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Pathobiology and Potential Therapeutic Value of Intestinal Short-Chain Fatty Acids in Gut Inflammation and Obesity

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Abstract

Background—The lumen of the gastrointestinal tract contains many substances produced from the breakdown of foodstuffs, from salivary, esophageal, intestinal, hepatic, and pancreatic secretions, and from sloughed cells present in the gastrointestinal lumen. Although these substances were traditionally regarded as waste products, there is increasing realization that many can be biologically active, either as signalling compounds or as nutrients. For example, proteins are broken down into amino acids, which are then sensed by nutrient receptors. The gut microbiome, which is at highest abundance in the ileocecum, has powerful metabolic activity, digesting and breaking down unabsorbed carbohydrates, proteins, and other ingested nutrients into phenols, amines, volatile organic compounds, methane, carbon dioxide, hydrogen, and hydrogen sulfide into volatile fatty acids, also called short-chain fatty acids (SCFAs).

Conclusion—These latter substances are the topic of this review. In this review, we will briefly discuss recent advances in the understanding SCFA production, signalling, and absorption, followed by a detailed description and discussion of trials of SCFAs, probiotics, and prebiotics in the treatment of gastrointestinal disease, in particular ulcerative colitis (UC), pouchitis, short bowel syndrome, and obesity.

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Conflict of interest The authors declare no conflict of interest with any products or commercial entities discussed herein.

Keywords

Probiotics; Short-chain fatty acids; Prebiotics; Synbiotics; Obesity; Colitis

Introduction

The lumen of the gastrointestinal tract contains many substances produced from the breakdown of foodstuffs, from salivary, esophageal, intestinal, hepatic, and pancreatic secretions, and from sloughed cells present in the gastrointestinal lumen. Although these substances were traditionally regarded as waste products, there is increasing realization that many can be biologically active, either as signalling compounds or as nutrients. For example, proteins are broken down into amino acids, which are then sensed by nutrient receptors. The gut microbiome, which is at highest abundance in the ileocecum, has powerful metabolic activity, digesting and breaking down unabsorbed carbohydrates, proteins, and other ingested nutrients into phenols, amines, volatile organic compounds, methane, carbon dioxide, hydrogen, and hydrogen sulfide into volatile fatty acids, also called short-chain fatty acids (SCFAs) [1-3]. These latter substances are the topic of this review.

In this review, we will briefly discuss recent advances in the understanding of SCFA production, signalling, and absorption, followed by a detailed description and discussion of trials of SCFAs, probiotics, and prebiotics in the treatment of gastrointestinal disease, in particular ulcerative colitis (UC), diversion colitis, pouchitis, short bowel syndrome, and obesity.

Short Chain Fatty Acids

SCFA are defined as 1–6 carbon volatile fatty acids existing in straight- and branched-chain conformations. Common SCFAs include formic, acetic, proprionic, butyric, isobutyric, valeric, isovaleric, and caproic acids [4, 5]. We will focus on SCFA production, absorption by the intestinal mucosa, and function, with discussion of selected disease entities, such as inflammatory bowel disease, diversion colitis, pouchitis, short bowel syndrome, and obesity which relate to SCFA production or may be ameliorated by SCFA therapy. In this fashion, we hope to inform the reader on their importance for the maintenance of mucosal integrity, their nutritional value, and also about their use in difficult-to-treat clinical situations.

Short Chain Fatty Acids in the Colon

Acetate, propionate, and butyrate constitute 90–95 % of the SCFA present in the colon [1]. The approximate molar ratios of acetate:propionate:butyrate are 60:20:20. Throughout the different regions of the colon, although absolute SCFA concentrations may vary, molar ratios appear to remain constant. Concentrations of SCFA are 40 % lower in the left than in right colon and are highest in the cecum and ascending colon [6]. In autopsies, Cummings et al. reported total SCFA concentrations of 123 ± 12 mmol/kg (ascending), 117 ± 9 mmol/kg (transverse), 80 ± 17 mmol/kg (descending) and 100 ± 30 mmol/kg (sigmoid and rectum), which agrees with the relative ratios found in another autopsy study by Macfarlane et al. [6,

7]. The pK_a of SCFA is ~4.8, qualifying them as weak acids. Because the colonic pH is 6.0–7.5, 99 % of SCFA are anionic (unprotonated) in this pH range [1].

