J Neurogastroenterol Motil, Vol. 28 No. 4 October, 2022
pISSN: 2093-0879 eISSN: 2093-0887
https://doi.org/10.5056/jnm22093
Journal of Neurogastroenterology and Motility

Review

The Role of Short Chain Fatty Acids in Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that is characterized by abdominal pain and disordered bowel habits. The etiology of IBS is multifactorial, including abnormal gut-brain interactions, visceral hypersensitivity, altered colon motility, and psychological factors. Recent studies have shown that the intestinal microbiota and its metabolites short chain fatty acids (SCFAs) may be involved in the pathogenesis of IBS. SCFAs play an important role in the pathophysiology of IBS. We discuss the underlying mechanisms of action of SCFAs in intestinal inflammation and immunity, intestinal barrier integrity, motility, and the microbiota-gut-brain axis. Limited to previous studies, further studies are required to investigate the mechanisms of action of SCFAs in IBS and provide more precise therapeutic strategies for IBS.
(J Neurogastroenterol Motil 2022;28:540-548)

Key Words
Fatty acids, volatile; Gastrointestinal microbiome; Irritable bowel syndrome

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) characterized by abdominal pain and changes in stool form or frequency. According to the Rome IV criteria, IBS can be classified into 4 subtypes based on the predominant clinical symptoms: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with a mixed stool pattern (IBS-M), and IBS unclassified.[1] It was estimated that the prevalence of IBS among different countries ranged from 10% to 20%.[2] IBS affects the patients' quality of life and places a heavy burden on both the healthcare systems and society.

The pathophysiology of IBS remains poorly understood, complex, and multifactorial. Abnormal gut-brain interactions, visceral hypersensitivity, altered colon motility, and psychological factors are considered as the triggers of IBS.[3] In addition, the gut microenvironment has been implicated in the pathophysiology of IBS. Patients with IBS have a different gastrointestinal microbiome to that of healthy controls.[4-9] Jeffery et al[6] analyzed fecal microbiota and found that subjects with IBS had lower microbiota diversity than healthy controls. They showed that the microbiota composition and IBS subtypes were associations. They found an increase in Firmicutes and a depletion in Bacteroidetes in patients with IBS-C and IBS-M. This resulted from an increase in *Dorea*, *Ruminococcus*, and *Clostridium* spp., and a decrease in the number of *Bacteroidetes*, *Bifidobacterium*, and *Faecalibacterium* spp.[9] A meta-analysis[8] indicated that bacterial colonization, including *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*, was significantly downregulated in patients with IBS-D. Moreover, Botschuijver et

Received: June 25, 2022 Revised: None Accepted: October 7, 2022

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al[5] found a loss of mycobiome diversity in patients with IBS compared to healthy volunteers. The results showed that the ratio of the predominant species, *Saccharomyces cerevisiae* and *Candida albicans*, increased, but the richness and evenness of the total species decreased.

Recently, gut microbiota-derived metabolites, such as short chain fatty acids (SCFAs), amino acid-derived metabolites, and bile acids, have been proposed as the possible etiologies of IBS, and may play an important role in the development of IBS.[10,11] SCFAs are the end products of non-absorbed carbohydrates fermented by obligate anerobic bacteria in the intestine.[12] The most abundant SCFAs in the colon were acetate (C2), propionate (C3), and butyrate (C4), which occurred in a molar ratio of 3:1:1. SCFAs concentrations are high in the proximal colon and cecum (70-140 mM for total SCFAs and 8-40 mM for individual SCFAs) and low in the distal colon (10-70 mM for total SCFAs and 1-20 mM for individual SCFAs).[13,14] Previous reports have indicated that SCFAs show promising effects against various diseases, including obesity, diabetes, cancer, inflammation, immunodeficiency, pain, and depression.[10,15] Increasing evidence has shown altered levels of SCFAs and abundance of SCFAs-producing bacteria in patients with IBS compared to healthy controls, revealing that SCFAs may affect the pathogenesis of IBS.[16]

Although intestinal bacteria and their metabolites, SCFAs, may be involved in the pathogenesis of IBS, their potential mechanism is still unclear. This review aim to summarize the alterations in intestinal bacteria and SCFAs in patients with different IBS subtypes and explore their underlying mechanisms in the development of the disease.

