The Implication of Short-Chain Fatty Acids in Obesity and Diabetes

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ABSTRACT: Evidence indicates that short-chain fatty acids (SCFAs) generated from the gut microbiota play crucial roles in host metabolism. They contribute to metabolic regulation and energy acquisition of the host by influencing the development of metabolic disorders. This review aims to synthesize recent advances from the literature to investigate the implication of SCFAs in the modulation of obesity and diabetes pathologies. For a better understanding of the relationships between SCFAs and host metabolism, we need to answer some questions: What is the biochemistry of SCFAs, and how they are generated by gut microbiota? What are the bacteria producing of SCFAs and from which routes? How SCFAs are absorbed and transported in the gut by different mechanisms and receptors? How SCFAs involved in obesity and diabetes pathologies?

KEYWORDS: SCFA, intestinal microbiota, GPR, obesity, diabetes, host metabolism

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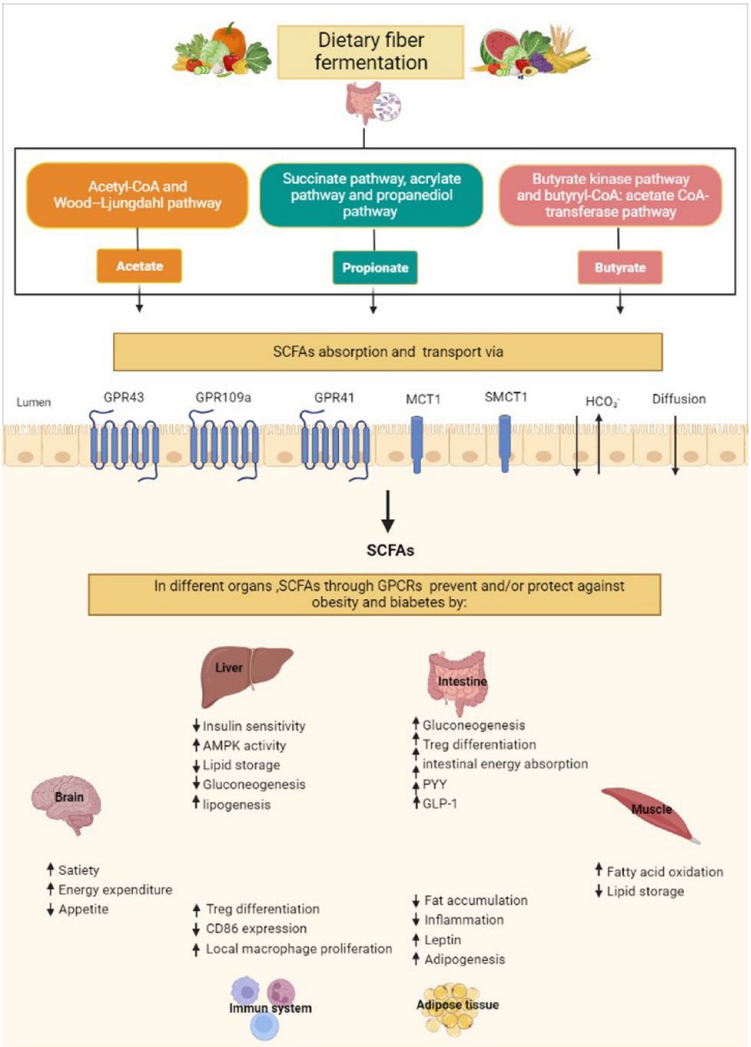
GRAPHICAL ABSTRACT



Introduction

Short-chain fatty acids (SCFAs) are the major end products of bacterial fermentation. They are produced by anaerobic microorganisms primarily from protein, peptide, oligosaccharide, glycoprotein precursors, polysaccharide, and carbohydrates progenitors.[1-4] Acetate, propionate and butyrate are the major SCFAs that are produced through the fermentation of both carbohydrates and amino acids.[5,6] These SCFAs that are transported across the intestine, can reach the bloodstream and have a direct impact on metabolism or peripheral tissue function.[7-9] Recent data suggest that SCFAs may play a crucial role in the etiology of several diseases, with systemic effects linked to human food and intestinal microbiota.[10]

SCFAs are thought to have a favorable rather than a harmful influence on host metabolism, according to rodent research.[9,10] However, evidence on the therapeutic benefits of SCFAs on glucose homeostasis in humans is conflicting, and more well-controlled long-term intervention studies are required to validate SCFA's beneficial involvement in metabolic diseases.[9,11-13] SCFAs appear to have 3 main mechanisms for influencing health: inhibition of HDAC (Histone deacetylase) activity, particular fatty acid-sensing G protein-coupled receptors (GPCRs) signaling, and anti-inflammatory mechanisms in the tissues and periphery resulting from to first 2 mechanisms.[10,14-16] According to emerging data, SCFAs have an important physiological impact on a variety of organs, including the pancreas, liver, and adipose tissue.[7] This hypothesis is confirmed by animal and human research which demonstrates that dysbiosis of the intestinal microbiota is linked to metabolic pathologies, such as type 1 diabetes (T1D) and obesity,[12,17] which become one of the most serious health issues linked to type 2 diabetes mellitus and a wide range of pathological abnormalities in metabolic organs prone to insulin resistance.[9]

Herein, we outline the current knowledge about the involvement of the main SCFAs, acetate, propionate and butyrate in intestinal microbiota-metabolism interaction. We also highlight how the development of future treatments for metabolic diseases can take advantage of the mutual interactions of the intestinal microbiota with other organs by exploring the role of SCFAs in the regulation of metabolic function.

