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Intestinal Secretory Mechanisms in Irritable Bowel Syndrome-Diarrhea

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Abstract

Although diarrhea is the predominant bowel dysfunction in as many as one-third of patients with irritable bowel syndrome (IBS), it is unclear whether there is a specific disorder of intestinal fluid or electrolyte secretion in IBS. Diarrhea is generally considered secondary to accelerated colonic transit in patients with IBS. Although a primary secretory diathesis has not been well documented in patients with IBS with diarrhea (IBS-D), several mechanisms that could potentially contribute to intestinal secretion have been reported. Some of these mechanisms also influence motor and secretory dysfunctions that contribute to the pathophysiology of IBS-D. We review the evidence supporting secretion in IBS-D caused by peptides and amines produced by enteroendocrine cells or submucosal neurons, enterocyte secretory processes, and intraluminal factors (bile acids and short-chain fatty acids). Understanding these mechanisms and developing clinical methods for their identification could improve management of patients with IBS-D.

Keywords

pathogenesis; intestine; SCFA; absorption

Introduction

Diarrhea (D) is the predominant bowel dysfunction of up to one-third of patients with irritable bowel syndrome (IBS) and it appears to be dominant, particularly in patients with post-infectious IBS (PI-IBS).[1] To date, there is no published evidence that there is a specific disorder of intestinal fluid or electrolyte secretion in IBS;[2] thus, the diarrhea in IBS is generally considered secondary to accelerated colonic transit and the reduced volume of the

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proximal colon. The 24-hour stool weight was significantly correlated with the rate at which radiolabeled solid residue emptied from the ascending and transverse colons, and there was also an inverse relationship between emptying rates of those colonic regions and the maxima1 volume of the proximal colon.[3] Reduced volume may result from the increased rectal or colonic tone postprandially and in response to lipids, described in IBS-D.[4,5] Although a primary secretory diathesis has not been well documented in IBS-D, several mechanisms that could potentially contribute to intestinal secretion have been reported, and some of these mechanisms also influence motor and secretory dysfunctions that contribute to the pathophysiology of IBS-D.

Peptides and Amines Produced by Enteroendocrine Cells or Submucosal Neurons

Several peptides and amines such as serotonin, as well as granins, are released from enteroendocrine cells by luminal factors in the diet, by metabolites produced following intraluminal digestion of nutrients [into short chain fatty acids (SCFAs)], and by endogenous chemicals such as bile acids.[6,7]

Table 1 summarizes the literature on the effects of enteroendocrine peptides and amines that may induce intestinal secretion or inhibit absorption of fluids and electrolytes, and the table summarizes information reported in IBS that supports the hypothesis of a role of intestinal secretion in IBS.

The prototype mediator of intestinal secretion is the amine, serotonin [5-hydroxytryptamine (5-HT)]; therefore this will be discussed in greater detail than the other mediators. Serotonin is synthesized primarily in the gastrointestinal tract, stored in the mucosal enterochromaffin cells,[8] and released in response to mechanical and chemical stimulation. It mediates intrinsic reflexes (e.g., stimulation of propulsive and segmentation motility, epithelial secretion and vasodilation) and activates extrinsic vagal and spinal afferents.[9–11]

Circulating 5-HT is derived primarily from the gut and represents the 5-HT that does not undergo re-uptake by the serotonin transporter (SERT) in the cells of the epithelial lining. Circulating postprandial 5-HT levels are increased in platelet-depleted plasma (PDP) in IBS-D[12,13] and PI-IBS,[14] and are reduced[14] or unchanged in IBS-C.[12] Elevated postprandial 5-HT in PDP in IBS-D and PI-IBS, but not IBS-C[12–14], might reflect differences in platelet uptake of 5-HT by SERT, which is disrupted in IBS-D.[15–17] The depletion of platelet SERT in IBS-D may reflect primary deficiency in SERT expression in gastrointestinal mucosa, which has been observed in adults and children with IBS.[18,19] This is supported by platelet 5-HT levels which are reduced in IBS-D[16] and are ~2-fold higher in IBS-C patients compared to healthy controls,[12] which, together with decreased postprandial release of 5-HT in IBS-C, suggests increased SERT reuptake activity.[14]. Alternatively, release of 5-HT to physiological stimuli appears impaired in IBS-C.[12]