Altered Short Chain Fatty Acids and Short Chain Fatty Acids-producing Bacteria in Irritable Bowel Syndrome

It was reported that fecal samples from patients with IBS expressed significantly higher levels of acetate, propionate, and total SCFAs than controls, which positively related to the severity of symptoms.[17] Altered fecal levels of SCFAs appeared to be associated with different IBS subtypes. Compared to controls, acetate, propionate, and butyrate levels were reduced in patients with IBS-C and increased in patients with IBS-D.[18,19] SCFAs in feces can become non-invasive and reliable biomarkers for the primary diagnosis of IBS, especially propionate and butyrate.[20]

Altered levels of SCFAs in feces is related to the distribution of intestinal bacteria in patients with IBS. It was reported that patients with IBS showed significantly higher counts of *Veillonella* and *Lactobacillus* than controls, which are producers of acetate and propionate.[17] The number of butyrate-producing *Roseburia-Eubacterium rectale* group was lower in patients with IBS-C than in controls.[21] Ruminococcaceae, Clostridiales, and Erysipelotrichaceae, which are butyrate-producing bacteria, decreased in patients with IBS-D and IBS-M.[22]

Short Chain Fatty Acid Receptors

G protein coupled receptors (GPRs), GPR41(known as FFA3), GPR43(known as FFA2) and GPR109A, are known SCFAs receptors (Table 1). GPR41 and GPR43 can be activated by all the 3 SCFAs, whereas GPR109A is activated only by butyrate.[23] All the receptors are coupled to Gi-type proteins, and GPR43 to Gq proteins.[24,25] Both GPR41 and GPR43 receptors are expressed in enterocytes and enteroendocrine L-cells, which release glucagon-like peptide 1 (GLP-1) and peptide YY (PYY).[26,27] GPR43 is expressed in 5-hydroxytryptamine (5-HT)-containing mucosal mast cells, enterochromaffin cells,[27,28] and immune cells such as neutrophils and eosinophils. GPR41 is specifically expressed in neuronal cells of the submucosal and myenteric ganglia[29] and autonomic ganglia such as the vagal, spinal dorsal root, and trigeminal ganglia.[30] GPR109A is reported to be present in the intestinal epithelial and immune cells such as neutrophils and macrophages.[25,31]

Table 1. Short Chain Fatty Acids Receptors Involved in Irritable Bowel Syndrome

Receptor	G protein	Ligand	Cell	Refs
GPR41 (FFA3)	Gi/o	Acetate, propionate, and butyrate	Enteroendocrine cells (L cells) and neuronal cells	23-24, 26, 29, 30
GPR43 (FFA2)	Gi/o, Gq	Acetate, propionate, and butyrate	Enteroendocrine cells, (enterochromaffin cells and L cells), mast cells, and immune cells (neutrophils and eosinophils)	23-24, 27, 28, 29
GPR109A	Gi	Butyrate	Intestinal epithelial cells and immune cells (neutrophils and macrophages)	23-25, 31

GPR, G protein coupled receptors; FFA, free fatty acid receptors.

Potential Mechanism of Short Chain Fatty Acids

Immunity and Inflammation

SCFAs binding to GPR43 and GPR109A in colonic epithelial cells induced an increase in intracellular Ca^{2+} and stimulated K^{+} efflux and hyperpolarisation, thus leading to nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome activation.[32] The NLRP3 inflammasome triggers caspase-1-dependent processing of inflammatory mediators such as IL-18and IL-1β, which play key roles in the maintenance of intestinal homeostasis and protection from colitis development.[33,34] Through GPR41 and GPR43, SCFAs activate the extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase signalling pathways in colonic epithelial cells. This recruits leukocytes and activates effector T cells in the gut, inducing the production of chemokines (C-X-C motif chemokine ligand 1 [CXCL1], CXCL2, and CXCL10) and cytokines (IL-6).[35] Chemokines and cytokines promoted by SCFAs are critical for immune response, the early clearance of pathogen or late excessive inflammatory response.[36] SCFAs can promote the differentiation of effector T cells and regulatory T cells, such as T helper type 1 (Th1) cells, T helper type 17 (Th17) cells, and IL-10-producing T cells, which produce IFN-γ, IL-17, and IL-10. This regulation could be independent of GPR41 and GPR43 through the inhibition of histone deacetylase (HDAC) and regulation of the mechanistic target of rapamycin (mTOR)-S6K pathway in T cells.[37] Alternatively, GPR43-dependent activation of the mTOR-STAT3 pathway promotes the expression of B lymphocyte-induced maturation of protein 1 in T-cells.[38]