Short Chain Fatty Acid Production

A variety of substrates may be metabolized by the intestinal microbiome, including resistant starch, dietary fiber, simple sugars, sugar alcohols, sloughed off epithelial cells, mucus, intestinal enzymes and other secretions, and unabsorbed or undigested proteins [1, 2, 8]. Resistant starch refers to starch and products of starch degradation that enter the colon after resisting digestion in the small intestine [3]. In humans, estimates of the amount of dietary starch entering the large intestine range from 5 to 20 % [9]. Fecal SCFA concentrations in humans increase in response to ingestion of resistant starch, which are accordingly considered prebiotics [3], defined as indigestible fermentable fibers that have beneficial effects on health and well being by altering the composition or activity of the gut microbiota [10]. Other prebiotics include fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), lactulose, and inulin [10].

Differences in the rate and ratio of SCFA production depend primarily on the type of substrate as opposed to the composition of the intestinal microbiota [1]. Englyst et al. reported that starch and pectin were degraded faster than xylan and arabinogalactan. The study also reported molar ratios of acetate, propionate and butyrate to be 50:22:29, 50:42:8, 82:15:3, and 84:14:2 from the fermentation of starch arabinogalactan, xylan and pectin, respectively [11]. Inulin and oligofructose produce low levels of butyrate, with oligofructose predominately producing acetate [12]. Branched-chain fatty acids are produced from proteins rather than from carbohydrates [1]. Substrates have varying levels of fermentability, with soluble fibers fermented more completely than insoluble fibers [9]. In vitro, 97 % of pectin, 6–7 % of cellulose, <50 % of wheat bran, and 20–50 % of psyllium are fermentable. Highly fermentable substrates produce greater amounts of SCFA [3].

Short Chain Fatty Acid Absorption

The colon absorbs more than 95 % of SCFA [3]. Although the mechanism of SCFA absorption is not entirely understood, several possibilities have been proposed. In the colon, SCFA absorption is coupled to HCO_3^- secretion [13, 14]. Evidence has been reported for apical SCFA/HCO_3^- in colonocytes [14-16], which is electroneutral with a coupling ratio of 1:1 [16]. The monocarboxylate transporter 1 (MCT1), which belongs to the solute carrier gene family SLC16 [17], is another proposed plasma membrane SCFA transport protein, expressed primarily in colonic epithelial cells [18-20]. MCT1 co-transports H^+ with monocarboxylic acids, such as SCFA, with an H^+:monocarboxylic acid ratio of 1:1 [17, 21]. Since this process is electroneutral, membrane potential is not affected, with the transmembrane SCFA concentration gradient driving SCFA to enter colonocytes from the lumen [21].

The SLC5A8 gene encodes another transporter with a similar functional identity to MCT1, although they do not share genetic similarity. While they both transport monocarboxylic acids, including SCFA, the transporter encoded by SLC5A8 is coupled to Na^+ as opposed to H^+, referred to as the sodium-coupled monocarboxylate transporter 1 (SMCT1) [21].

SMCT1 expression was reported on the apical membrane of human colonic epithelial cells [22, 23]. Unlike the electroneutral transport involved with MCT1, transport via SMCT1 is electrogenic with the stoichiometry of Na^+:monocarboxylic acid varying from 2:1 to 4:1 depending on the substrate [17, 24-26]. SMCT1 has a fairly high affinity for monocarboxylates, with affinity for butyrate >propionate > L-lactate > D-lactate > acetate [25].

Short Chain Fatty Acid Chemosensing

In the wake of the Human Genome Project and other large-scale gene sequencing efforts, thousands of gene sequences that corresponded to known protein families were identified that had no known function. These “orphans” were ascribed function in many cases via subsequent experimentation through the process of “de-orphanization.” One of the largest protein families is the 7 transmembrane (7TM) receptor family, also termed G-protein coupled receptors (GPCRs), which include most of the well-described receptors for neurotransmitters, hormones, and drugs, in addition to other endogenous and exogenous ligands. About ten of the de-orphanized GPCRs have been identified as nutrient receptors, and of those, five have been identified as fat receptors, more specifically, for long chain, medium chain, and SCFAs. The two SCFA GPCRs, termed GPR43 [free fatty acid receptor2 (FFAR2) and GPR41 (FFAR3)] were formally described in 2008 [27] and only recently have been attributed with intestinal chemosensing function, such as in mediating the release of the incretin glucagon-like peptide 1 (GLP-1) from colonic enteroendocrine L-cells [28]. Expression of these SCFA sensing receptors on the apical membrane of L-cells, expressed in particular in intestinal segments exposed to high SCFA concentrations such as the ileocecum and the bovine rumen [29, 30], suggests a plausible mechanism in which luminal SCFAs signal hormonal responses.