In a study combining IBS-C and PI-IBS patients, there was a negative correlation between plasma 5-HT and colonic transit time;[14] although not specifically studied, the transit time may reflect effects of 5-HT on both motor and secretory functions, given the well-

established effects of 5-HT on intestinal secretion and colonic transit, as observed in the carcinoid syndrome.[20,21]

Rectal or colonic mucosal 5-HT levels were increased in PI-IBS[22] and in IBS-C and functional constipation,[23–26] though no statistically different intensity of serotonin immunoreactivity was observed in any IBS group.[27] The increased mucosal content in IBS-C may reflect mucosal storage without release into the lumen or plasma, potentially explaining the lack of fluid secretion, more solid consistency of bowel movements, and low postprandial plasma 5-HT in IBS-C.

The potential role of serotonin in the induction of loose bowel movements in IBS-D is supported by the therapeutic effects of selective serotonergic receptor type 3 ($5\text{-}HT_3$) antagonists (ondansetron, alosetron, ramosetron). These agents are effective in the overall relief of IBS-D and, particularly, in the normalization of bowel function and reduction of urgency in these patients.[28,29]

Chromogranins (Cg) and secretogranins (Sg) are present in secretory vesicles of nervous, endocrine, and immune cells, and CgA appears to be involved in intestinal secretion by inducing formation of secretory granules and release of other peptide hormones such as from enteroendocrine cells.[30] IBS patients with faster colonic transit have higher levels of fecal CgA, SgII, and SgIII, but lower levels of CgB relative to healthy controls,[31] and increased duodenal CgA cell density.[27, 32] Overall, the data suggest that granins packaging neuropeptides indirectly stimulate colonic secretion or motility.[33,34]

Other biogenic peptides that may influence intestinal secretion or absorption are detailed in Table 1. These include somatostatin,[35] PYY,[36–40] and NPY, all of which increase fluid absorption, and their tissue expression is generally reduced in patients with IBS-D.[11,41,42] The mechanism of increased absorption by somatostatin is mediated in part by stimulation of apical membrane Na/H exchange (NHE3 transporter).[43] In contrast, IBS-D is associated with increased mucosal expression of VIP and purinergic receptors,[44] which are associated with intestinal secretion, and histamine, derived predominantly from mast cells, is generally associated with intestinal secretion.[45–51]

Intraluminal Factors: Bile Acids and Short Chain Fatty Acids

Bile acids (BA) stimulate colonic motility,[52] transit,[53] and secretion, primarily through electrogenic chloride secretion (apical chloride channels) and through increase in colonic mucosal permeability[54,55] or activation of colonocyte apical Cl^-/OH^- exchange.[56] An additional mechanism mediating effects of intraluminal BAs is the BA receptor, GPBAR1 (or TGR5),[57] which is expressed in enteric neurons, enteroendocrine cells,[58] and primary spinal afferent and spinal neurons involved in sensory transduction.[59] GPBAR1 mediates the prokinetic actions of intestinal BAs, is required for normal defecation in mice, and mediates colonic fluid secretion.[60]

A systematic review documented bile acid malabsorption (BAM) in a sizeable proportion of patients with chronic functional diarrhea, or IBS-D. BAM was typically identified by the ^{75}SeHCAT retention test which uses a synthetic ^{75}selenium homotaurocholic acid, a BA

that is resistant to bacterial degradation, does not undergo passive absorption, and is actively absorbed in the terminal ileum to enter the enterohepatic circulation or excreted into stool, unaltered by its passage through the colon. Normal retention is >15% at 7 days, and moderate and severe malabsorption are respectively defined by retention <10% and<5% respectively; the level of isotope retention predicts response to BA sequestrants. Five studies (429 patients) indicated that 10% (CI: 7–13) of patients had severe BAM (^{75}SeHCAT 7 day retention <5%); and 17 studies (1073 patients) indicated that 32% (CI: 29–35) of patients had moderate BAM (^{75}SeHCAT retention <10%).[61] Patients with increased fecal BA excretion (>2337mM/48h, the 90th percentile in healthy controls) have increased small bowel permeability, borderline faster colonic transit and higher CDCA proportion in stool and fecal fat excretion compared to IBS-D patients without increased fecal BA excretion.[62]