Butyrate can act on GPR109A in colonic macrophages and dendritic cells, enabling them to induce the differentiation of regulatory T cells and IL-10-producing T cells, and promote the expression of IL-10 and IL-18, thereby suppressing intestinal inflammation.[39] Binding to GPR41, butyrate inhibits HDAC, activates the mTOR-STAT3 pathway, and increases the expression of aryl hydrocarbon receptor and hypoxia-inducible factor 1α, thus upregulating IL-22 production by CD4+ T cells and innate lymphocytes.[40] IL-22 is central to host mucosal antimicrobial defense. The direct inhibition of IL-22 in intestinal innate lymphoid cells increases the risk of pathogen-mediated diarrhoea.[41,42] In addition, butyrate downregulates lipopolysaccharide-induced pro-inflammatory cytokine production by neutrophils and macrophages, including IL-6, IL-12, and nitric oxide.[43]

These studies have shown that SCFAs can regulate immune and inflammatory responses of the intestinal epithelium, protect the intestinal mucosa, and maintain intestinal homeostasis.

Intestinal Barrier Integrity

SCFAs, mainly butyrate, increase the secretion of the goblet cell-specific mucin 2 (MUC2) and promote reassembling of tight junctions, improving the protective effect of the intestinal epithelium and enhancing the integrity of the intestinal barrier.[44-46] However, this protective effect was dose-dependent, with small doses of SCFAs increasing MUC2 secretion and vice versa at high doses. Propionate and butyrate at concentrations of 1-15 mM have been reported to increase MUC2 expression. The effect of butyrate on MUC2 mRNA level is mediated through active activating protein-1 cis-element, acetylation of histone H3 and H4, and methylation of histone H3 at the promoter.[44] One study showed that butyrate stimulated MUC2 production in individual cells by HDAC inhibition,[45] while another study indicated that a decrease in MUC2 was associated with the ability of butyrate to repress HDAC.[47] This was presumably related to the different butyrate concentrations used in these studies. SCFAs stimulate the expression of MUC2 in intestinal epithelial cells by regulating prostaglandin (PG) production in subepithelial myofibroblasts and increasing the PG1/PG2 ratio.[48] These myofibroblasts are an important source of PGs and are therefore crucial for mucoprotection. Sodium butyrate has been reported to promote the reassembling of tight junctions by inhibiting the myosin light chain kinase/myosin II regulatory light chain pathway and phosphorylation of PKCβ2 in Caco-2 cells.[49] It acts on the Akt signaling pathway to increase the expression of tight junction proteins claudin-3, occludin, and zonula occludens-1 in the colon in a GPR109A-dependent manner.[50]

Motility

SCFAs play an important role in the regulation of gut motility. This modulation varies depending on the type and dose of SCFAs, animal species, and experimental models. In IBS-D mice, the fecal SCFA levels were higher and colonic contractions were stronger than those in controls. SCFAs dose-dependently (0.5-30 mM) reduced the tonic tone, frequency, and amplitude of proximal colonic contractions. Exogenous administration of butyrate (5 mM) increased the colonic transit rate.[51] In a rat model of IBS, total SCFAs potentiated proximal colonic contractions at low concentrations (5-50 mM) and inhibited contractions at high concentrations (50-150 mM).[52] Studies have investigated the effects of SCFAs on proximal and distal colonic contractions in guinea pig models. In the proxi-

mal colon, butyrate increased the frequency of contractions, whereas propionate and acetate decreased the frequency of contractions. In the distal colon, butyrate increased and propionate decreased the rate of colonic propulsion.[53]

SCFAs (100 mM) promotes the secretion of 5-HT from enterochromaffin cells, acted on 5-HT_3 receptors on sensory fibres of the vagus nerve, and stimulates the colonic submucosal plexus and myenteric plexus. Increased Ca^{2+} signalling triggers action potential generation in neurones, resulting in the release of acetylcholine and muscle contraction, which contribute to proximal colonic contractions.[54-56] However, another study came to the opposite conclusion that SCFAs (> 5 mM) inhibited the distal colon contraction frequency through the above mechanism, which may be related to the different concentrations of SCFAs and the different segments of the colon.[57] SCFAs promote the release of 5-HT from intestinal mucosal cells and activated 5-HT_4/5-HT_{1p} receptors in intrinsic calcitonin gene-related peptide-containing sensory neurones. It causes proximal colon contraction and distal colon relaxation, which enhances the peristaltic reflex induced by mechanical stimulation of the colonic mucosa and accelerates colonic transit.[13,58,59] SCFAs increase intestinal contractility by upregulating L-type calcium channels in intestinal smooth muscle cells and/or increasing the number of interstitial cells of Cajal through 5-HT_{2B} receptors.[60-62] The long-term increase in butyrate can significantly increase the number of nitrogenic and cholinergic neurones that promote submucosal and myenteric neuromuscular signal transmission in the colon and enhance intestinal contraction and peristalsis.[63-65]