Biochemistry of SCFAs

Short-chain fatty acids are organic monocarboxylic acids composed of an aliphatic chain of 1 to 6 carbons, derived from the bacterial fermentation of undigested dietary fiber in the human small intestine.[1,7] The main SCFAs produced by colonic anaerobic bacteria are acetic acid (C2:0), propionic acid (C3:0), and butyric acid (C4:0) (Table 1), which represent 90% to 95% of the SCFAs, with a proportion of about 60%, 20%, and 20% respectively.[18,19]

In addition to dietary fiber fermentation, SCFAs can also be produced from peptide and amino acid metabolism.[23] However, amino acid metabolism is only used by the gut microbiota to a degree of less than 1%.[7,24,25] Moreover to the production of SCFAs, acetate, butyrate, and propionate,[26,27] this metabolism leads to the production of potentially harmful metabolites such as branched-chain fatty acids including isobutyrate (iC4), valerate (C5), or isovalerate (iC5) (Table 1), phenolic and indolic chemicals, ammonia, and amines.[2,7,28] The production of SCFAs varies according to several factors including the composition of bacterial species of the microbiota, the quantity and quality of substrates[8,17,29] as well as the time of intestinal transit, stress, and aging.[1,7] According to these factors, approximately 500 to 600 mmol of SCFAs are produced daily by the human colon.[30]

Table 1. Main short-chain fatty acids and branched-chain fatty acids.[20-22]

TRIVIAL NAME	NUMBER OF CARBON ATOMS	CHEMICAL FORMULA
Acetate	2	$C_2H_4O_2$
Propionate	3	$C_3H_6O_2$
Butyrate	4	$C_4H_8O_2$
Isobutyrate	4	$C_4H_8O_2$
Valerate	5	$C_5H_{10}O_2$
Isovalerate	5	$C_5H_{10}O_2$

Metabolic Routes of SCFAs

The primary precursor of SCFAs is pyruvate, which most bacteria synthesize after carbohydrate glycolysis.[17,31,32] Main SCFAs, acetate, propionate and butyrate are generated from non-digestible carbohydrates by specific types of gut bacteria, via 4 metabolic pathways (acetyl CoA, lactate, succinate, propanediol) (Figures 1 and 2).[31,33,34]

Acetate metabolic pathways

The most abundant SCFA in the colon is acetate, which accounts for more than half of the total SCFAs found in feces.[45] The intestinal bacteria have been shown to produce acetate from pyruvate via 2 different metabolic pathways (Figure 1).[2,35] The enteric bacteria produce the majority of acetate from acetyl-CoA as a result of CHO fermentation.[2] Furthermore, the acetate produced by the acetogenic bacteria can account for about a third of total colonic acetate. It is synthesized via the Wood–Ljungdahl pathway, which includes 2 branches: (1) the C_1-body branch via reduction of CO_2 to formate and (2) the carbon monoxide branch via reduction of CO_2 to CO, which is combined with a methyl group to form acetyl-CoA (Figure 1).[2,21,31]

Propionate metabolic pathways

The succinate pathway, acrylate pathway, and propanediol pathway are used by colonic bacteria to produce propionate