The human small intestine also secretes fluid in response to perfusion with conjugated di-α hydroxyl BAs.[63,64] In patients with IBS-D, there is evidence that the small intestinal mucosa is more sensitive to secretory effects of BAs compared to mucosa from healthy controls.[65] Variation in *GPBAR1* genotype (rs11554825, which is in strong linkage disequilibrium with mutations that alter expression and function of the receptor)[66] was significantly associated with colonic transit at 48 hours,[67] a surrogate of the intestinal secretory effects of BAs; these genotype data are consistent with a secretory diathesis in patients with IBS-D and could potentially explain the increased secretory response of ileal mucosa to infused BAs.[65]

Short Chain Fatty Acids

In healthy volunteers, 2 to 20% of dietary starch escapes absorption in the small bowel,[68] providing substrate for the generation of short-chain (<6 carbon) fatty acids (SCFAs) by colonic bacteria and increased delivery of water to the colon.[69] SCFAs stimulate intraluminal colonic release of 5-hydroxytryptamine (5-HT)[70] from enteroendocrine cells in rats.[71] The SCFA, propionate, induced transepithelial ion and fluid secretion in guinea pig distal colon mucosal preparations *in vitro* and increased the expression of receptor FFA_2, which co-localizes with chromogranin A in enteroendocrine cells.[72] However, the overall effect of SCFAs is generally to enhance absorption of fluids and electrolytes, effects that are mediated through a common mechanism, that is, the SCFA induced increase in expression of NHE3,[73] although the magnitude of effect may differ among the SCFAs. Moreover, the fecal SCFA profile of patients with IBS-D is characterized by lower concentrations of total SCFA, acetate, and propionate, and a higher concentration and percentage of n-butyrate, which is pro-absorptive. Fecal flora from these patients produced less SCFA in an *in vitro* fermentation system in response to incubations with various carbohydrates and fibers.[74] Overall, since the SCFA composition in stool of IBS-D patients has lower amounts of the pro-secretory propionate and higher amounts of the pro-absorptive butyrate, these data suggest that the SCFAs in stool would be associated with less fluid secretion in patients with IBS-D.

Enterocyte Secretory Processes

There are two lines of evidence that support the existence of enterocyte secretory mechanisms in IBS or functional diarrhea. Guanylate cyclase C (GUCY2C) is a

transmembrane receptor whose extracellular domain is activated by ligands that may be endogenous (e.g. guanylin and uroguanylin) or exogenous (e.g. *E. coli* enterotoxin).

A dominant inheritance gain of function variation in *GUCY2C* gene was reported in a Norwegian family[75] with a rare form of familial diarrhea (FD), characterized by onset of symptoms in infancy, chronic, relatively mild diarrhea, diagnosed as IBS-D. Subsequently, it was demonstrated that this dominantly inherited, fully penetrant disease was due to a heterozygous base substitution, c.2519G→T, in exon 22 of chromosome 12, *GUCY2C*. This functional mutation encodes for the guanylate cyclase-C (GC-C) receptor which induces enterocyte secretion. Conversely, an autosomal-recessive phenotype of meconium ileus (associated with inadequate intestinal fluid and electrolyte secretion) was observed in two unrelated consanguineous Bedouin kindreds, caused by different homozygous loss of function mutations (c.1160A>G; c.2270dupA insertion) in *GUCY2C*.[76]

In order to determine whether this mutation might be overlooked in patients with IBS-D outside Norway or this specific family, we explored the association of *GUCY2C* (c. 2519G→T) mutation in 406 patients with IBS and 227 healthy controls from the upper Midwest U.S.A. None of our IBS patients or controls carried the c.2519G→T mutation in *GUCY2C*, and these results were confirmed by sequencing in 5 randomly selected DNA samples. We concluded that this c.2519G→T mutation in *GUCY2C* is unlikely to be responsible for IBS in patients from the Midwest U.S.A.; however, the identification of the genetic mutation in association with chronic functional diarrhea or IBS-D in the Norwegian family is consistent with the concept that variations in the functional expression of such receptors involved in enterocyte chloride secretion may result in chronic diarrhea that is mistakenly attributed to IBS-D.

