Role of short chain fatty acids in gut health and possible therapeutic approaches in inflammatory bowel diseases

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Abstract

Inflammatory bowel diseases (IBDs) are characterized by inflammation in the gastrointestinal tract and include Ulcerative Colitis and Crohn’s Disease. These diseases are costly to health services, substantially reduce patients’ quality of life, and can lead to complications such as cancer and even death. Symptoms include abdominal pain, stool bleeding, diarrhea, and weight loss. The treatment of these diseases is symptomatic, seeking disease remission. The intestine is colonized by several microorganisms, such as fungi, viruses, and bacteria, which constitute the intestinal microbiota (IM). IM bacteria promotes dietary fibers fermentation and produces short-chain fatty acids (SCFAs) that exert several beneficial effects on intestinal health. SCFAs can bind to G protein-coupled receptors, such as GPR41 and GPR43, promoting improvements in the intestinal barrier, anti-inflammatory, and antioxidant effects. Thus, SCFAs could be a therapeutic tool for IBDs. However, the mechanisms involved in these beneficial effects of SCFAs remain poorly understood. Therefore, this paper aims to provide a review addressing the main aspects of IBDs, and a more detailed sight of SCFAs, focusing on the main effects on different aspects of the intestine with an emphasis on IBDs.

Key Words: Ulcerative colitis; Crohn’s disease; Short-chain fatty acid; Butyrate; Inflammatory bowel diseases; Free fatty acid receptor

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INTRODUCTION

Inflammatory bowel diseases (IBDs) comprise ulcerative colitis (UC) and Crohn’s disease (CD) and are characterized by inflammation in the gastrointestinal tract (GIT)[1]. They are expensive diseases to health services, and their prevalence is increasing every year[2]. Abdominal pain, stool bleeding, diarrhea, and weight loss are some of the most frequent symptoms of IBDs[3].

The pathogenesis of IBDs remains unclear, but there is evidence of a relationship between genetic factors associated with the dysregulation of the immune system and intestinal microbiota (IM)[4]. The treatment of these diseases aims to relieve the initial symptoms and seek to keep the patient in remission. Anti-inflammatory drugs, immunosuppressants, analgesics, and monoclonal antibodies are used for this[5].

Under physiological conditions, the intestine presents a heterogeneous and symbiotic community of microorganisms such as fungi, viruses, and bacteria[6]. These microorganisms that colonize the intestine constitute the IM and provide beneficial effects to the host as protection against pathogens, strengthening of intestinal barrier integrity, and production of short-chain fatty acids (SCFAs)[7].

SCFAs are produced from dietary fibers fermentation by IM. Acetate, Propionate, and Butyrate are the most abundant SCFAs and exert several beneficial effects on the body[8]. Among the three most abundant types of SCFAs, Butyrate has been widely studied due to its anti-inflammatory and antioxidant effects[9]. SCFAs can bind to G-protein-coupled receptors such as GPR41 and GPR43 and exert several intracellular effects that benefit intestinal health[10-12]. In this context, SCFAs may represent an alternative to conventional therapy for IBDs. Therefore, this review aims to provide the main aspects of IBDs and a more detailed sight of SCFAs, elucidating their main effects, possible mechanisms involved, and possible applications in IBDs.

INFLAMMATORY BOWEL DISEASES

IBDs are characterized by inflammation in GIT and comprise CD and UC[13]. These diseases are a serious health problem because they substantially reduce patients’ quality of life, are expensive to health services, and can lead to complications such as cancer and even death[14].

Between 1990 and 2017, the overall number of people with IBDs increased from 3.7 million to more than 6.8 million and affected more women (57%) than men (43%)[2]. Countries with a high sociodemographic index had higher rates of age-standardized prevalence, with Western Europe and North America presenting the highest age-standardized mortality rates in 2017[2].