Functions of Short Chain Fatty Acids

SCFA produced in the colon contribute approximately 5–10 % towards human energy requirements [31], presumably through their uptake by specific apical solute carriers such as SMCT1 with subsequent hepatic metabolism to CO_2, the tricarboxylic acid cycle and other metabolic pathways. In the colon, preference for oxidation is butyrate > acetate > propionate, glucose and glutamine [32]. By providing additional calories, SCFA maintain energy homeostasis, in particular with loss of small intestinal surface area or function, with resultant insufficient capability to absorb adequate nutrients [21]. SCFA affect cell proliferation and differentiation and can evoke hormone release [1, 33-36]. In colon cancer cell lines, SCFAs induce apoptosis [37-39]. SCFA function as histone deacetylase (HDAC) inhibitors, which are pro-differentiation, pro-apoptosis, and can induce cycle growth arrest in cancer cells [40].

SCFA also modulate inflammation and can affect several leukocyte functions. They suppress production of pro-inflammatory mediators such as TNF-α, IL-6 and NO. Butyrate can enhance the release of the anti-inflammatory cytokine IL-10. SCFA are involved with leukocyte chemotaxis, affecting migration to inflammatory sites. The anti-inflammatory effects of SCFA may be related to the activation of their cognate G protein-coupled receptors GPR41 and GPR43 in addition to their function as HDAC inhibitors [41].

Disease States Linked with SCFAS

Several intestinal diseases, in particular those of mucosal inflammation, are thought to result from SCFA dysbiosis. Accordingly, therapies have been proposed to restore SCFA production or to provide exogenous SCFAs in an attempt to reduce inflammation.

Ulcerative Colitis

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that predominantly affects the colon. In patients with UC, bloody diarrhea and abdominal cramping often occur [42, 43]. Although the pathogenesis of UC is incompletely understood, a combination of factors including genetics, abnormal intestinal microflora, an anomalous immune response to intestinal bacteria, diet, and intestinal barrier dysfunction are thought to contribute [10]. Patients with IBD have an altered composition of the intestinal microbiota compared to healthy individuals [44-46]. Differences in the intestinal microbiota have also been reported between active and inactive IBD and within patients when comparing mucosal samples between inflamed with non-inflamed mucosa [45, 46]. Nuclear factor kappa B (NF-κB) may also contribute to UC pathogenesis. Genes induced during inflammation of the mucosa, such as TNF-α, IL-1β, IL-6, and IL-8, are regulated by NF-κB whereas products of some of these genes can activate NF-κB [47].

The standard treatment for mild UC is 5-aminosalicylic acid (5-ASA), also known as mesalamine, which can be given topically, either orally or rectally. Corticosteroids, such as prednisone, or other immunomodulators such as thiopurines or cytokine blocking antibodies are recommended for patients who do not respond to mesalamine [42]. Some data, however, suggests that altering the gut microbiome may have a salutary effect on IBD. For example, in UC patients, decreased fecal concentrations of butyrate and propionate have been reported [44]. Impaired butyrate oxidation was also reported in patients with UC [48, 49].

In order to restore the hypothesized microbial dysbiosis associated with UC, several therapies have been proposed which are directed at either restoring “beneficial” flora, generating endogenous SCFAs, or providing exogenous SCFAs.