The same principle applies to congenital Na^+ diarrheas (rare autosomal recessive disorders characterized by polyhydramnios, hyponatremia, metabolic acidosis, and diarrhea with high sodium content) associated with genetic variations in the SLC9/NHE gene family. The latter is a plasma membrane and organellar family of Na^+/H^+ exchangers (particularly NHE3 and NHE8) which constitute the major way Na^+ is absorbed in the kidney and GI tract.[77]

Congenital chloridorrhea is an autosomal recessive disorder involving the gene, solute carrier family 26 member 3 (SLC26A3), which encodes a transmembrane protein that functions as an apical epithelial $Cl^-/HCO3^-$ exchanger in the colon. The defect in this transporter hinders the absorption of chloride and the secretion of bicarbonate. SLC26A3 is coupled to a Na^+/H^+ exchanger (NHE2 and/or NHE3) that leads to intestinal loss of sodium, chloride, and fluid due to a chloride-rich diarrhea.[78] These congenital diarrheas usually present in infancy; however, they may also cause chronic diarrhea,[79] and the patients may rarely present with chronic diarrhea later in life and may receive a diagnosis of IBS-D.[80]

A second line of evidence comes from recent observations based on expression studies of jejunal or colonic mucosa in patients with IBS. Several groups have reported alterations in expression of tight junction proteins in the jejunal[81] or rectosigmoid mucosa of patients with IBS-D; in some studies, these changes were associated with increased mucosal

permeability.[82,83] However, these alterations do not necessarily prove an intestinal secretory mechanism in IBS-D.

On the other hand, increased mucosal expression of genes demonstrated on RNA sequencing for ion channels suggests more directly that the mucosa of patients with IBS-D may have intrinsic secretory properties.[44] Thus, there are two enterocyte secretory mechanisms that are overexpressed in rectosigmoid mucosa of patients with IBS-D: *GUC2AB* (guanylate cyclase 2B receptor associated with enterocyte chloride channel activation in response to uroguanylin); and *PDZD3* (a protein that associates with guanylate cyclase C and regulates cGMP production following receptor stimulation and chloride secretion).[84]

Conclusion

Although a primary secretory diathesis has not been well documented in IBS-D, several mechanisms that could potentially contribute to intestinal secretion have been reported. Understanding these mechanisms and developing clinical methods for their identification have the potential to enhance management of patients with IBS-D.

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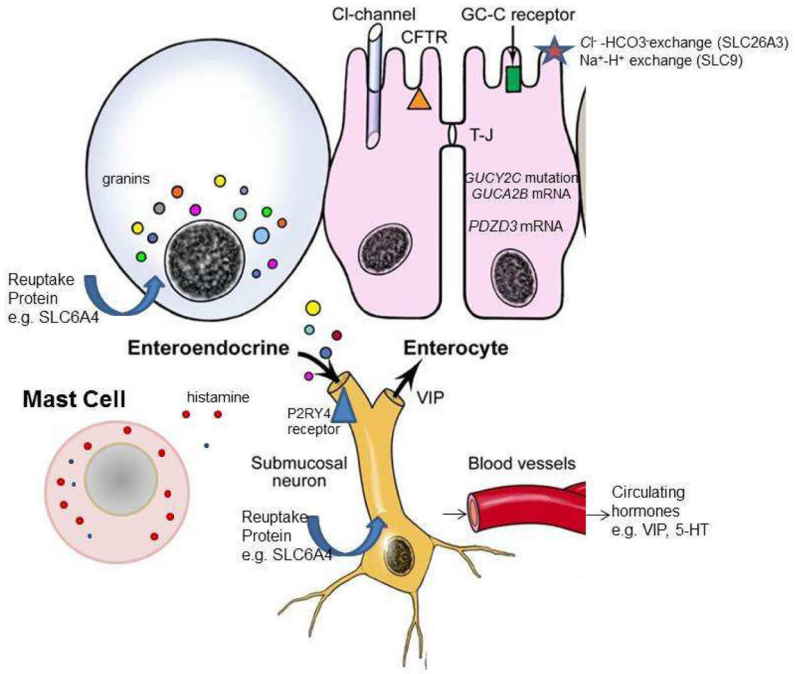

Figure 1.

The critically important cells involved in intestinal secretory processes are the enteroendocrine cells and enterocytes in the epithelium, as well as mast cells and submucosal neurons in the lamina propria and submucosa. From granin vesicles in the enteroendocrine cells, a number of peptides or amines are released to induce intestinal secretion of chloride ions, typically by activation of submucosal neurones or the enterocytes. Similarly, release of proteases and histamine from mast cells induces intestinal secretion. Ion transport channels such as SLC26A3 and SLC9 are important in absorption of sodium and chloride ions and may be mutated to result in congenital diarrhea that may be identified later in life. Rare familial mutations in the gene for the guanylate cyclase C receptor may result in familial diarrhea that is attributed to chronic functional diarrhea. In patients with IBS-diarrhea, increased expression of factors involved in intestinal secretion (e.g., PDZD3, GUCA2B, VIP) or reduced expression of pro-absorptive peptides (e.g., somatostatin) have been reported and are the subject of ongoing research.