The diagnosis of IBDs requires endoscopic/colonoscopic, imaging, and laboratory exams associated with biopsy of the affected areas, and despite having similar symptoms, CD and UC have considerable pathophysiological differences[1]. CD can affect, usually discontinuously, any segment of the GIT. Microscopically, it is possible to observe transmural inflammation, penetrating ulcers, and the presence of granulomas[15,16]. UC, in turn, is characterized by a limited inflammation of the colon, usually continuous, which begins in the rectum and can extend to the colon at varying distances[3]. Microscopic findings of UC include reduction of goblet cells, superficial and mucosal-limited inflammation, and presence of ulcers and abscesses[16-18].

The pathogenesis of IBDs is still not fully understood[19-21], but several studies indicate that it tends to be caused by an association between genetic susceptibility and environmental alterations in the gut microbiota, along with an intestinal barrier dysfunction, causing a dysregulation of the immune system[22,23]. Genome-wide association studies identified 201 IBD-related loci, 41 of which were specific for CD and 30 for UC[23,24]. Mutations in the NOD2 gene, as well as mutations in the interleukin (IL) 10 receptor gene region and polymorphisms in the 16-like 1 gene are examples of genetic alterations related to the development of IBDs[25-28]. In addition, many of the IBD-related loci are also associated
with autoimmune and immunodeficiency diseases, indicating the important relationship of IBDs to immune system disorders[23,29].

The host-microbiota interaction also plays an important role in the pathogenesis of CD and UC and involves gene regions that regulate microbial defense and intestinal inflammation[4,30-32]. Changes in the gut microbiota are frequent among individuals with IBDs[33,34]. However, it is not known whether the alteration of the microbiota is a cause or a consequence of these diseases[35,36]. Furthermore, eating habits are also related to IBDs[37]. A diet rich in processed foods, with high amounts of saturated fat and filled with protein is often associated with a higher chance of developing IBDs[38,39], while a high fiber diet reduces the chances of developing these disorders[40,41].

Treatment for IBDs seeks to control initial symptoms, normalizes evacuations frequency, promotes histological recovery of the mucosa, and prevents recurrences[5,42]. Therapeutic strategies include the use of anti-inflammatory drugs, analgesics, immunosuppressants, monoclonal antibodies, and, in more severe cases, surgeries[43-46]. In addition to conventional treatments for IBDs, several studies have investigated the modulation of the IM as one of the possible therapeutic/adjuvant approaches in the treatment of IBDs[47-49].

INTESTINAL MICROBIOTA

GIT harbors a complex and heterogeneous population of bacteria, fungi, viruses, and other microorganisms[6]. These microorganisms constitute the IM and establish a symbiotic relationship with the organism[50]. About 70% of all human microbiota is found in the intestine[51] and it is estimated that there are about $10^{10}$ to $10^{12}$ bacterial cells per gram of colonic content[52] and more than 1000 bacterial species in the human intestine[53].

In the colon, all microorganisms that constitute the IM, anaerobic bacteria are seen in greater quantity, with a predominance of the phyla *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria* and *Proteobacteria*, although this composition may vary between individuals and among the different structures of the GIT[54,55]. The profile of these bacteria is influenced by diet and by the use of medications, particularly antibiotics[56-58].

IM can interact with the immune system, causing tolerance to symbiotic microorganisms and an effector response to pathogenic microorganisms[50,59]. In addition to being involved in this mechanism of communication with the immune system[60,61], the IM contributes to the protection against pathogens[62] through the production of bactericidal and/or bacteriostatic molecules, competition for nutrients, and stimulation of mucus secretion[63-65].

In addition, a healthy IM, under symbiosis conditions, promotes structural benefits to the host such as strengthening the integrity and modulation of the intestinal barrier[7] and metabolic benefits through the fermentation of complex carbohydrates, SCFAs production, energy uptake, increasing of intestinal hormones such as the Peptide YY (PYY), glucagon-like peptide 1 (GLP1) and vitamin synthesis[66].

Many of these beneficial effects of IM have been related to the production of SCFAs, which, in addition to being one of the main energy sources for colonocytes, can interfere in cellular mechanism, modifying the expression of some genes and promoting changes, including, to extra-intestinal levels such as in the Central Nervous System (CNS)[67-69]. In this context, SCFAs has been the target of studies by the scientific community due to its beneficial effects in GIT and to the possible therapeutic potential in some diseases, including IBDs[70,71].