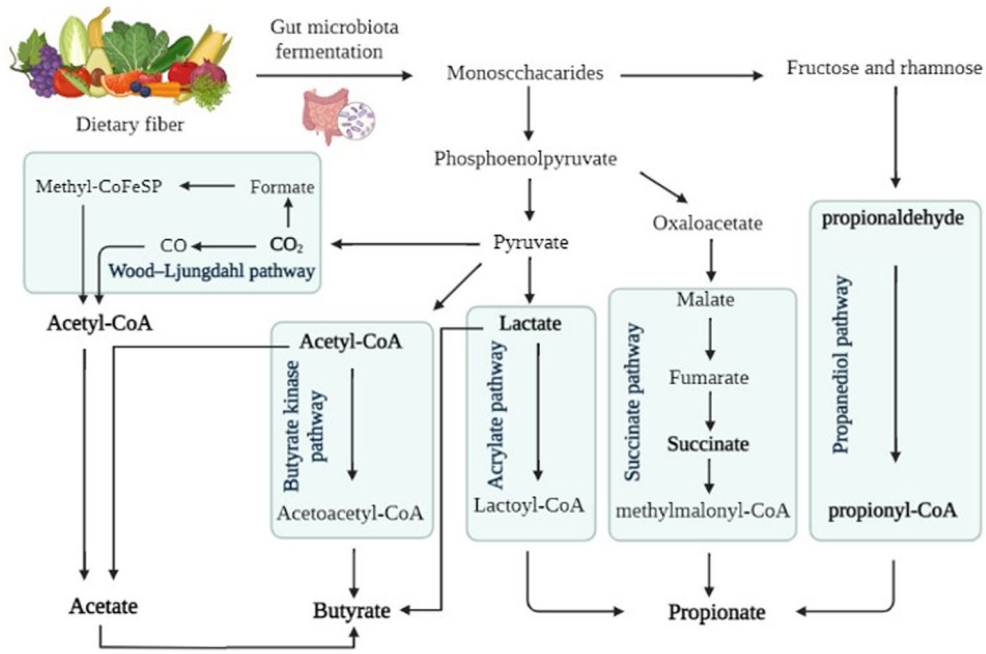


Figure 1. Pathways for the biosynthesis of short-chain fatty acids by gut microbiota. Acetate, propionate, and butyrate are the most SCFAs that are generated from the fermentation of dietary fiber by gut microbiota, through different pathways. Acetate is produced from pyruvate via acetyl-CoA and via the Wood-Ljungdahl pathway. Butyrate is formed from acetoacetyl-CoA after the condensation of 2 molecules of acetyl-CoA, it also can be synthesized from lactate and acetate. Propionate can be formed via the acrylate and succinate pathway from phosphoenolpyruvate and also via the propanediol pathway from deoxyhexose sugars, like fucose and rhamnose.

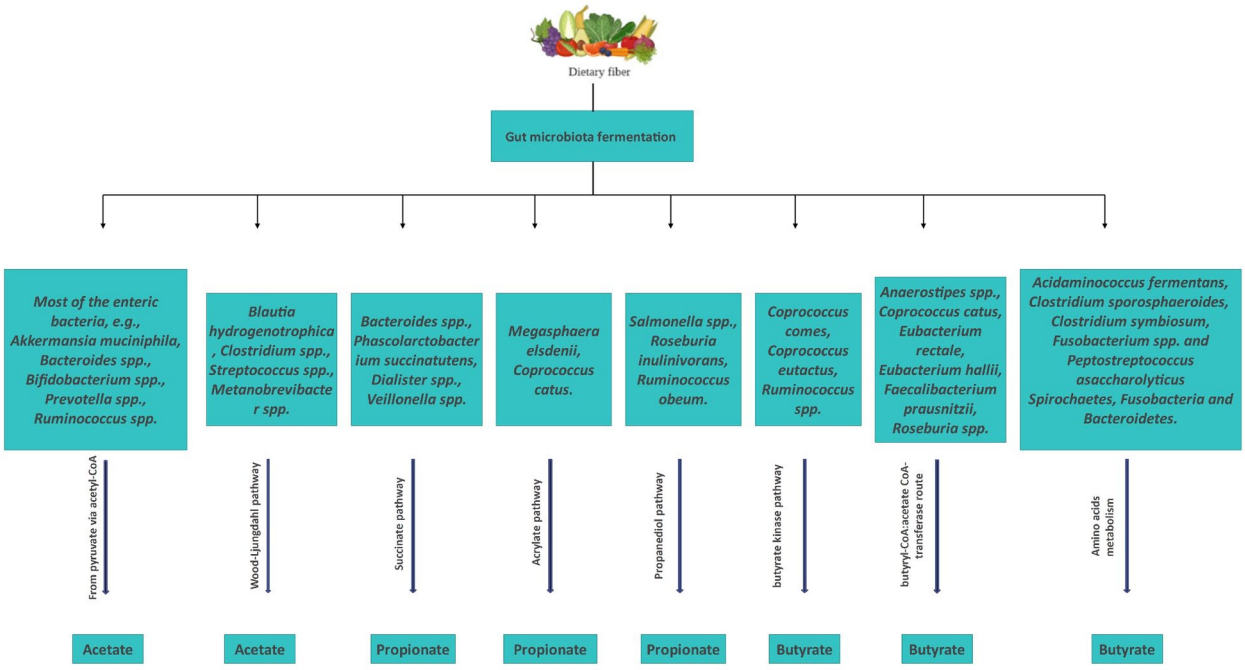


Figure 2. Intestinal microbiota producing SCFAs through different routes.
Source: Koh et al,[2] van der Hee and Wells,[10] Smith and Macfarlane,[24] Louis and Flint,[27] Louis et al,[35] Nogal et al,[36] Reichardt et al,[37] Neri-Numa and Pastore,[38] Ashaolu,[39] Barker et al,[40] Hayashi et al,[41] Chiu et al,[42] Fu et al,[43] and Murugesan et al.[44]

(Figure 1).[10,36,37,46] The production of this latter by succinate pathway involves the conversion of succinate to methylmalonyl-CoA, then methylmalonyl-CoA to propionyl-CoA by decarboxylation.[2,22,37,45] This route uses a four-carbon pathway made up of the 4 intermediates, malate, fumarate, succinate, and methylmalonyl-CoA, and generates for 2 molecules of propionate 1 molecule of acetate.[21] In the acrylate pathway, lactate is used like a precursor,[2,31] and is converted easily to

Table 2. SCFA-producing bacteria families.[3,23,37,54,60].