Table 1

Examples of Altered Functions of Peripheral Hormones, Amines and Peptides in IBS

Mechanisms	Pathophysiology	Release, distribution, action	Biological and clinical correlates	References
Granins	Chromogranins (Cg) or secretogranins (Sg) in secretory granules mobilize release of peptide hormones from EC cells	Release of (e.g.) 5-HT, PYY, somatostatin (SS) from secretory granules of EC cells into lumen or interstitial fluid	IBS-D or -A higher fecal Cg A, SG II and III and duodenal CgA cell density; changes not specific for IBS; higher CgA and SG associated with faster colonic transit and weakly with symptoms	Montero-Hadjadje 2009; Ohman 2012; El-Salhy 2012,
Serotonin	Derived primarily from EC cells and neurons: mediates intrinsic reflexes (stimulates motility, secretion and vasodilation); activates extrinsic afferents that mediate extrinsic reflexes, sensation	Release from EC cells with re-uptake by the serotonin transporter (SERT) in epithelial cells or platelets; circulating 5-HT represents 5-HT that does not undergo re-uptake	*Plasma* post-prandial 5-HT elevated in IBS-D, and PI-IBS; reduced in IBS-C; *Platelet* SERT uptake is disrupted in IBS-D; *Mucosal 5-HT* elevated in IBS-C and in PI-IBS; *Mucosal SERT* mRNA expression and immune-reactivity decreased in some reports	Donowitz and Binder 1975; Spiller 2000; Mawe, Hofmann 2013; Houghton 2003, and 2007; Atkinson 2006; Bellini 2003; Franke 2010; Foley 2011; El-Salhy 2013
Histamine	Derived primarily from mast cells	Locally released histamine stimulates ileal fluid secretion via H1 receptors, and sensation (possibly via H1 receptors)	Mucosal extracts from IBS activate submucosal and sensory neurons; possible therapeutic benefit with H1 antagonists ketotifen and ebastin in IBS	Linaker 1981 Coelho 1998 Mobarakeh 2000 Barbara 2007 Buhner 2009, Klooker 2010 van Wanrooij 2013
Peptide YY	Derived primarily in enteroendocrine cells	Intraluminal PYY induces small bowel and colon fluid/electrolyte absorption	Rectal biopsy PYY elevated during acute Campylobacter enteritis; normal in PI-IBS by 12 weeks; lower PYY in colonic mucosa in IBS	Playford 1990; Bilchik 1993, and 1994; Liu 1997; Spiller 2000; El-Salhy 2013
NeuropeptideY	Derived from enteric neurons	NPY Y2 receptor agonists reduce intestinal fluid secretion (mice)	NPY levels in both plasma and the sigmoid lower in IBS patients than controls	Zhang et al 2008; Moriya 2010;
Somatostatin (SS)	Derived primarily from enteroendocrine cells and neurons:	SS inhibits NHE1 (basolateral in enterocytes), involved in HCO_3^- secretion	Expression of SS in serum and colonic or rectal mucosa of IBS higher compared with controls; SS in mucosa in IBS-C greater than in IBS-D	Han 2013; Zachos 2005; El-Salhy 2013
Vasoactive Intestinal Peptide (VIP)	Derived mainly from gut secretomotor neurons	VIP modulates secretion and vasodilatation	Sigmoid mucosa and plasma VIP higher in IBS than controls; Rectosigmoid expression of VIP increased on RNA-Seq	Zhang 2008; Han 2013; Camilleri 2014
Purines	P1 and P2 ubiquitous receptors activated by adenosine and extra-cellular nucleotides e.g. ATP	$P1A_{2B}$ receptor regulates colonic Cl^- and water secretion; P2Y activates K^+, Cl^-, HCO_3^- secretion; inhibits Na^+ absorption	Rectosigmoid expression of P2RY4 increased on RNA-Seq	Camilleri 2014

EC=enteroendocrine cells; CHO=carbohydrates; RNA-Seq=mRNA sequencing