When a variation in the composition and diversity of the microorganisms that make up the IM happens, it generates an imbalance between symbiotic and pathogenic microorganisms, promoting an instability in the IM-host relationship[20,33]. This harmful alteration of the IM is called dysbiosis[72]. Intestinal dysbiosis leads to a pro-inflammatory response with the activation of immune system cells and, in addition, causes a reduction in the synthesis of vitamins as well as in the carbohydrate metabolism, consequently, the beneficial effects of a healthy IM are suppressed, and individuals become more susceptible to the development of diseases[73,74]. Dysbiosis is associated with the pathogenesis of several diseases, including IBDs[34,75-77].

SHORT-CHAIN FATTY ACIDS

*Production and metabolism*

SCFAs are produced by IM bacteria through the fermentation of dietary fibers[67]. SCFAs are saturated carboxylic acids, with a chain of one to six carbons, and among these, Acetate, Propionate, and Butyrate are the most abundant SCFAs in the colon[78,79] in a molar ratio of 60:20:20, respectively, although this proportion is different along the large intestine[78,80]. The production of SCFAs is influenced by the composition of IM, the anatomical site of the GIT and by the diet, differing in the type and quantity produced according to different substrates[79,81].
The fermentation of dietary fibers and the production of SCFAs is promoted by specific enzymes of IM microorganisms[82]. Under certain physiological conditions, the main SCFAs, namely the acetate, propionate and butyrate are produced by intestinal bacteria such as, for example, the Bacteroides spp., the Bifidobacterium spp. and the Faecalibacterium prausnitzii[83-85]. Acetate is produced from pyruvate via acetyl-CoA[83]. Propionate is produced via the succinate, acrylate, and propanediol pathways[84,86]. In turn, butyrate is produced from two molecules of acetyl-CoA, which are transformed into butyrate via phosphotransbutyrylase and butyrate kinase[85]. The butyryl-CoA:acetate CoA-transferase also leads to the production of butyrate, and some bacteria use acetate as a substrate for butyrate production[82].

In a dysbiosis condition, the composition and diversity of SCFA-producing microorganisms are altered[33,34]. A particular reduction in butyrate-producing bacteria such as Faecalibacterium prausnitzii is seen in patients with IBDs[87], as well as reduced levels of propionate and butyrate in the feces of these patients[88,89].

Once produced, most SCFAs are absorbed by the colonocytes. This absorption can occur by passive diffusion, through an exchange with bicarbonate, and mainly through monocarboxylate transporters (MCTs), by active transport (Figure 1)[67]. There are several types of MCTs, with different affinities for different types of SCFAs, which transport the SCFAs to the intracellular environment, including in the CNS, liver, kidneys, heart, lungs, skeletal muscle, and defense cells[90-94].

Among the MCTs, MCT1 stands out, due to its ubiquitous feature, and the sodium- dependent MCT1 (SMCT1), due to the greater amount in the large intestine. MCT1 has an affinity for Acetate, Propionate, and Butyrate is the main carrier responsible for the absorption of Butyrate, and transports SCFAs in a dependent way of H⁺ ions[67,92-94]. In turn, SMCT1 also has an affinity for Acetate, Propionate, and Butyrate, especially for Butyrate, and performs the transport in a sodium-dependent manner[95-97]. After being absorbed by the colonocytes at mitochondrial levels, SCFAs are converted into adenosine triphosphate (ATP), serving as an energy source for these cells (Figure 1)[69].

SCFAs that are not metabolized by the colonocytes, cross the basolateral membrane, and reach the portal circulation to the liver. In the liver, these SCFAs will serve as an energy source for hepatocytes and will participate in the synthesis of cholesterol and glucose[98,99]. A small amount of SCFAs, not metabolized by colonocytes and hepatocytes, actually reach the systemic circulation and have access to other organs (Figure 1)[67,100].