The short chain fatty acid receptors GPR41 and GPR43 are considered to be involved in intestinal motility.[29] Activation of GPR41 in nitrergic and cholinergic neurones in the submucosal and myenteric plexus suppresses nicotinic acetylcholine receptor-mediated neural activity and reduces intestinal motility.[66,67] Moreover, the activation of GPR43/GPR41 located in enteroendocrine cells releases anorectic PYY and GLP-1, which functionally inhibit gut transit.[68-71] GPR43 selective agonist stimulated GLP-1 secretion in vivo and PYY secretion in the colonic mucosa.[71] Colonic infusion of SCFAs, such as propionate, stimulated PYY release via GPR3.[68,70] Contrary to many previous reports, one study showed that SCFAs increased colonic GLP-1/PYY secretion, but this seemed to be independent of GPR41 and GPR43.[72]

These studies suggest that the effects of SCFAs on colonic motility are not absolute. Promotion or inhibition depends on the homeostasis of SCFA concentrations in different colonic segments.

Microbiota-Gut-Brain Axis

The microbiota-gut-brain axis is crucial in maintaining homeostasis and may impact psychiatric disorders and IBS. Psychological disorders appear to be risk factors for IBS.[73] The gut microbiota communicates with the brain through the neural (autonomic and enteric nervous system), endocrine (hypothalamic-pituitary-adrenal axis and enteroendocrine cells), and immune signaling channels.[74-76] SCFAs have been implicated in microbiota-gut-brain axis interactions. However, the results of different studies vary. Studies have shown negative correlations between the levels of SCFAs (eg, acetate and propionate) and the degree of depression in a patient's stool.[77,78] Exogenous SCFA supplementation reduces stress-induced psychological and behavioral deficits.[79] Another study suggested that emotional problems were significantly related to higher fecal butyrate levels.[80]

Activation of the hypothalamic-pituitary-adrenal-axis is critical for psychoneurological-related diseases, such as depression and anxiety.[81] SCFAs attenuate stress-induced behavioral and physiological alterations by downregulating stress signaling and reducing the responsiveness of the hypothalamic-pituitary-adrenal axis.[79] SCFAs modulate the activity of the sympathetic nervous system at the sympathetic ganglion level via GPR41. Propionate was reported to promote sympathetic activation and adrenaline secretion by activating GPR41.[82] In PC12 cells, the administration of propionate and butyrate increased the expression of tyrosine hydroxylase and the ability of cells to produce catecholamines.[83] In mouse models, gut microbiota dysbiosis and its reduction in SCFAs adversely affect epinephrine release, and oral SCFA supplementation improves the stress-induced epinephrine response.[84] Vagus nerve stimulation was a form of neuromodulation which provided a treatment for chronic pain and depression.[85,86] SCFAs such as butyrate can directly activate vagal afferent nerve terminals in the gut.[87] They stimulated vagal afferents by activating GPR41 in vagal neurones.[30,88,89]

Taken together, SCFAs coordinate pain transmission, depression, anxiety, and stress through neuroendocrine mechanisms.

Future Perspectives

The concentration of SCFAs is susceptible to external conditions such as dietary patterns, antibiotics, and probiotics. A low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol diet was able to improve bloating, flatulence, diarrhea, and systemic symptoms of IBS by reducing microbial fermentation products, including SCFAs.[90] Dietary fiber intake is beneficial for regulat-

Table 2. Selective Short Chain Fatty Acid Receptor Agonists Involved in Irritable Bowel Syndrome

Agonist	Receptor	Function	Model	Refs
AR420626	GPR41	Stimulate anion secretion, suppress neural activity, and inhibit muscle contractions	Rat	66, 99
4-CMTB	GPR43	Stimulate anion secretion	Rat	99
AZ1729	GPR43	Activated and desensitize of neutrophils	Human neutrophil	101
phenylacetamide-1	GPR43	Modulate the intestinal mucosa protection	Mice	102
Compound 1	GPR43	Slow intestinal transit	Mice	71
Compound 58	GPR43	Activate and desensitize of neutrophils	Human neutrophil	101
Compound 110	GPR43	Attenuate intestinal inflammation	Mice	100
Compound 187	GPR43	Attenuate intestinal inflammation	Mice	100

GPR, G protein coupled receptors.