Endogenous Short Chain Fatty Acids: Probiotics and Prebiotics—Probiotics, defined as ingestible bacterial cultures which can survive transit through the GI tract, are believed to promote human health. Prebiotics, which are believed to increase the preponderance of beneficial bacteria by supplying specific nutrients, increase cecal and fecal concentrations of SCFA [50-58]. Several human studies have reported increases in fecal SCFA after probiotic or prebiotic supplementation [54-58]. In one study, patients with active mild to moderate UC were randomized to receive either a bifidobacteria-fermented milk (BFM) or placebo for 12 weeks. Of the 18 patients whose fecal SCFA acid concentrations were collected and analyzed at the end of the 12 weeks, participants in the BFM group experienced significant increases in fecal total SCFA, butyrate, and propionate concentrations over baseline, whereas the placebo group did not [54]. Probiotics and prebiotics can alter intestinal microbiota while having beneficial effects for the host. Probiotics are living microorganisms whereas prebiotics are usually indigestible fermentable fibers. Synbiotics are a combination of probiotics and prebiotics [10]. While prebiotics may

benefit animal models of colitis, results remain inconclusive, with effects dependant on the type of prebiotics and model of colitis used [10, 50, 51, 53, 59-69]. Similarly, the beneficial effects of probiotics in colitis models are strain dependent [52, 53, 70-73]. Very few studies of prebiotics and synbiotics in patients with IBD have been carried out in humans. While some of these studies report reduced inflammation and other protective indicators, small sample sizes and a short treatment duration impair interpretability, with inconclusive data supporting the claimed benefits for UC patients [74-76].

A recent Cochrane publication reviewed the efficacy of probiotics in the treatment of UC. Only four studies that met inclusion criteria were included in the review. These studies included between 32 and 327 patients and were carried out for 3–12 months. Probiotics were compared to mesalamine in three of the studies and to placebo in the fourth. The authors reported no statistically significant differences in the maintenance of remission of probiotics versus mesalamine or placebo. In a pooled analysis of the three studies examining probiotics versus mesalamine, 40.1 % of patients in the probiotic group and 34.1 % of patients in the mesalamine group reported relapse (OR 1.33, 95 % CI 0.94–1.90). In a study of 32 patients, 75 % versus 92 % of patients experienced relapse in the probiotic versus placebo group, respectively (OR 0.27, 95 % CI 0.03–2.68). The authors concluded that there was insufficient evidence to support the efficacy of probiotics in ulcerative colitis for the maintenance of remission [77].

Another Cochrane review evaluated publications designed to assess the efficacy of probiotics for inducing remission in UC. Perhaps due to stringent quality criteria, only four studies again were included. No statistically significant differences were present between the probiotic and the comparison groups. Like the evidence for the use of probiotics in the maintenance of remission in UC, there is insufficient evidence to recommend the use of probiotics in UC for inducing remission [78].

Being a live material and nonstandardized, comparison among probiotic preparations can be difficult. A recent meta-analysis evaluated the use of probiotics in UC according to strain and UC activity. In patients with inactive UC, *E. coli* Nissle 1917 was comparable to mesalamine in preventing relapse. Promising evidence was also presented supporting the induction of remission with the commercial probiotic preparation VSL#3—a proprietary mixture containing viable lyophilized bacteria of four strains of lactobacillus (*L. casei, L. plantarum, L. acidophilus*, and *L. delbrueckii subsp. bulgaricus*), three strains of bifidobacterium (*B. longum, B. breve*, and *B. infantis*), and one strain of *Streptococcus salivarius* subsp in patients with mild to moderately active UC. Interpretation of these studies is however limited by small sample size, high dropout rates, and inadequate controls [43].

Exogenous Short Chain Fatty Acids—Exogenous SCFA administration has been studied in experimental models of colitis in addition to small clinical trials.

Experimental UC Models: A study of male Wistar rats with 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis reported clinical and functional recovery in rats treated with butyrate enemas. Compared to rats that were untreated or treated with saline enemas, rats in

the butyrate group had improvements in inflammation, diarrhea, colonic damage score, tissue myeloperoxidase (MPO) activity, and electrolyte absorption [79]. In male Wistar rats with TNBS-induced colitis, rats treated with sodium butyrate enemas, 5-ASA, and a combination of sodium butyrate and 5-ASA all showed improvements in diarrhea, colonic damage score, and MPO activity. These improvements were accompanied by markers of mucosal inflammation and integrity such as increased trefoil factor3 (TFF3) mRNA expression, which is believed to stabilize colonic mucus, decreased production of the serum cytokine IL1β and tissue expression of the pro-inflammatory protein NF-κB, with the greatest effects in the combination treatment group [80]. Not all studies of SCFA enemas in experimental colitis have shown benefit. For example, bowel thickness and lesion scores increased in Sprague–Dawley rats with TNBS-induced colitis following administration of SCFA enemas compared to saline enemas [81].

