Role of Short-Chain Fatty Acids in Human Diseases

Subjects: Gastroenterology & Hepatology

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Short-chain fatty acids (SCFAs) are organic acids whose carbon chain is composed of less than six carbons. Short-chain fatty acids (SCFAs) play a key role in health and disease, as they regulate gut homeostasis and their deficiency is involved in the pathogenesis of several disorders, including inflammatory bowel diseases, colorectal cancer, and cardiometabolic disorders. SCFAs play a significant anti-inflammatory role in the regulation of immune function, taking part in the prevention of various inflammatory chronic disorders. SCFAs are metabolites of specific bacterial taxa of the human gut microbiota, and their production is influenced by specific foods or food supplements, mainly prebiotics, by the direct fostering of these taxa.

Keywords: short-chain fatty acids ; butyrate ; gut microbiota ; SCFA-producing bacteria ; gut health ; prebiotics ; probiotics ; diet

1. Introduction

Short-chain fatty acids (SCFAs) are organic acids whose carbon chain is composed of less than six carbons. Among these, acetate (C2), propionate (C3) and butyrate (C4) are the most represented [1]. Acetate contributes to approximately 60% of the total SCFAs while propionate and butyrate comprise 20% each [2]. Additional acids, including lactate isomers, valerate, and branched chain SCFAs such as isobutyrate and iso-valerate, can be found in our gut metabolome (the metabolites of our gut microbiome), but their levels are noticeably lower compared with the main acids [3].

The main functions of SCFAs are carried out with the aid of Free Fatty Acid Receptor 2 (FFAR2) and FFAR3, while FFAR1 and FFAR4 are used by medium- and long-chain fatty acids. FFARs are G-protein-coupled transmembrane receptors located on the surface of many different cells (neurons, colonocytes, pancreatic cells, neutrophils, adipocytes, enteroendocrine cells, etc.) [4]. Acetate, a C2 SCFA, is more effective in the activation of the FFAR2 receptor, while propionate, a C3 SCFA, mainly effects the FFAR3 receptor. These receptors play key roles in various cells. FFAR2 and FFAR3 could mediate both the anti-inflammatory effect of acetate and propionate, and the proinflammatory effect of butyrate on innate immune system cells [5]. Moreover, the action of those two receptors may influence the energy consumption of neurons [6], insulin secretion from Langerhans islets beta cells [7][8] and enteroendocrine function [9][10].

The effects of SCFAs on the human gut are mediated by the presence of SCFA transporters on colonic epithelium. These transporters can be grouped into three main transporter classes: proton-coupled transporters, such as MCT1 and MCT4; sodium-coupled transporters, using the energy of two sodium ions, such as SMCT1; and ATP-dependent transporters, such as ABCG2, also known as breast cancer resistance protein (BCRP) [11].

SCFAs have several beneficial effects on human health, at different levels and on body sites.

First, SCFAs promote the integrity and permeability of the gut barrier in different ways. These molecules, mainly butyrate, increase the concentration of tight junctions, such as claudin-1, zonula occludens-1 and occludin through the upregulation of genes that encode for these proteins [12]. Moreover, butyrate is able to strengthen the mucus layer of the gut epithelium by increasing the expression of Mucin 2 [13]. Butyrate is also involved in the modulation of oxidative stress, as it reduces H_2O_2-induced DNA damage, restoring the levels of antioxidant glutathione. Additionally, SCFAs can induce both the differentiation and apoptosis of colonic cells, ideally preventing the development of colon cancer, as discussed further in this research [14].

SCFAs also play an important role in the regulation of several physiological pathways within the nervous system. First, SCFAs modulate brain-induced intestinal gluconeogenesis. In particular, when propionate is absorbed and passes through the portal vein, it activates the FFAR3s present on the surface of afferent periportal neurons [15]. SCFAs also regulate the inhibition of histone deacetylase (HDAC), with a potential impact on several neuropsychiatric diseases such

as depression, schizophrenia and Alzheimer's disease [16]. Moreover, SCFAs control systemic and neuroinflammation through the modulation of functions and structures of microglia cells, resulting in the modulation of emotion, cognition and mental disorders. Additionally, high concentrations of SCFAs seem to be related to the major expression of neurotrophic factors [17]; SCFAs may induce the expression of tryptophan 5-hydroxylase 1, an enzyme involved in serotonin biosynthesis [18], and there is also evidence that they may positively affect the brain barrier's integrity [19][20].

SCFAs, especially acetate, are also involved in the regulation of appetite and human metabolism. In animal models, diets with a high abundance of fermentable carbohydrates, whose catabolism in the colon generates SCFAs, relate to a minor appetite [21]. Moreover, acetate may reduce body weight through the secretion of glucagon-like peptide 1 and peptide YY [22]. SCFAs are also able to modulate both glucose and lipid metabolism. Propionate suppresses hepatic gluconeogenesis [23], while both acetate and butyrate reduce lipogenesis and increase leptin secretion [24][25][26][27]. Furthermore, SCFA administration in animal models seems to reduce liver steatosis [28][29], and vinegar, a food rich in acetate, was demonstrated to be useful in reducing body weight, serum triglycerides and body fat mass [30]. However, most experiences on humans are biased by a small sample size, and more evidence from adequately sized clinical studies is needed to understand the effects of SCFAs on lipidic metabolism [31].