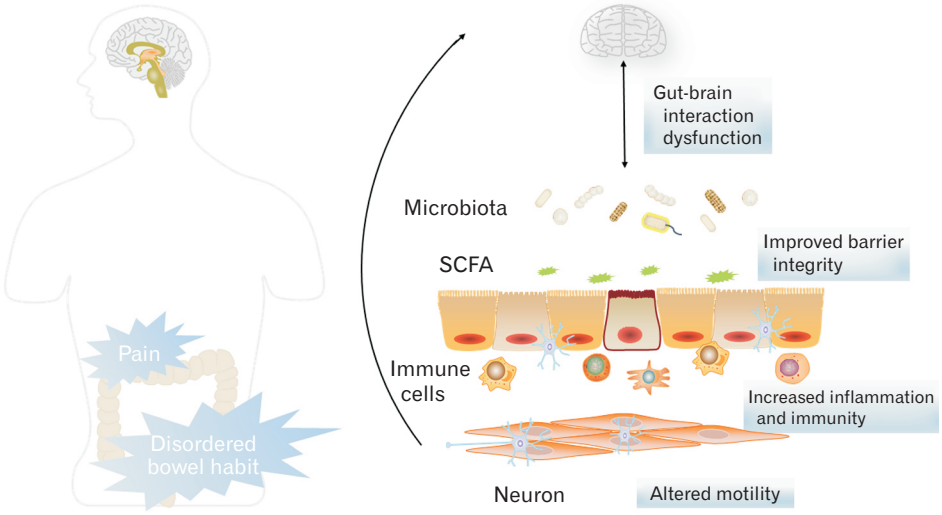

Figure. The mechanism of short chain fatty acids (SCFAs) in irritable bowel syndrome (IBS). The metabolites of gut microbiota SCFAs can modulate intestinal epithelial immunity and inflammation, maintain gut barrier integrity, alter gut motility, and act as part of the microbiota-gut-brain axis, which may underlie the potential mechanisms of SCFAs in the pathogenesis of IBS.

ing gut bacteria and increasing the production of SCFAs.[91] The use of antibiotics could lead to sustained changes in the intestinal microbiota composition and lower concentrations of SCFAs, which is accompanied by a decrease in the immunoreactivity of GPR41 and GPR43 in the intestinal mucosa.[92,93] Although probiotics increase the number of bifidobacteria in the gut, they have no effect on SCFA levels.[94,95] Fecal microbiota transplantation increased the concentration of SCFAs in the stool of patients with IBS and improved their symptoms. Further studies have shown that increased butyrate levels are inversely associated with IBS symptoms after fecal microbiota transplantation.[96-98]

In addition, a series of agonists of SCFA receptors can affect gut function through different mechanisms (Table 2).[66,71,99-102] Selective GPR41 agonists are expected to become promising targets for the treatment of neurogenic diarrheal disorders because of their anti-dynamic and anti-secretory functions.[66] Selective GPR43 agonists inhibit gut transit via the PYY pathways.[71] The selective GPR43 agonist phenylacetamide-1 stimulates enterochromaffin cells and releases 5-HT, which enhances intestinal mucosal defences. However, excessive phenylacetamide-1 leads to injury of the intestinal mucosa by decreasing the blood flow.[102]

Conclusions

In the past decade, many studies have explored the relationship between SCFAs and IBS. Increasing evidence has revealed an important role of altered SCFAs in the pathophysiology of IBS. This review demonstrates the possible mechanism of SCFAs in IBS in terms of inflammation and immunity, intestinal barrier integrity, motility, and the microbiota-gut-brain axis (Figure). As discussed in this review, SCFAs were considered to exert a vital impact to the development of IBS, and modulating the concentration of SCFAs or the activity of SCFA receptors may be a new strategy for treating IBS. However, limited to different models and conditions of previ-

ous studies, further studies are required to investigate the mechanism of SCFAs in IBS and to provide more precise therapeutic strategies for IBS.

Financial support: This study was supported by Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents.

Conflicts of interest: None.

Author contributions: Zhe Shen: guarantor of the article; Shefeng Zhu and Linying Xin completed the literature search; Jiali Wu and Wenxi Jiang wrote the paper; and Chaohui Yu and Zhe Shen reviewed and edited the article. All authors approved the final version of the manuscript.

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