SCFA-PRODUCING BACTERIA
Lachnospiraceae, Streptococcaceae, Peptostreptococcaceae, Lactobacillaceae, Clostridiaceae, Erysipelotrichaceae, Eubacteriaceae, Enterococcaceae, Pasteurellaceae, Pseudomonadaceae, Fusobacteriaceae, Bacteroidaceae, Porphyromonadaceae, Aerococcaceae, Veillonellaceae, Verrucomicrobiaceae, Alcaligenaceae, Alicyclobacillaceae, Oxalobacteraceae, Defluviitaleaceae, Christensenellaceae Bifidobacteriaceae, Rhodospirillaceae, Synergistaceae, Acidaminococcaceae, Rikenellaceae, Prevotellaceae, Enterobacteriaceae, Micrococcaceae, Coriobacteriaceae, Burkholderiaceae, Nocardiaceae, Carnobacteriaceae, Peptococcaceae, Flavobacteriaceae, Erysipelotrichaceae, Actinomycetaceae, Leuconostocaceae, Desulfovibrionaceae, Streptococcaceae, and Ruminococcaceae

propionate through the lactoyl-CoA dehydratase's activity (Figure 1).[45] Propionate can also be synthesized by the propanediol pathway by the conversion of deoxy-sugars, fucose, and rhamnose.[2,27] It has been suggested that the conversion of propionaldehyde to propionyl-CoA via Co-dependent propionaldehyde dehydrogenase, is a marker of the propanediol route.[45]

Butyrate metabolic pathways

The last major SCFA, butyrate can be produced mostly via glycolysis from carbohydrates[47] and formed by 2 different pathways (Figure 1).[48] Butyrate is formed from acetoacetyl-CoA by phosphotransbutyrylase and butyrate kinase (butyrate kinase pathway) after condensation of 2 molecules of acetyl-CoA.[38,39] Moreover, the acetate can be converted to butyrate via the butyryl-CoA: acetate CoA-transferase route, which is used by mainly butyrate-producing bacteria.[49,50] Butyrate can also be synthesized from lactate to stabilize the intestinal environment and prevent its accumulation.[50,51] Lysine pathway was suggested such as the route to produce butyrate too.[2,40] An in vitro study showed that butyrate was produced from lysine, glutamate, cysteine, serine, and histidine, whereas propionate was a major fermentation product from alanine, aspartate, methionine, and threonine.[24,27,52] The 3 major SCFAs can also be further metabolized from lactate by many cross-feeding organisms.[26,38,51,53]

SCFAs Production by Intestinal Microbiota

The identification of bacteria that produce SCFAs was facilitated by metagenomic approaches and bioinformatics tools.[26,36] Well-known SCFA-producing bacteria in the gut include 41 families and are summarized in Table 2.[3,23,37,41,54-60] Acetogenic bacteria such as *Blautia hydrogenotrophica*, are expected to contribute little to acetate production but play an essential role in gas clearance in the digestive tract, which improves intestinal health.[61,62] Probiotics like *Bifidobacterium* and *Lactobacillus* have enhanced lipid metabolism in the liver by increasing the generation of SCFAs.[63] *Akkermansia muciniphila* transforms dietary fiber to SCFAs, making it a promising probiotic for lowering metabolic syndrome risk.[64] In humans and animals, *Akkermansia muciniphila* also helps to reverse metabolic dysbiosis caused by antibiotics or a high-fat diet, such as insulin resistance.[12,65]

Acetate, which represents 50% to 60% of SCFAs, is synthesized by the genera *Bifidobacteria* and *Lactobacilli* [29,66] and other bacteria such as*Clostridium* spp., *Lachnospira, Anaerotruncus, Parabacteroides, Roseburia*[17,67] *Blautia hydrogenotrophica, Akkermansia Muciniphila*, and *streptococcus* spp.[2,56,62,66] Most enteric bacteria use the acetyl-CoA pathway to produce acetate from pyruvate.[2,68]

Propionate is produced by the *Bacteroidetes* and Negativicutes class of *Firmicutes* via a succinate pathway by using vitamin B_{12} to convert succinate to propionate.[27,29,46] Other Negativicutes bacteria formed propionate from lactate via the succinate like *Veillonella* spp[64] or acrylate pathways such as *Megasphaera elsdenii, Lachnospiraceae*, and *Coprococcus catus*.[21,37] Propionate and propanol can also be produced from deoxy sugars by *Lachnospiraceae*, including *Roseburia inulinivorans* and *Blautia* species.[27] *Dialister, Lactobacillus paracasei, Odoribacter, Salmonella* spp., *Megasphaera esdenii*, and *Ruminococcus* are also propionate-producing bacteria.[2,17,21]

Butyrate can be synthesized by *Roseburia* spp. and *Eubacterium rectale*, which belong to the *Clostridium coccoides* group (clostridial cluster XIVa), and *Faecalibacterium prausnitzii*, which belongs to the *Clostridium leptum* group (clostridial cluster IV).[10,17,33,56,69] In addition to these 2 abundant clusters in humans, butyrate can also be synthesized by clostridial cluster I, III, XV, and XVI.[10] We should note that butyrate can also be formed from amino acids by lysine, glutamate, and 4-aminobutyrate pathways.[10,70] These routes are found in Firmicutes such as *Fusobacterium* spp., P*eptostreptococcus asaccharolyticus, Clostridium sporosphaeroides, Acidaminococcus fermentans*, and *Clostridium symbiosum*[27] and other phyla which including *Spirochaetes*, *Fusobacteria*, and *Bacteroidetes*.[40,42,43] Amino acids metabolism has been overlooked as a possible butyrate-producing pathway in intestinal environments.[70] Figure 2 summarizes all the bacterial genera and species producing the 3 main SCFAs as well as the metabolic pathways involved.