Increasing evidence suggests that SCFAs are able to influence other components of cardiometabolic health. Increased levels of butyrate and propionate are associated with the reduction in blood pressure [32] and plasminogen activator inhibitor-1 (PAI-1) levels, a pro-thrombotic factor [33].

Notably, SCFAs have a relevant impact on both innate and adaptive immunity. Regarding innate immunity, SCFAs can act directly on neutrophils, reducing their production of reactive oxygen species (ROS) and myeloperoxidase (MPO), and can even enhance their apoptosis [34]. They also reduce the chemotaxis of inflammatory cells due to a decrease in the expression of monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM1) and chemokines signals [35][36]. In addition, regarding the T cell lineage, SCFAs can increase the T_{reg} cell number and their activity and inhibit CD4+ [37][38]. Finally, treatment with SCFAs, and especially with butyrate, is able to reduce gut inflammation, reducing the NF-κB signaling pathway and enhancing the expression of anti-inflammatory cytokines such as IL-10 [39].

In gut diseases, both acute and chronic inflammation are relevant. Transient acute inflammation, an essential defense mechanism of the immune system against injurious stimuli, is of particular relevant [40][41]. In this condition, when cells are damaged, instead of directly targeting the injurious stimuli, such as any invading viruses or bacteria, the immune system will use the "self-destroy and rebuild" strategy, targeting the damaged cells. By using a programmed cell death such as pyroptosis [42] and necroptosis [43] to actively destroy the cells, stimuli such as viruses or bacteria are also effectively cleared. On the other hand, chronic inflammation develops when the stimulus cannot be removed and is associated with diseases like IBDs, where SCFAs play a key role [44].

2. SCFAs and IBD

IBD includes chronic inflammatory disorders of the gastrointestinal tract associated with a gut microbiota imbalance. Patients with IBD are known to share, compared with healthy subjects, a reduction in butyrate producers of the Firmicutes phylum, mainly Roseburia spp and *Faecalibacterium prausnitzii*, and an increase in opportunistic bacteria [45][46].

In addition to a reduced SCFAs production, the uptake and oxidation of butyrate appears to be inhibited in patients with UC [47]. This leads to a weakening of their anti-inflammatory activity, thus promoting disease progression. More specifically, propionate and butyrate stimulate T-reg proliferation and function through GPR-43 pathways and HDACs' inhibition [48][49][50]. SCFAs also lead to a downregulation of proinflammatory cytokines levels because of the inhibition of NF-κB and HDCAs activity [51][52][53], and to an increase in the anti-inflammatory ones through GPCRs [36].

Furthermore, acetate controls tissue homeostasis through NLRP-3 activation [54] and butyrate regulates the intestinal barrier, which is known to be impaired in IBD, through increased AREG, IL-22 and claudin-1 production [55][56].

3. SCFAs and Colorectal Cancer (CRC)

CRC is a multifactorial disease and the gut microbiota play an important role in its development [57]. Patients with CRC showed an increase in pathogenic bacteria (e.g., *Fusobacterium nucleatum*) and a depletion in butyrate producers [52][58][59]. The reduced production of SCFAs leads to a pro-inflammatory environment, which can contribute to the initiation and progression of CRC [60]. In addition, butyrate can change redox state and D-glucose metabolism, enhancing cancer cells'

apoptosis [61], while the inhibition of HDCAs regulates the expression of p21, arresting cell cycle and consequent cancer proliferation [62]. Proliferation is also inhibited by propionate via GPR-43, which is often lost in colon cancer cells [63].

4. SCFAs and Cardiovascular Diseases (CVDs)

There is a large body of evidence suggesting that SCFAs play a role in the pathogenesis of CVDs, a group of disorders that include hypertension and atherosclerosis. A reduction in butyrate producers in the gut microbiota and the deficient intestinal absorption of SCFAs have been observed in patients with hypertension [64][65]. Moreover, SCFAs appear to have a dual effect on the regulation of blood pressure. For example, when binding Olfr-78, acetate and propionate lead to renin release, increasing blood pressure [66]. By contrast, when binding GPR-41, they reduce blood pressure via vasodilatation [67], which is also obtained by the effect of butyrate on afferent vagal terminals [68]. In atherosclerosis, a similar pathway has been noted [69], as SCFAs, mainly butyrate, appear to play a protective role in the regulation of inflammation and stabilization of plaques by downregulating the expression of CCL-2, VCAM-1, and MMP-2, resulting in the lower migration of macrophages, increased collagen deposition and ultimate plaque stability [70].

5. SCFAs and Metabolic Diseases

As anticipated above, SCFAs regulate metabolic pathways and food intake, thereby playing a role in the development of metabolic diseases. Obesity is associated with an imbalance in the gut microbiota, mainly an increased Firmicutes/Bacteroidetes ratio, and an increase in fecal-SCFAs [71][72], although circulating SCFAs are reduced [73]. Type 2 diabetes (T2D) is instead characterized by a decrease in butyrate producers in the gut microbiota [74].

