rate-limiting enzyme in bile acid biosynthesis. In patients with primary bile acid malabsorption, ileal bile acid transport is impaired and FGF19 release is decreased, leading to increased bile acid bile synthesis. Increased bile acids in the colon may cause diarrhea. *BA* bile acid. (*From* Hofmann et al. [33], with permission.)

the resulting reduced absorption of bile acids exceeds the liver's ability to synthesize adequate replacement, resulting in a decreased bile acid pool, impaired micelle formation, and fat malabsorption. Moreover, the absence of the ileum contributes to diarrhea, with both the loss of absorptive capacity and loss of "ileal brake" [25]. Bile acids in the colon can cause diarrhea by several mechanisms: stimulating sodium and water secretion, inducing mucus secretion, increasing colon motility, stimulating defecation, and/or damaging the mucosa with decreased intestinal permeability [26–28].

The concept of primary or idiopathic bile acid malabsorption (BAM) as a cause of diarrhea dates to the late 1960s, but is controversial. Evidence in support is twofold: first, the improved symptom response of some patients with watery diarrhea to bile salt binders (eg, cholestyramine); second, the demonstration of bile acid malabsorption by the selenium homocholic acid taurine (SeHCAT) test, not available in the United States. The SeHCAT test involves oral administration of selenium-labeled bile acid and measuring retention at 7 days. Retention of less than 10% is abnormal. This test indicates a defect in ileal bile acid retention, but mechanisms are unknown. There is an excellent recent review by Pattni and Walters [29].

New physiologic evidence supports the existence of idiopathic BAM. In mice, fibroblast growth factor (FGF) 15 is synthesized in the ileum and regulates bile acid synthesis and homeostasis. Knockout mice have watery diarrhea that responds to FGF15 therapy [30, 31]. FGF19 is the human ortholog of mouse FGF15. In humans, FGF19 is thought to mediate regulation of hepatic bile acid synthesis. Walters et al. [32•] identified a group of patients with primary BAM, defined by SeHCAT testing and measured blood levels of FGF19 and serum bile acid C4. They found that serum C4 levels were higher than in controls, and FGF19 levels were lower. They postulated that reduced serum FGF19 impairs normal feedback of bile acid synthesis, with resulting increased synthesis that exceeds normal ileal absorption capacity and results in diarrhea. Patients with BAM were shown to have lower levels of FGF19, which could result in larger bile acid pools, with incomplete absorption and increased delivery to the colon (Fig. 1). Thus, an increased bile acid pool resulting from abnormal negative feedback regulation of bile acid synthesis may exist, and may explain BAM in some individuals. Lacking diagnostic testing in the United States, the usual approach is to treat empirically with bile salt binders [33].

Zinc

Recent randomized, controlled trials and meta-analyses show that zinc (Zn^{2+}) decreases severity and duration of diarrhea [34]. The mechanisms are not known but may relate to interactions with enteric pathogens. Enteric pathogens alter fluid secretion via four major intracellular signal transduction pathways: cAMP, cGMP, intracellular calcium, and nitric oxide [35]. A recent study may shed light on the mechanism of action of zinc. Berni Canani et al. [36] showed that zinc ($ZnCl^2$) stimulated ion absorption in human enterocytes and prevented cholera toxin-induced active ion secretion by modulating intracellular cAMP concentration, but not cGMP. To study further effects on the calcium and nitric oxide pathways, the same investigators studied the effect of Zn^{2+} on intestinal ion secretion in these two pathways, using a human enterocyte cell model. They found that Zn^{2+} inhibits Ca^{2+} and that nitric oxide elicited ion secretion in this model, suggesting that zinc interferes with three of the four main intracellular pathways of intestinal ion secretion [37•]. They point out clinical relevance of their work. Rotavirus, a major cause of acute diarrhea, stimulates Cl^- secretion through a phospholipase C− dependent Ca^{2+} signaling pathway. [38]. The finding that Zn^{2+} exerts an effect on Ca^{2+} intestinal ion secretion supports its use in treating rotavirus childhood diarrhea.