Metabolism of SCFAs in Host

Absorption of SCFAs in the gut

About 60% to 70% of the energy needs of colon cells and enterocytes are provided by SCFAs, the remaining SCFAs enter the bloodstream to cover 5% to 15% of the body's total energy needs.[17] SCFA absorption in the colon is effective and rapid, with only 5% to 10% of the SCFAs excreted in the feces.[9,71] SCFAs are absorbed by the apical membrane of colonocytes through different mechanisms: (a) non-ionic diffusion, (b) SCFA/HCO_3^- exchange, (c) active transport, via

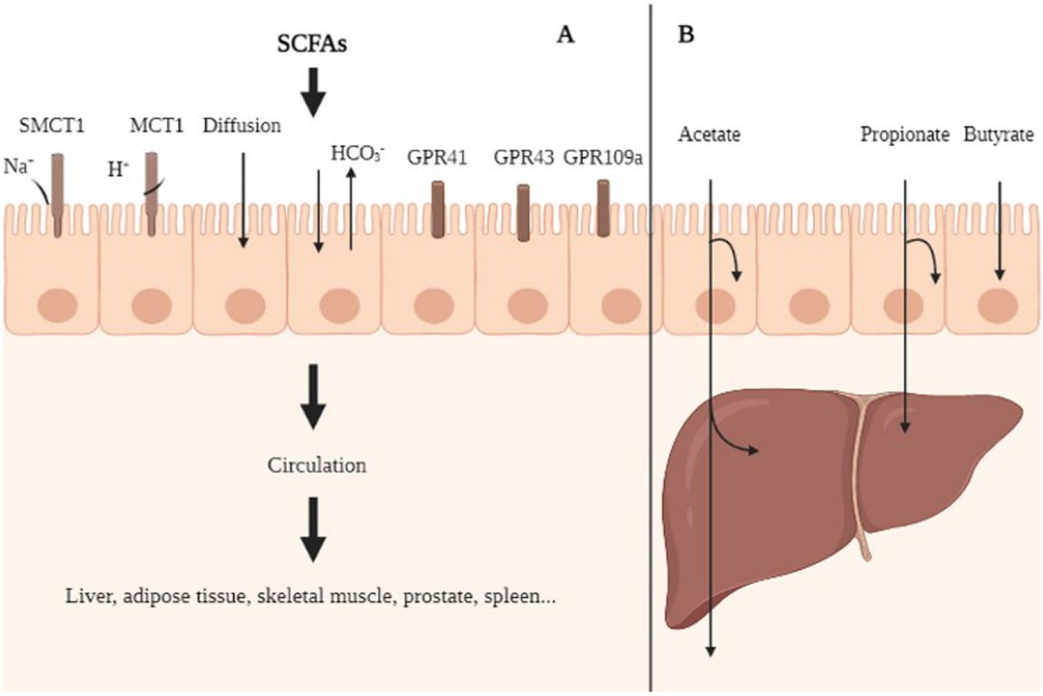


Figure 3. Absorption and transportation of SCFAs. (A) SCFAs are utilized in the enterocytes through different pathways: nonionic diffusion; SCFA/HCO_3^- exchange; active transport via SMCT1 and MCT1; and binding GPR41, GPR43, and GPR109a. After their absorption, SCFAs are transported into the portal vein and dispersed to peripheral tissues. (B) Acetate is largely absorbed going to the periphery and the liver. Propionate is transported to the liver, and metabolized by hepatocytes. Almost all of the butyrate produced remains in the colonic mucosa and it is used as an energy source by colonocytes. Abbreviations: GP, G-protein-coupled receptors; MCT1, hydrogen-coupled monocarboxylate transporter 1; SCFA, short-chain fatty acids; SMCT1, sodium-coupled monocarboxylate transporter 1.

hydrogen-coupled monocarboxylate transporter 1 (MCT1) or via sodium-coupled monocarboxylate transporter 1 (SMCT1).[2,31] This latter transporter coupled to Na^+ has a preference for butyrate but transports propionate and acetate at a slower rate[21,53,72,73]

SCFAs signaling through GPCRs

SCFAs act as signal transduction molecules by binding and activating cell surface GPCRs, like G-protein-coupled receptors 41 (GPR 41) and G-protein-coupled receptors 43 (GPR 43).[22,74] This activation might affect the intestine and host metabolism. GPR 43 is activated at a similar rate by all 3 SCFAs, but propionate remains the most important GPR 43 activator, while propionate and butyrate are the most potent activator of GPR 41, followed by acetate.[15,44,53,75] Both receptors are expressed in human colonic tissue and also in adipocytes, skeletal muscle, and liver.[14,36] All this suggests that SCFAs may have an effect on substrate and energy metabolism in peripheral tissues.[14,36,76]

The third SCFAs receptor, G protein-coupled receptor 109a (GPR109a) which is activated by butyrate, was found in the intestinal tract, partial immune cells, brain, prostate, spleen and adipocytes.[9,14,77] Colonocytes are used local butyrate as an energy source, whereas other SCFAs that escape colonic metabolization are transported by the portal vein.[53,69] Propionate is transported to the liver, metabolized by hepatocytes, and serves as a precursor of gluconeogenesis, protein synthesis, liponeogenesis, and an inhibitor of fatty acid production. Propionate consequently only exists in low amounts in the peripheral circulation, leaving acetate as the most abundant SCFAs, which can control appetite by crossing the blood-brain barrier (Figure 3B).[2,17,21,78] Figure 3A schematizes the different mechanisms of absorption and transport of SCFAs.