**Shortchain fatty acid receptors**

In addition to entering the intracellular environment, SCFAs can also bind to G-protein-coupled receptors. The main SCFAs receptors studied are GPR43 and GPR41, also known as free fatty acid receptor-2 (FFAR2) and free fatty acid receptor-3 (FFAR3), respectively[67,101]. They are transmembrane receptors, which recognize SCFAs, with different affinities for the different types of SCFAs, and promote signaling cascades mediated by G Protein (Figure 2)[12].

Both the GPR41 receptor and the GPR43 receptor are coupled to the G-protein subunit G_i, however only the GPR43 receptor is coupled to the G_subunit[102,103]. Activation of GPR41 and GPR43 receptors at G_i level promotes inhibition of cyclic adenosine monophosphate (cAMP) production and activation of extracellular signal-regulated kinases (ERK) cascade. In turn, GPR43 receptor activation through G_i promotes the elevation of calcium levels and activation of the mitogen-activated protein kinases (MAPKs) cascade[102-104]. The activation of these receptors is also capable of inhibiting the nuclear translocation of nuclear factor kappa B (NF-KB), altering the expression of certain proteins (Figure 2)[105].

GPR43 is expressed mainly in the colonic epithelium, enteroendocrine L-cells, and immune system cells[11,106]. In turn, GPR41 is expressed in the colon, kidneys, blood vessels, peripheral nervous system, and enteric nervous system (ENS)[107-109]. The activation of these receptors contributes to the maintenance of intestinal homeostasis and plays important roles in pathological conditions such as IBDs.

**Effects of SCFAs on the intestinal**

The intestinal barrier consists of simple cylindrical epithelial cells, mucus, immunoglobulins (Ig), and intercellular binding proteins such as tight junction proteins (Figure 3)[110,111]. The function of the intestinal barrier is to prevent the passage of pathogens, toxins, and other undesirable substances from the intestinal lumen into the paracellular space[110]. Tight junctions play an important role in the effectiveness of the intestinal barrier[112] by keeping epithelial cells well adhered to each other, and are composed of transmembrane proteins such as occludin, claudins, junctional adhesion molecules (JAM), and accessory cytoplasmic proteins such as zonulas occludens (ZO)s[113-115].

The occludins form a barrier mainly to macromolecules[116,117], while the claudins, particularly claudin-1, can maintain the intestinal barrier functionality even in the absence of other tight junctions[113,118-120]. The JAM, a protein belonging to the Immunoglobulins (Ig) superfamily[121-123], is capable of forming homophilic interactions adjacent to tight junctions as well as interacting with integrins or other members of the JAM family[122,123], playing an important role in the constitution of the intestinal barrier[115,124,125]. The ZOs proteins, such as ZO-1, ZO-2, and ZO-3 are located in the cytoplasm[126,127] acting as an anchor for proteins by joining them to the cytoskeleton and, therefore, are key to maintaining the integrity of the intestinal barrier, mainly due to its relationship with the
Caetano MAF and Castelucci P. Potential therapeutic effects of SCFAs in IBDs

Figure 1 Production and metabolism of shortchain fatty acids. Short-chain fatty acids (SCFAs) are produced by the intestinal microbiota from the fermentation of dietary fibers. SCFAs are absorbed by coloocytes mainly through monocarboxylate transporter 1 (MCT1), sodium-dependent monocarboxylate transporter 1 (SMCT1) and passive diffusion. At intracellular levels, SCFAs are metabolized and converted into ATP that will serve as energy source for these cells. Unmetabolized SCFAs cross the basolateral membrane and reach the portal circulation. In the liver, SCFAs are used in the synthesis of cholesterol and glucose. Only a small amount of SCFAs not used by the liver reach the systemic circulation[221]. The authors have obtained the permission for figure using from the BioRender.com (Supplementary material).

A deregulated intestinal barrier is associated with IBDs. It is not known for sure if the corrupted intestinal barrier is the cause or consequence of these diseases, but there are reports that an increase in intestinal permeability is an antecedent to recurrence of CD[129,130], which provides evidence that the functionality of the intestinal barrier is linked to the development/manifestation of IBDs. Architectural and functional disorganizations of the intestinal barrier, mucus reduction, and changes in the expression of tight junctions are associated with IBDs[131-133]. In addition, the loss of intestinal barrier integrity exposes the mucosa to luminal microbial antigens, which trigger inflammatory responses, sometimes hyper-responsive, causing extra-intestinal manifestations[132,134].