Uncontrolled Trials: Small, uncontrolled clinical studies dating from the 1990s have reported beneficial effects of SCFA on UC (Table 1). Breuer et al. administered 100 ml SCFA (80 mM sodium acetate, 30 mM sodium propionate, 40 mM sodium butyrate) intra-rectally twice a day for 6 weeks in 12 patients with active UC. Nine out of the ten subjects who completed the trial were at least “much improved” by trial’s end. Significant improvements were reported for stool frequency, rectal bleeding, and lifestyle impact; improvements in endoscopic mucosal appearance, erosions, and exudates, with decreased frequency of crypt abscesses and mucin depletion were also reported [82]. In ten patients with ulcerative proctosigmoiditis, 60 ml of 80 mM sodium butyrate was administered nightly for 6 weeks. Six of these patients responded with a fall in the ulcerative colitis disease activity index (UCDAI) score by 3 or more points, with four judged to have a complete response, with a UCDAI of 3 or less at the end of the trial [83]. Nine patients with distal UC received an enema twice a day of 100 ml 80 mM sodium butyrate plus 2 g 5-ASA for four weeks. Seven of the nine patients had significant improvement in clinical scores and decreases of reported blood in stool, stool frequency and endoscopic scores [84].

Controlled Studies: Several controlled studies, listed in Table 2, address the administration of exogenous SCFAs on UC. A double-blind placebo-controlled trial by Scheppach et al. randomized 47 patients with distal UC to receive a mixed SCFA enema (60 mM sodium acetate, 30 mM sodium propionate, 40 mM sodium acetate), 100 mM sodium butyrate alone, or a saline placebo twice a day for 8 weeks. UCDAI decreased significantly in all groups with no significant differences between groups. Remission was 47 % for SCFA, 38 % for butyrate, and 25 % for placebo [86]. Breuer et al. randomized 103 patients with distal UC to receive an enema of mixed SCFA (80 mM sodium acetate, 30 mM sodium propionate, 40 mM sodium butyrate) or saline for 6 weeks. While more patients receiving the SCFA enema showed improvement, the results were not statistically significant, possibly related to poor compliance. Every patient in the SCFA group who improved, compared to 37 % who did not, was compliant [87]. A double-blind placebo controlled trial by Vernia et al. of 51 patients with chronically active mild to moderate distal UC randomized patients to receive 2 g topical mesalamine with 80 mM sodium butyrate or 2 g topical mesalamine with 80 mM NaCl b.i.d. for 6 weeks. A significant difference in the rate of remission, with 25 % of the treatment group compared to 4 % of the control group responding, was reported. Compared

to baseline values, both groups had significant improvement in clinical scores and improvement in UCDAI scores. The butyrate group had significant improvements compared to the control group for clinical scores, stool frequency, urgency, and self-assessment [88]. Lührs et al. randomized 11 patients to receive a 60 ml b.i.d. enema of 100 mM sodium butyrate or saline for 8 weeks. DAI scores were significantly lower in the butyrate group compared to the control group at trial completion, accompanied by reduced NF-κB translocation in lamina propria macrophages [89]. In 35 UC patients in clinical remission randomized to receive a 60 ml enema daily for 20 days containing either 100 mM sodium butyrate or saline, butyrate had only minor effects on inflammatory measures, with significant increases in colonic IL-10/IL-12 ratios and increased colonic concentrations of chemokine (C–C motif) ligand 5 (CCL5) in the butyrate group compared to placebo. No significant differences were found on oxidative stress parameters [90].

In 39 patients with distal UC treated with a 60 ml daily enema of 80 mM sodium butyrate or control solution of NaCl (with 0.8 mM sodium butyrate added to produce a butyrate odor), no statistically significant differences were found in clinical improvement or remission, mucosal appearance scores, or histological scores [91]. Finally, in a randomized administration of hydrocortisone, 5-ASA, and SCFA enemas, patients with proctosigmoiditis had similar improvements in endoscopic scores, histological scores, and symptom improvement, although SCFA were more cost effective [92].