SCFAs-Metabolic Pathologies Axis

Dietary fiber confers a lot of metabolic benefits in the host, such as a decreased incidence of obesity and diabetes.[10] SCFAs and their receptors are becoming better known as a key mediator that connects diet and intestinal microbiota to host physiology through modulating activity of enzymes, development and functioning of leukocytes, endocrine responses, and transcription factors.[77,79] Thus, it is necessary to investigate and define the role of SCFAs receptors in the effectiveness of dietary therapy and gut microbiota alterations in the treatment of obesity, metabolic energy syndrome, and diabetes.[77,79]

SCFAs and obesity

Recent evidence indicates that SCFAs play an essential role in human health.[23] Studies have revealed that on enteroendocrine cells, activation of GPR41 boosts the hormone peptide YY (PYY) production and secretion, which promotes satiety by slowing gut motility, reducing stomach emptying and boosting

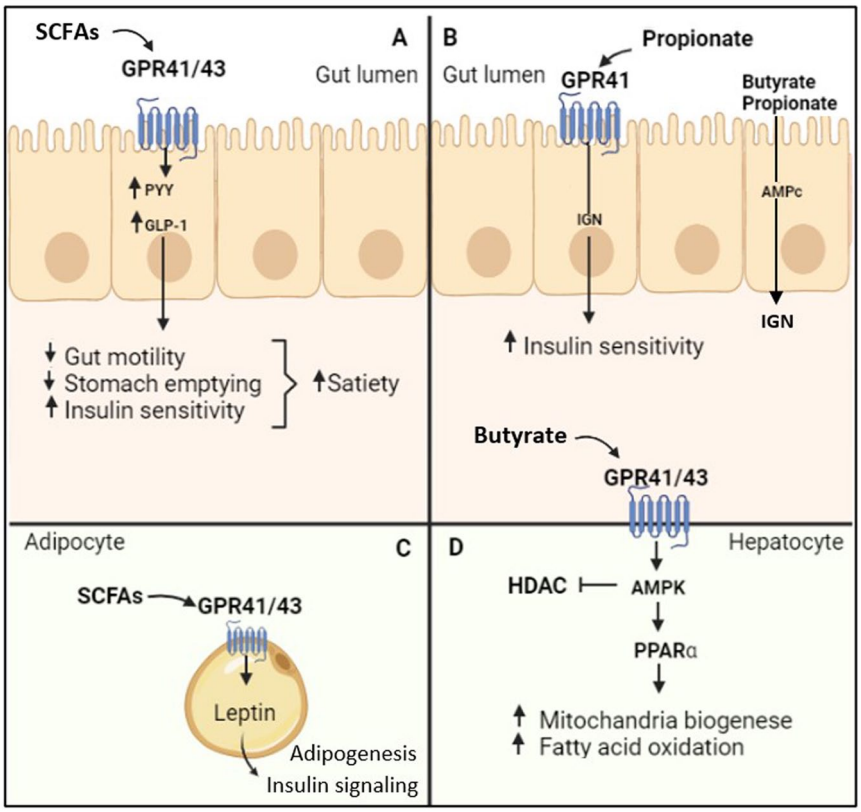


Figure 4. Mode of action of SCFAs: (A) activation of GPR41 and GPR43 boosts the hormone peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) production and secretion, which promotes satiety by slowing gut motility, reducing stomach emptying, and boosting insulin sensitivity, (B) SCFAs activate IGN via GPR 41, whereas the expression of IGN genes could be directly induced by butyrate and propionate via a cAMP-dependent mechanism, (C) SCFAs act on insulin signaling and adipogenesis by increasing the production and secretion of leptin via GPR 41 and GPR 43, and (D) butyrate stimulates fatty acid oxidation by inhibiting HDAC and PPARα via the AMPK pathway. Abbreviations: AMPK, AMP-activated protein kinase; GP, G-protein-coupled receptors; GLP-1, glucagon-like peptide-1; HDAC, inhibiting histone deacetylases; IGN, gluconeogenesis; PPARα, peroxisome proliferator-activated receptor alpha; PYY, hormone peptide YY; SCFA, short-chain fatty acids.

insulin sensitivity (Figure 4A).[53,78,80] While SCFA-dependent GPR43 signaling has been suggested to mediate host insulin sensitivity secretion by promoting glucagon-like peptide-1 (GLP-1) (Figure 4A).[19,81,82] Pingitore et al[83] show that insulin secretion is dependent on GPR43 and it is stimulated by acetate and propionate via the phospholipase C/protein kinase C pathway.