Conclusions

Diarrhea has several distinct mechanisms. Studies of serotonin have led to new drugs and new understanding of IBS and IBD pathophysiology. Patients with IBD may demonstrate dysregulated sodium transport. Abnormal feedback of intestinal bile salts may lead to the diarrhea experienced by patients with primary bile acid malabsorption. Zinc was shown to decrease severity of acute diarrhea; intracellular mechanisms of action were evaluated. Basic understanding of normal absorption should lead to insights into pathophysiology and development of novel therapies.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. World Health Organization: Diarrhoeal disease. Available at http://www.who.int/mediacentre/factsheets/fs330/en/index.html. Accessed March 2010.
2. • Binder HJ: Mechanism of diarrhea in inflammatory bowel disease. Ann N Y Acad Sci 2009, 1165:285–293. *This article provides an excellent review of the multiple mechanisms that contribute to diarrhea, and a good overview of normal absorption*.
3. Kiela PR, Fayez G: Ion transport in the intestine. Curr Opin Gastroenterol 2009, 25:87–91.

4. Zachos NC, Kovbasnjuk O, Donowitz M: Regulation of intestinal electroneutral sodium absorption and the brush border Na^+/H^+ exchanger by intracellular calcium. Ann N Y Acad Sci 2009, 1165:240–248.
5. Khurana S, Ganguly NK, Khullar M, et al.: Studies on the mechanism of Salmonella typhimurium enterotoxin-induced diarrhea. Biochim Biophys Acta 1991, 1097:171–176.
6. Kaur T, Singh S, Gorowara S, Ganguly NK: Role of enteric nervous system in Shigella dysenteriae type 1 toxin-induced fluid secretion in rabbit ileum. J Diarrhoeal Dis Res 1995, 13:159–165.
7. Kanwar RK, Ganguly NK, Kanwar JR, et al.: Impairment of Na^+, $K(^+)$-ATPase activity following enterotoxigenic Campylobacter jejuni infection: changes in Na+, Cl- and 3-O-methyl-D-glucose transport in vitro, in rat ileum. FEMS Microbiol Lett 1994, 124:381–385.
8. • Gershon M: Nerves, reflexes, and the enteric nervous system: pathogenesis of the irritable bowel syndrome. J Clin Gastroenterology 2005, 39:S184–S193. *This article is an outstanding review of normal physiology with insights into pathophysiology. It is extremely well written, a "must read" for anyone interested in this topic*.
9. Gershon MD, Tack J: The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 2007, 132:397–414.
10. Sanders KM, Koh SD, Ward SM: Intestinal cells of Cajal as pacemakers in the gastrointestinal tract. Annu Rev Physiol 2006, 58:307–343.
11. Streutker CJ, Huizinga JD, Driman DK, Riddell RH: Intestinal cells of Cajal in health and disease. Part1: normal ICC structure and function with associated motility disorders. Histopathology 2007, 50:176–189.
12. Moriya R, Shirakura T, Hirose H, et al.: NPY Y2 receptor agonist PYY (3–36) inhibits diarrhea by reducing intestinal fluid secretion and slowing colonic transit in mice. Peptides 2010, 31:671–675.
13. Margolis KG, Gershon MD: Neuropeptides and inflammatory bowel disease. Curr Opin Gastroenterol 2009, 25:503–511.
14. Esmaili A, Nazir SF, Borthakur A, et al.: Enteropathogenic *Escherichia coli* infection inhibits intestinal serotonin transporter function and expression. Gastroenterology 2009, 137:2074–2083.
15. Harris J, Archampong EQ, Clark CG: The effect of salazopyrin on water and electrolyte transport in the human colon measured in vivo and in vitro. Gut 1972, 13:855.
16. Hawker PC, McKay JS, Turnberg LA: Electrolyte transport across colonic mucosa from patients with inflammatory bowel disease. Gastroenterology 1980, 79:508–511.
17. • Sullivan S, Alex P, Dassopoulos T, et al.: Downregulation of sodium transporters and NHERF proteins in IBD patients and mouse colitis models: potential contributors to IBD-associated diarrhea. Inflamm Bowel Dis 2009, 15:261–274. *Dysregulation of neutral salt absorption in biopsies from patients with IBD suggests new insights into pathophysiology of diarrhea in these patients. Studies in animal models of colitis provide support*.