In this context, Butyrate, more than others SCFAs, has shown an interesting increase in intestinal barrier function[135] and could represent a possible ally in the treatment of IBDs, regarding the integrity of the intestinal barrier. In vitro and in vivo studies using Butyrate as intervention reported increased Transepithelial Electrical Resistance, rapid structuring of the intestinal barrier, and increase of tight junctions proteins (Figure 3)[136,137].

Although most of the beneficial effects of SCFAs at the intestinal barrier are attributed to the butyrate, some studies have shown recently that the propionate is also able to improve the functionality of such barrier[138]. In an experimental model of UC, propionate was able to attenuate the decrease in the expression of tight junctions such as ZO-1 and occludin in the large intestine[139]. These SCFAs were also able to attenuate the intestinal barrier dysfunction induced in Caco-2 Cell monolayers, however, the amount of propionate needed in order to observe its effects on the intestinal barrier is greater than that of butyrate[140]. In addition, propionate also appears to influence the differentiation and proliferation of the intestinal epithelium[141].

The molecular mechanisms behind these effects are unclear, but there are reports that Butyrate is capable of promoting positive regulation in the expression of tight junctions proteins by activating AMP-activated protein kinase (AMPK), mediated by activation of receptors such as GPR41 and GPR43, reduction of the phosphorylation of the myosin light chain 2 (MLC2), increased phosphorylation of the protein kinase C β2 (PKCβ2) or by negative regulation of channel formers proteins, such as claudin-2[137,142,143].

Another possible mechanism involved in the regulation of junction proteins by Butyrate may be associated with its ability to inhibit histone deacetylases[144,145]. When histones are deacetylated, that is, without acetyl groups, their conformation is more tangled which makes chromatin more condensed and promotes gene silencing[146,147]. On the other hand, when these histones are acetylated, there is a repulsion between these groups, so histone becomes more distant from each other, causing chromatin to become decondensed and, consequently, activate gene transcription (Figure 4)[148,149].
Short-chain fatty acids (SCFAs) binds to G-protein coupled receptors such as GPR41 and GPR43 receptors also known as free fatty acid receptors (FFAR) 3 and FFAR2, respectively. The activation of GPR41 and GPR43 receptors through G\textsubscript{i} subunit promotes inhibition of adenylate cyclase which inhibit cyclic adenosine monophosphate (cAMP) that inhibit protein kinase A. GPR43 receptor activation through G\textsubscript{q} subunit promotes activation of phospholipase C which activate inositol 1,4,5-trisphosphate (IP\textsubscript{3}) leading to the elevation of intracellular calcium levels. GPR43 receptor activation through G\textsubscript{q} subunit also promotes activation of phospholipase C which activate protein kinase C leading to activation of extracellular signal-regulated kinase 1/2 (ERK1/2) cascade. The activation of these receptors inhibits translocation of nuclear factor kappa B (NF-κB), altering the expression of certain proteins, promotes an increase in the release of gut hormones such as Peptide YY (PYY) and Glucagon-like peptide 1 (GLP-1), increase intestinal barrier integrity and Transepithelial Electrical Resistance (TEER), reduce pro-inflammatory markers levels, and increase anti-inflammatory markers levels. The authors have obtained the permission for figure using from the BioRender.com (Supplementary material).

The removal of acetyl groups is done by the histone deacetylases enzymes[146,150]. Inhibition of these enzymes can occur directly, through intracellular SCFAs, which entered through MCTs or SMCTs, or indirectly, through the activation of SCFAs receptors[32]. On the other hand, Butyrate also increases the activity of histone acetylase enzymes, which promote the acetylation of histone[60].