It has been shown that body weight, insulin resistance and dyslipidemia, which are metabolic markers associated to obesity can be reduced by dietary fiber supplementation.[84-86] Human studies have confirmed the molecular mechanisms of SCFA receptor-mediated metabolic responses by finding that administrating propionate to obese patients resulted in increased production and secretion of PYY and GLP-1 with a reduction in adiposity and overall weight gain.[87,88] Butyrate has received a lot of attention in recent studies because it seems to play a key role in the pathogenesis of obesity and diabetes.[81,89-91]

Propionate and butyrate may contribute to metabolic health by activation of intestinal gluconeogenesis (IGN).[84,92] This activation permitted to explain of the anti-obesity and anti-diabetic effects of dietary fibers.[92] The expression of IGN genes could be directly induced by butyrate and propionate via a cAMP-dependent mechanism, whereas the gut-brain axis that involves GPR41 was proposed to be the mediator of IGN activation by propionate (Figure 4B).[17,84,93,94] Butyrate upregulates the adiponectin-mediated AMPK pathway that stimulates mitochondria biogenesis and fatty acid oxidation by inhibiting histone deacetylases (HDACs) and increasing peroxisome proliferator-activated receptor alpha (PPAPα) (Figure 4D).[73,84,95,96] All of this demonstrated that SCFAs regulate the epigenome by modifying HDACs in addition to acting as signaling molecules.[17,96-100]

GPR109a activated by butyrate has been shown to induce lipid homeostasis by promoting local macrophage growth in adipose tissue.[77] Wang et al demonstrated that GPR109a which is expressed in human isolated β cells, prevented the insulin secretion stimulated by glucose and was down-regulated in type 2 diabetic patients.[101] In contrast, the treatment of the isolated β cells with a GPR43-specific agonist enhances the glucose-stimulated insulin secretion, β cell proliferation and gene expression.[77,81] GPR41 and GPR43, when expressed in the adipose tissue, function to stimulate leptin secretion and serves to suppress insulin signaling and adipogenesis, respectively (Figure 4C).[87,102,103] Acetate and propionate are notified

to induce adipogenicity through GPR43.[44] Therefore GPR41/GPR43 signaling mediated by SCFAs has been shown to modulate insulin secretion directly in pancreatic β cells.[77,104,105] Also, it has been shown that genetically modified mice deficient in GPR43 are overweight on a normal diet.[74]

Body weight can be controlled by propionate via sympathetic nervous system activity.[10,106] In addition, the increase of oxidative metabolism in the liver and adipose tissue as well as the reduction of body fat accumulation, hepatic steatosis and increasing insulin sensitivity are a result of the decreasing expression of PPARα by SCFAs.[10] Divers studies have shown that SCFAs can protect against obesity by increasing appetite control and energy expenditure.[9,84,107,108] Other reports suggested that increased fecal concentrations of SCFAs are associated with obesity.[85,109] However, Lu et al[74] showed that dietary supplementation of SCFAs can prevent body weight gain induced by high-fat diet feeding in overweight humans, this supplementation caused significant changes in GPR43 and GPR41 expressions and was characterized by increases in the adipose tissue and reductions in the colon.

Studies have shown that the binding of SCFAs to GPCRs as signal transduction molecules may be reduced in the presence of high-carbohydrate meals and obesity, which could increase intestinal energy absorption and hepatic lipogenesis.[109,110] Furthermore, and in contrast to obesity, dietary SCFAs have an impact on the structure of the bacterial community in feces, with an increase in the percentage of *Bacteroidetes* and a reduction in the percentage of *Firmicutes*.[85] Globally, body weight reduction is related to enhancing triglyceride hydrolysis and free fatty acid oxidation in the adipose tissue, stimulating mitochondrial biogenesis and increasing beige adipogenesis.[74]

Further exploration of SCFAs and their receptors, could open new possibilities for treating obesity and associated health risks by stimulating or disrupting SCFA signaling in combination with their potential as epigenetic modulators.[85,100] High fecal SCFAs concentrations may be associated with gut dysbiosis.[109,111] some bacterial components related to the latter, have altered the gut microbiota and have caused low-grade inflammation in adipose tissue, which has both been correlated to the development of obesity and other metabolic diseases.[109,111] Because SCFAs may contribute to the pathophysiology of obesity, they may also have a significant impact on obesity-related illnesses like type 2 diabetes mellitus (T2DM), by influencing body weight control across effects on energy expenditure, energy intake, systemic low-grade inflammation, and insulin sensitivity.[9,45,64,72]

SCFAs and diabetes

It's known that SCFAs can protect from diabetes via the engagement of metabolite-sensing GPCRs, like GPR43, on enteroendocrine-producing cells and pancreatic β cells, which are crucial for glucose tolerance.[112] Mechanistic insight into the protective effects of SCFAs against type 1 diabetes (T1D) has been suggested using non-obese (NOD) mice. Diabetes-free NOD mice had effectively higher SCFAs levels in their peripheral blood than diabetes-prone NOD mice. T1D was more likely to develop in germ-free mice than in conventional mice, showing a favorable function for microbiota in T1D suppression.[10,113,114] Furthermore, acetate-fed mice via drinking water developed T1D at a lower rate.[113] Acetylated or butylated resistant starches decreased T1D better than SCFAs provided via drinking water.[10,114] So, high-fiber diets and the microbiota may cooperate to minimize the risk of T1D in susceptible individuals.[10]

Suppressing of T1D development by fecal transfer of the expanded bacteria into NOD recipients indicated that a change in bacterial composition is crucial for SCFA-mediated T1D protection.[10,113,114] Butyrate- and acetate-yielding diets decreased the frequency of autoreactive T cells in lymphoid tissue and reduced CD86 expression in IL-12-producing mature marginal-zone B cells, a sub-assembly implicated in autoimmune disease pathogenesis.[113] While acetate was more effective at suppressing T1D than butyrate, butyrate and propionate were more effective at generating T regs, probably due to their HDAC inhibition activity.[98,113,115]