18. Guilarte M, Santos J, de Torres I, et al.: Diarrhoea predominant IBS patients show mast cell activation and hyperplasia in the jejunum. Gut 2007, 56:203–209.
19. Coates MD, Mahoney CR, Linden DR, et al.: Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and IBS. Gastroenterology 2004, 126:1657–1664.
20. Barbara G, Stanghellini V, de Giorgio R, et al.: Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004, 126:693–702.
21. Dunlop SP, Coleman NS, Blackshaw E, et al.: Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. Clin Gastroenterol Hepatol 2005, 3:349–357.
22. Kerckhoffs AP, Ter Linde JJ, Akkermans LM, Samsom M: Trypsinogen IV, serotonin transporter transcript levels, and serotonin content are increased in small intestine of irritable bowel syndrome patients. Neurogastroenterol Motil 2008, 20:900–907.
23. Buhner S, Li Q, Vignali S, et al.: Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. Gastroenterology 2009, 137:1425–1434.
24. Krause R, Ameen V, Gordon SH, et al.: A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg Alosetron in women with severe diarrhea-predominant IBS. Am J Gastroenterol 2007, 102:1709–1719.
25. Spiller IF, Trotman BE, Higgins MA, et al.: The ileal brake-inhibition of jejunal motility after ileal fat perfusion in man. Gut 1984, 25:365–374.
26. Mekhjian HS, Phillips SF, Hofmann AF: Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. J Clin Invest 1971, 50:1569–1577.
27. Aldini R, Roda A, Festi D, et al.: Bile acid malabsorption and bile acid diarrhea in intestinal resection. Dig Dis Sci 1982, 27:495–502.
28. McJunkin B, Fromm H, Sarva RP, Amin P: Factors in the mechanism of diarrhea in bile acid malabsorption: fecal pH-a key determinant. Gastroenterology 1981, 80:1454–1464.
29. Pattni S, Walters JRF: Recent advances in the understanding of bile acid malabsorption. Br Med Bull 2009, 92:79–93.
30. Inagaki T, Choi M, Moschetta A, et al.: Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab 2005, 2:217–225.
31. Jung D, Inagaki T, Gerard RD, et al.: FXR agonists and FGF15 reduce fecal bile acid excretion in a mouse model of bile acid malabsorption. J Lipid Res 2007, 48:2693–2700.
32. • Walters JRF, Tasleem AM, Omer OS, et al.: A new mechanism for bile acid diarrhea: defective feedback inhibition of bile acid biosynthesis. Clin Gastroenterol Hepatol 2009, 7:1189–1194. *Patients with primary bile acid malabsorption were found to have a decrease in fibroblast growth factor 19 (FGF19), which may impair normal regulation of bile acid synthesis and explain choleretic diarrhea.*
33. Hoffmann AF, Mangelsdorf DJ, Kliewer SA: Chronic diarrhea due to excessive bile acid synthesis and not defective ileal transport: a new syndrome of defective fibroblast growth factor 19 release. Clin Gastroenterol Hepatol 2009, 7:1151–1154.
34. Bhutta ZA, Bird SM, Black RE, et al.: Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000, 72:1516–1522.
35. Fasano A: Toxin and the gut: role in human disease. Gut 2002, 50:9–14.
36. Berni Canani R, Cirillo P, Buccigrossi V, et al.: Zinc inhibits cholera toxin-induced, but not *Escherichia coli* heat-stable enterotoxin-induced, ion secretion in human enterocytes. J Infect Dis 2006, 191:1072–1077.
37. • BerniCanani R, Secondo A, Passariello A, et al.: Zinc inhibits calcium-mediated and nitric oxide-mediated ion secretion in human enterocytes. Eur J Pharmacol 2010, 626:266–270. *This article is a basic science paper that elucidates intracellular mechanisms of zinc action. Zinc appears to decrease infectious diarrhea*.
38. Lorrot M, Vasseur M: How do the rotavirus NSP4 and bacterial enterotoxins lead differently to diarrhea? Virol J 2007, 4:31.