Another effect of SCFAs, mainly Butyrate and Acetate, on the intestinal barrier is related to increased mucus production, which acts as a lubricant and physical barrier against microorganisms, toxins, and acidity resulting from the digestion process[111,151]. Studies with mice have reported that Butyrate is capable of stimulating the production of mucin and affected the expression of the mucus-producing gene, MUC-2[152,153]. In this sense, molecules, such as Butyrate, that can strengthen the intestinal barrier or recover its functionality in IBDs seem to be an interesting therapeutic strategy to avoid the development/recurrence of these diseases.

**Effects of SCFAs on Intestinal Inflammation**

SCFAs, especially Butyrate, also play anti-inflammatory roles[154,155]. Studies have reported that Butyrate is capable of promoting a reduction in pro-inflammatory cytokines such as interleukin (IL)-8, IL-6, IL-12 and tumor necrosis factor (TNF)-α and an increase in the production of anti-inflammatory cytokines such as IL-10[60] and IL-18, which is important for the maintenance of intestinal barrier epithelium[156]. It is believed that the anti-inflammatory effects of Butyrate are related due to its ability to inhibit the signaling pathway of NF-κB and Histone Deacetylases[157-159], reducing macrophage activation, oxidative stress, recruitment of inflammatory cells, and consequently intestinal inflammation[145,160,161].

In addition, SCFAs also influences the differentiation, maturation, and activation of immune system cells such as macrophages, dendritic cells, and lymphocytes[60,162], and this influence can be mediated by activation of GPR43 receptors that are present in immune system cells[67,104,106]. In synergy with
Figure 3 Intestinal barrier constitution and short-chain fatty acids effects. The intestinal barrier is composed by simple cylindrical epithelial cells, mucus, microbiota, immunoglobulins A (IgA), antimicrobial proteins, and intercellular binding proteins such as tight junction proteins. Tight junctions play an important role in the integrity of the intestinal barrier by keeping epithelial cells well adhered to each other, and are composed of transmembrane proteins such as Claudins, Occludin, Junctional adhesion molecules (JAM), and accessory cytoplasmic proteins such as Zonulas Occludens (ZO). Claudin-1 pairs with other Claudin-1 Loops of the adjacent cell, decreasing paracellular permeability. Like Claudin-1, Occludin pairs with other Occludin loops of the adjacent cell forming a barrier mainly to macromolecules. JAM-A belongs to immunoglobulins superfamily and can form homophilic interactions adjacent to tight junctions and interacting with integrins or other members of the JAM family. ZO-1 are located on the cytoplasm and perform the anchorage of proteins joining them to the cytoskeleton through actin filaments. Short-chain fatty acids (SCFAs), mainly Butyrate, are capable of increase Claudin-1, Occludin, JAM, ZO proteins and increase mucus secretion by goblet cells. The authors have obtained the permission for figure using from the BioRender.com (Supplementary material).

Its anti-inflammatory effects, Butyrate also has antioxidant effects indicated by the increase of antioxidant enzymes such as catalase and superoxide dismutase-2 and by the reduction of uric acid, glutathione, and IL-β levels[163,164].

In animal models, Butyrate, by inhibiting Histone Deacetylase-1, was able to maintain a balance between Th17 lymphocytes (auxiliary T lymphocytes) and Treg lymphocytes (regulatory T lymphocytes) and to exert anti-inflammatory effects by inhibiting IL-6, signal transducer, and activator of transcription 3 (STAT-3) and IL-17[165]. In addition, in a double-blind, placebo-controlled study with patients with IBDs, Butyrate considerably reduced fecal calprotectin levels in patients with UC[166].

In experimental Colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS), treatment with Sodium Butyrate was able to improve intestinal inflammation, reduce histological injury scores, promote significant recovery of animal weight, and increase IL-10 levels[167]. In dextran sulfate sodium (DSS)-induced colitis, pretreatment with Sodium Butyrate was able to prevent weight loss of animals, recover colon shortening caused by colitis, reduce intestinal mucosa lesions, attenuate the production of pro-inflammatory cytokines such as IL-6 and TNF-α and increase IL-10 levels[160].

Still in a DSS-induced colitis model, the propionate was able to inhibit the expression of pro-inflammatory markers such as IL-6, IL-1β and TNF-α in the colon[139]. Moreover, the propionate is also capable of modulating the activation of immune system cells and reducing the levels of reactive oxygen species in the tissues[168,169].