Furusawa et al[115] demonstrated that butyrate stimulates regulatory T-cell differentiation via increased histone H3 acetylation in the Foxp3 locus promoter and the conserved non-coding sequence region. On pancreatic β cells and enteroendocrine-producing cells which are crucial for glucose tolerance, SCFAs may have a role in the engagement of metabolite-sensing GPCRs to protect from T1D.[10] Compared to lean people, obese and type 2 diabetic patients had considerably lower levels of gut microbiota diversity and GPR41 promoter region methylation, showing a link between a higher body mass index and less GPR41 methylation.[100,116] SCFAs binding to GPCRs may contribute to the regulation of the microbiota and epigenetic processes.[100] Thus, epigenetic regulation may also be related to the positive impact of SCFAs on host metabolism.[10,100] Figure 5 shows the effects of SCFAs on host metabolism and physiology through different receptors.

Conclusion and Future Perspectives

In summary, there is evidence suggesting that SCFAs have a crucial role in preventing pathological diseases, such as obesity and diabetes. This effect results from different tissues expressing SCFAs receptors, which are capable of responding to the beneficial effects induced by these molecules. Furthermore, studies evaluating the potential effects of SCFAs in metabolic diseases are needed, due to inconsistent findings regarding the impact of various SCFAs. According to recent evidence, potential effects of SCFAs could occur through metabolic pathways other than those mediated by a specific receptor, and they

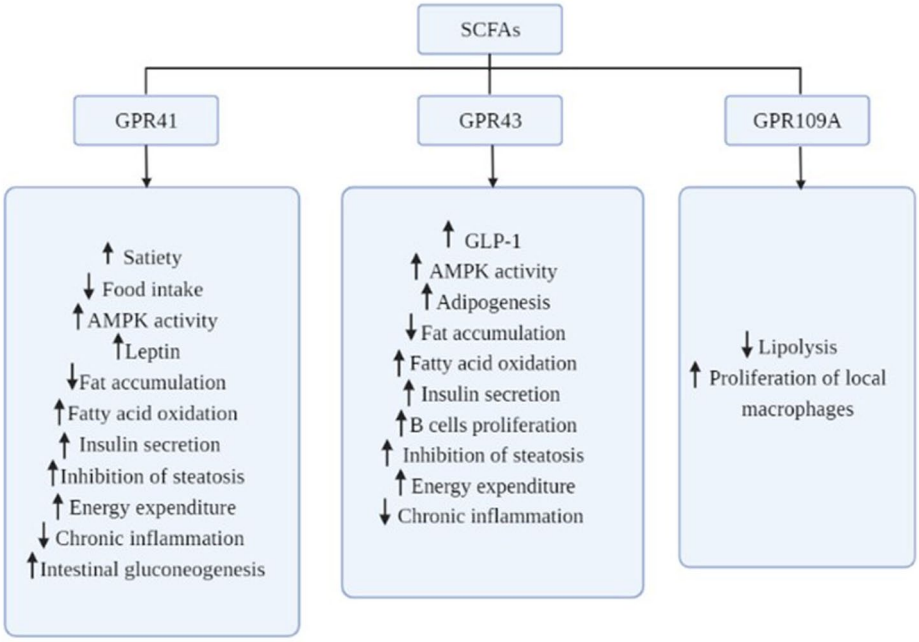


Figure 5. Metabolism and physiology of the host affected by SCFAs. SCFAs affect the metabolism and physiology of the host through complementary receptors found in different host tissues. Abbreviations: AMPK, AMP-activated protein kinase; GP, G-protein-coupled receptors; GLP-1, glucagon-like peptide-1; SCFA, short-chain fatty acids.

might cause distinct reactions in physiological versus pathological conditions.

Butyrate has been the subject of the majority of studies so far, even though, in contrast to acetate and propionate, it normally exists in very undetectable amounts in the body. As more is learned about the beneficial functions of the microbiota and SCFAs, there is a need to demonstrate how they increase or decrease the risk of metabolic diseases. Additionally, a better understanding of the molecular interactions between intestinal metabolites and host signaling pathways will lead to new treatment and prevention options for a variety of metabolic syndromes, especially T2DM.

The potential for wide impacts of SCFAs on GPCRs signaling as well as epigenomic changes make figuring out the particular mechanisms by which SCFAs enhance intestinal homeostasis, and protect from ameliorate illnesses, even more difficult. In addition, little is currently known about how SCFAs affect transcription factors' function, activity, and stability as a result of HDAC-mediated post-translational modification.

In the future, it will be benefic to clarify how to supplement SCFAs, which administration routes, and what doses ought to be advised in clinical practice. Therefore, devise strategies to increase SCFAs in the colon, and develop pharmacological drugs that are selective for the SCFAs receptors to investigate the potential for metabolic pathologies prevention and treatment. Also, the development of drug therapy targeting the physiological factors responsible for insulin resistance will be beneficial in the treatment and prevention of obesity and T2DM.

Author Contributions

Oumaima Anachad: Conceptualization, Investigation, Visualization, Writing - Original draft. Amine Taouil and Wafaa Taha: Investigation. Faiza Bennis and Fatima Chegdani: Conceptualization, Validation, Reviewing, Editing and Supervision. All authors contributed to manuscript revision, read and approved the submitted version.

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