Since drug administration by enema is cumbersome, inconvenient and disliked by many, oral SCFA administration has been advocated. For example, mice with DSS-induced colitis fed a control diet plus sodium butyrate had improvements in mucosal inflammation, diarrhea, crypt length, and the inflammatory profile of the intestinal mucosa, with improvements in the cytokine pattern of the small intestine [94]. In an uncontrolled trial of 216 patients with mild to moderate UC, patients were given three tablets containing 307 mg butyrate and 250 mg of the prebiotic inulin t.i.d. in addition to 300 mg of mesalamine t.i.d. for 6 months. At the study end, of the 196 subjects completing the trial, compliance was 92 %, 110 (56 %) patients had complete clinical and endoscopic remission, 46 (23 %) had clinical remission and endoscopic improvement, 14 (7 %) had complete clinical remission and slight endoscopic improvement, and 26 (13 %) had no clinical or endoscopic improvement, with lower ulcerative colitis disease activity index (UCDAI) scores [85]. In a randomized double-blind placebo-controlled trial, 30 patients with mild to moderate UC colitis received 2.4-g oral mesalamine combined with either 4 g butyrate or placebo daily for 6 weeks. Both groups showed significant decreases in UCDAI scores and improvement in clinical index and histological scores. When considering clinical and UCDAI scores, there was significantly greater improvement in the butyrate versus placebo group [93].

Pouchitis

The ileal pouch-anal anastomosis procedure is performed in some patients with UC or familial adenomatous polyposis (FAP) in order to avoid ostomy creation. Pouchitis, or inflammation of the ileoanal reservoir, is a common complication occurring in 20–50 % of UC and 0–11 % of FAP patients [95]. Fecal SCFA are reduced in patients with pouchitis

[96, 97]. Since the pathogenesis of pouchitis is thought to be similar to UC, probiotics and SCFA have been studied as treatments.

Using meta-analysis, probiotics were reported to be effective in the prevention and treatment of pouchitis [98, 99]. VSL#3 was the most effective probiotic in the treatment of pouchitis [99]. SCFA enemas do not improve symptoms, although only a very few small studies have been published [97, 100].

Diversion Colitis

Diversion colitis, an inflammatory condition that occurs in nonfunctioning segments of the colon, develops in most patients after surgical diversion of the fecal stream. Several mechanisms for the development of diversion colitis have been proposed, including a nutritional deficiency of SCFA in the colonic lumen [101, 102]. Studies in Wistar rats suggest that the use of SCFA enemas may improve symptoms [102, 103]. Harig et al. [101] successfully treated patients with diversion colitis using SCFA enemas. Not all studies, however, have found improvements with the use of SCFA enemas in diversion colitis. A study by Guillemot et al. [104] found no endoscopic or histological improvements, although this study was shorter in duration than the study by Harig et al.

Short Bowel Syndrome

Short bowel syndrome (SBS) is associated with numerous complications including dehydration, diarrhea, electrolyte disturbances, malabsorption and malnutrition. Patients with a resected bowel may undergo intestinal adaptation, where the residual intestine undergoes structural and functional enhancements. Total parenteral nutrition is sometimes used in patients with SBS, although this may inhibit intestinal adaptation as the residual gut is not being stimulated [105]. In rat and neonatal pig models, supplementation of TPN solutions with SCFA may enhance intestinal adaptation [106-109]. Possible mechanisms for the effects of SCFA on intestinal adaptation include upregulation of glucose transporter 2 (GLUT2) [107], upregulation of proglucan and ornithine decarboxylase [106], and increases of the plasma concentrations of the intestinotrophic hormone GLP-2 [105, 109]. SCFA absorption in the colon may also have beneficial effects for SBS patients by serving as a source of calories [105]. A recent study in patients with SBS reported that the primary carbohydrate substrate for fermentation by the colonic microbiota is starch, with pectin also increasing SCFA production by the colonic microbiota [110].