Although many anti-inflammatory and antioxidant effects of SCFAs, most notably Butyrate, have been described in the literature, the mechanisms involved in these effects remain unclear. However, these properties have attracted the attention of the scientific community, as these metabolites could be configured as therapeutic tools in the prevention of recurrences and/or as adjuvants in the treatment of active IBDs.
Histone modifications and short-chain fatty acids influence. Histones are proteins that interact with DNA and play an important role in organizing the double strand. When histones contain acetyl (Ac) groups they become acetylated and there is a repulsion between these groups, so histone becomes more distant from each other, causing chromatin to become decondensed and, consequently, more accessible which activate transcription. Otherwise, when histones are deacetylated, without Ac groups, DNA becomes more tangled which makes chromatin more condensed and promotes gene silencing. Histone Deacetylases (HDAC) are enzymes that remove Ac groups from Histones making them deacetylated. Otherwise, Histone Acetylases (HAT) are enzymes that insert Ac groups in Histones making them acetylated. Short-chain fatty acids (SCFAs), mainly Butyrate, inhibit HDAC and increase HAT activity. The authors have obtained the permission for figure using from the BioRender.com (Supplementary material).

**Effects of SCFAs on the Enteric Nervous System**

The GIT has an extensive intrinsic nervous system called the ENS, which consists of an interconnected network of neurons, axons, and enteric glial cells[170]. The ENS can even isolated from the CNS, control several functions[171] such as intestinal motility, regulation of blood flow, regulation of fluids through the mucosa, secretion of digestive substances and intestinal hormones, and communication with the immune system[170,172].

The ENS has two plexus: the myenteric plexus (Auerbach’s plexus) and the submucosal plexus (Meissner plexus)[170,173]. The myenteric plexus is located, throughout the digestive system, between the outer longitudinal muscle layer and the circular muscle layer and is mainly responsible for intestinal motility[170,173]. The submucosal plexus is located between the circular muscle layer and the muscularis mucosae layer of the small and large intestines and its function is related to the control of intestinal secretions and blood flow of the mucosa[170].

In IBDs, even in mild cases, promotes changes in neurons and nerve endings of the ENS, as well as in the patterns of motility and secretion of the intestine[172]. These changes may persist even after the resolution of inflammation in the intestine, as it generates prolonged hyperexcitability of enteric neurons, persisting symptoms such as cramps, abdominal pain, and diarrhea[174].

Studies with experimental models have shown that intestinal inflammation causes changes in the number and size of enteric ganglia, glia, and neurons in addition to degeneration, necrosis, and neuronal apoptosis[174-177] In addition to morphological changes, colitis also promotes changes in the expression of neurotransmitters and their receptors, consequently altering the chemical code of neurons [178,179].

It is known that enteric neurons have GPR41 receptors and are responsive to SCFAs[180]. Studies have reported that Butyrate also has effects on ENS[181] and is capable of causing increased excitatory motor neurons, increased intestinal motility and contractile response induced by electrical stimulus [182]. However, the way the interaction of SCFAs with ENS occurs in the face of intestinal inflammation and how it interferes in the different neuronal classes, enteric glial cells, in the expression of SCFAs receptors, and the neurochemical dynamics is not yet clarified[183].

The results so far available in the literature encourage further investigations on the effects of SCFAs on enteric neurons, once ENS exerts a remarkable influence on homeostasis and intestinal functionality and the beneficial effects of SCFAs could recover/prevent changes in ENS due to IBDs and other
intestinal diseases.

MODULATION OF SCFAs PRODUCTION AND FUTURE PROSPECTS

The production of SCFAs depends mainly on two major variables: the characteristic of IM and the supply of substrates used by microorganisms. For SCFAs production, there must be a healthy IM rich in fermenting microorganisms[184]. The logic behind the modulation of SCFAs production involves two pathways: increase of living beneficial microorganisms (probiotics) and increase of substrates used by microorganisms (prebiotics), giving the host health benefits[185,186].