Normally, SCFAs moderate food intake, stimulating the secretion of satiety hormones such as PYY and GLP-1 via GPR-41 and GPR-43 [75][76] and through the inhibition of HDACs [77]. Furthermore, acetate can cross the blood–brain barrier, causing a decreasee in appetite [21]. SCFAs can also improve glucose homeostasis in an AMPK-dependent manner involving PPARγ-regulated effects on gluconeogenesis and lipogenesis [24]. Moreover, propionate enhances glucose-stimulated insulin release via GPR-43 and increases β-cell mass [78]. SCFAs can stimulate adipocyte differentiation [79][80] and decrease lipid plasma levels through the inhibition of lipolysis and stimulation of lipogenesis [81][82][83] and cholesterol plasma levels, enhancing its hepatic uptake [84].

Overall, these mechanistic pathways of SCFAs in different disorders pave the way for the therapeutic use of SCFAs in clinical practice. **Table 1**.

Table 1. The role of short-chain fatty acids in different disorders.

Disease	SCFA	Model	Function	Ref.
Inflammatory bowel disease	Acetate	Gpr43−/−, Gpr109a−/−, Nlrp3−/− and Nlrp6−/− mice	Induces NLRP3 inflammosome activation to maintain tissue homeostasis	[47]
	Butyrate	Niacr1+/− Apc min/+ and Niacr1−/− Apc min/+ mice	Increases colonic DCs and macrophages' production of IL-10, inducing Treg generation	[40]
		Foxp3 ΔCNS1, Foxp3 GFP, Foxp3 Thy1.1 and Gpr109a−/− mice	Promotes Treg differentiation through enhancing Foxp3 activity	[41]
		GPR109a−/− and WT mice	Inhibits AKT and NF-κB p65 signaling pathways in macrophages	[44]
		BMDM cells, C57BL/6 and CX3CR1-GFP/+ mice	Reduces NO, IL-6 and IL-12p40 secretion by macrophages	[46]
		GPR43−/−, Prdm1−/− and WT mice	Increases AREG expression levels in DCs to promote tissue repair	[48]
		Cdx2-IEC monolayer	Induces production of claudin-1 to enhance barrier functions	[52]
	Propionate	Gpr43−/− and Gpr43+/+ mice	Promotes Treg differentiation through GPR-43	[42]
	All SCFAs	HeLa and HEK293 cell lines	Inhibit NF-κB activity through GPR43—βarrestin interactions	[43]

Disease	SCFA	Model	Function	Ref.
		Isolated human neutrophils, monocytes and PBMC	Promotes anti-inflammatory effects via the regulation of PGE2, cytokine and chemokine release	[34]
		CD4+ T cells and ILCs	Induces production of IL-22 to promote barrier functions	[49]
Colorectal cancer	Butyrate	Caco-2 cell line	Enhances cancer cells' apoptosis by alterations in the redox state and D-glucose metabolism	[54]
		MCF-7 (T5) and MDA MB 231 cell lines	Arrests cancer cells' proliferation through upregulation of p21	[55]
	Propionate	Caco-2, HCT116, HCT8, HT-29, SW620, SW480, CBS, FET and MOSER cell lines	Arrests cancer cells' proliferation through p21 upregulation and decrease in cyclin D3, CDK-1 and CDK-2	[56]
Hypertension	Acetate and propionate	Olfr78−/− and Gpr41−/− mice	Increase blood pressure through Olfr-78	[58]
		Gpr41−/− and WT mice	Reduces blood pressure by binding GRP-41	[59]
	Butyrate	Vagotomized Sheffield strain male Wistar rats	Reduces blood pressure through the regulation of afferent vagal terminals	[60]
Atherosclerosis	Butyrate	ApoE −/− mice	Reduces CCL-2, VCAM-1, and MMP-2 production to stabilize atherosclerotic plaques	[62]
Obesity	Acetate	C57BL/6 male mice	Decreases appetite through central hypothalamic mechanisms	[19]
	Propionate	Isolated human colonic cells	Reduces food intake through the secretion of PPY and GLP-1 via GPR-41	[68]
	Propionate and butyrate	NCI-h716 and HuTu-80 cells	Reduce food intake through the secretion of PPY via inhibition of HDACs	[69]
Metabolic syndrome	Acetate	Isolated adipocytes from GPR43 knockout mice	Decreases lipid plasma levels through inhibition of lipolysis via GPR-43	[75]
	Propionate	Human subjects and in vitro isolated human islets	Enhances glucose-stimulated insulin release and increases β-cell mass	[70]
		Human adipose tissue culture	Decreases lipid plasma levels by stimulating lipogenesis	[76]
	Propionate and butyrate	Stromal vascular fraction of the porcine subcutaneous fat	Stimulates adipocyte differentiation	[72]
	All SCFAs	PPARγ f/f and PPARγ lox/lox mice	Regulate gluconeogenesis and lipogenesis through PPARγ downregulation	[22]
		Male Golden hamsters	Decrease cholesterol plasma levels by enhancing its hepatic uptake	[77]

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