Obesity

Exogenous SCFA, and endogenous SCFA derived from dietary fiber and prebiotics, may participate in the pathogenesis of obesity. As discussed above, SCFA are ligands for the SCFA GPCRs GPR41 and GPR43. GPR43 may be involved in appetite regulation by increasing secretion of peptide YY (PYY) and GLP-1, which regulate digestive enzymes and satiety [28, 111, 112]. In mice, exogenous SCFA prevented the occurrence of diet-induced obesity, with butyrate and propionate being more effective than acetate. Butyrate and propionate supplementation prevented weight gain induced by a high-fat diet, whereas acetate prevented 40 % of this weight gain. SCFA also inhibited food intake and stimulated the anorexigenic peptides GLP-1, PYY and amylin, with butyrate > propionate > acetate

[113]. Through the activation of GPR43, acetate and propionate inhibit lipolysis [114, 115], reduce plasma levels of FFA [114], and stimulate adipogenesis in mice [115]. Xiong et al. [35] reported that propionate activates GPR41, stimulating leptin production in mouse adipocytes. Propionate and butyrate stimulated leptin secretion in mouse epididymal adipocytes whereas acetate stimulated leptin secretion in mesenteric adipocytes in a study by Zaibi et al. They suggest that GPR43 as opposed to GPR41 is involved, as they were unable to detect GPR41 mRNA in mouse adipose tissue sites [34]. In human adipose tissue, propionate increased leptin expression while reducing the expression of the proinflammatory factor resistin [36]. Propionate is anti-inflammatory, increasing lipogenesis and glucose uptake in human omental adipose tissue [116]. These functions of SCFA, in particular with regard to their effects on satiety-related hormones and on adipocytes, may find therapeutic utility in the prevention of obesity.

Conclusions

SCFAs, a major component of the intestinal luminal content, can act as signalling molecules or nutrients. Recent advances in the understanding of intestinal epithelial biology have included the identification of a likely SCFA uptake mechanism and of two SCFA GPCRs that likely transduce the presence of luminal SCFA into neurohormonal signals that can affect appetite, glycemic control, intestinal growth and gut motility. Due to their anti-inflammatory effects, SCFAs may be beneficial for treating patients with UC. Although probiotics, prebiotics, and synbiotics enhance gut SCFA production, it remains inconclusive whether or not they are beneficial in the treatment of UC. Exogenously administered SCFA also have had variable success in UC treatment, with uncontrolled studies reporting benefit, but many randomized controlled trials reporting no significant improvements, although SCFA may be more cost effective than are mesalamine compounds due to comparable efficacy at lower cost [92]. Although the majority of studies were designed to study rectally-administered SCFA, trials of oral SCFA are promising, offering the possibility of increased efficacy and convenience. Evidence also suggests that SCFA have beneficial effects in pouchitis, SBS and obesity, although present results are preliminary.

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Table 1

Uncontrolled trials of SCFA and colitis

Patients, *n*	Treatment	Results	Reference
12	SCFA enema	Improvements in stool frequency, rectal bleeding, mucosal appearance, lifestyle impact, erosions exudate, cryptitis abscesses, and mucin depletion	[82]
10	NaB enema	Six out of ten patients responded to treatment and four of these had complete response	[83]
9	5-ASA and NaB	Improvements in clinical scores and decreases in blood in stool, number of bowel movements, and endoscopic scores	[84]
216	Butyrate and inulin tablets	Improvement in UCDAI scores	[85]

SCFA short-chain fatty acids, *UCDAI* ulcerative colitis disease activity index

Table 2

Controlled trials of SCFA and colitis

Patients, *n*	Treatment	Results	Reference
47	SCFA enema versus placebo	No significant differences	[86]
103	SCFA enema versus placebo	No significant differences	[87]
51	5-ASA and NaB enema versus 5-ASA and placebo	Significant increase in remission and improvements in clinical scores, stool frequency, urgency, and self-assessment	[88]
11	NaB enema versus placebo	Significant decrease in DAI scores, reduction of NF-κB translocation in lamina propria macrophages	[89]
335	NaB enema versus placebo	Minor effects on inflammatory parameters and no significant effects on oxidative stress parameters	[90]
39	NaB enema versus placebo	No significant differences	[91]
45	Corticosteroids versus 5-ASA versus SCFA enema	Similar improvement, although SCFA more cost-effective	[92]
30	Oral mesalazine and butyrate versus oral mesalazine and placebo	Improvement in clinical and UCDAI scores	[93]

SCFA short-chain fatty acids, *UCDAI* ulcerative colitis disease activity index