In this context, the production of SCFAs, such as Butyrate, for example, can be increased through the use of probiotics with butyrogenic microorganisms, that is, capable of producing Butyrate or by the use of prebiotics, such as fibers and complex starches, which acts as energetic substrates for microorganisms, increasing the proliferation of IM microorganisms and the production of SCFAs[82,187,188].

In other words, a person’s diet exerts a strong influence on the composition of their IM and, consequently, on the modulation of the SCFAs production[187,189]. A plant-based diet, such as the Mediterranean diet, tends to increase the source of dietary fiber and, consequently, the production of SCFAs[190-192]. On the other hand, a diet low in vegetables and rich in meats, sugars or saturated fats, such as the Western diet, not only alters the IM profile, but reduces the availability of fiber and, consequently, the production of SCFAs[193,194]. In this sense, the association between the use of probiotics, prebiotics and a Mediterranean-like diet optimizes the production of SCFAs in the intestine[184,190,195,196].

Many animal models of IBDs seek to identify a possible effectiveness of the use of probiotics as a treatment for this disease[197]. In the TNBS-induced UC models, the microorganisms Bifidobacterium infantis and Bifidobacterium bifidum demonstrated beneficial effects in animals by attenuating the clinical manifestations of UC, promoting a greater preservation of the mucus layer and a reduction of pro-inflammatory cytokines such as the IL-10 and the IL-1β in the intestine[198,199]. In the DSS-induced UC model, the microorganisms Bifidobacterium longum subsp. infantis BB-02 and the Bifidobacterium animalis subsp. lactis BB12 also demonstrated to have a positive influence on the clinical, histological and inflammatory manifestations of this disorder[200,201]. Ultimately, a reduction of potentially pathogenic microorganisms was observed after the administration of Bifidobacterium lactis[202]. The improvement of the results observed with the administration of these probiotics may be related to an increase in the production of the SCFAs[203].

As for the clinical studies, the effectiveness of using probiotics in patients with IBDs is controversial[204]. The Bifidobacterium bifidum, Lactobacillus acidophilus, Escherichia coli Nissle1917 and Bifidobacterium breve appear to exert favorable effects on UC remission[205-207]. In addition, the use of the referred probiotics caused an increase of butyrate and propionate levels in the subject’s fecal matter[207]. The combination of some microorganisms has also been used in clinical studies. This is the case of VSL#3, consisting essentially of 8 strains of microorganisms: Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis and Streptococcus thermophilus[208]. Patients with UC who used VSL#3 showed a clinical improvement, with a reduction in fecal bleeding as well as a decrease in the frequency of stool evacuation[209,210]. These findings do not appear to be applicable to CD[211]. It is important to mention that VSL#3 microorganisms are producers of SCFAs and this may be related to the improvements observed with the use of this probiotic for UC[203]. Pathophysiological differences between CD and UC, the great abundance of probiotics studied and the difficulty in obtaining a standardized sample population are some of the limitations of studies involving the use of probiotics and prebiotics in IBDs[48].

Another approach studied for the modulation of SCFAs production and for the treatment of IBDs is the Fecal Microbiota Transplantation (FMT)[212]. FMT is able to change the composition of the recipient’s IM, in order to reduce the proliferation of potentially pathogenic microorganisms and increase the production of SCFAs, especially butyrate[213-215]. Furthermore, fecal levels of Eubacterium and Lactobacillus spp. increased after the FMT, which are producers of Butyrate[213,216,217]. Although FMT is classically studied for the treatment of Clostridium difficile infection, several studies have observed that FMT has proven to be an effective, safe, and promising alternative to the treatment of IBDs, including UC and CD[212,218-220].

CONCLUSION

This review approached the main points about SCFAs, its main characteristics and contributions for gut health and potential benefits related to IBDs. In this context, this review encourages further studies on SCFAs, reinforces the importance of IM and healthy eating habits for the maintenance of intestinal health.
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FOOTNOTES

Author contributions: Caetano MAF was responsible for the literature review, and analysis and written; Castelucci P performed the critical interpretation and revised the manuscript for intellectual content.

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