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Opinion

Therapeutic Potential of Human Microbiome-Based Short-Chain Fatty Acids and Bile Acids in Liver Disease

Raja Ganesan and Ki Tae Suk *

Institute for Liver and Digestive Disease, Hallym University, Chuncheon 24253, Korea; vraja.ganesan@gmail.com
* Correspondence: ktsuk@hallym.ac.kr; Tel.: +82-33-248-3480; Fax: +82-33-248-3481

Abstract: Microbiome-derived short chain fatty acids (SCFAs: acetate, propionate, and butyrate) and bile acids (BAs: primary BAs and secondary BAs) widely influence liver metabolic inflammation, immune responses, and carcinogenesis. In recent literature, the role of SCFAs and BAs in various liver diseases has been discussed. SCFAs and BAs are two types of microbiome-derived metabolites and they have been shown to have immunoregulatory ability in autoimmunity, inflammation, and liver-cancer microcellular environments. SCFAs and BAs are dependent on dietary components. The numerous regulatory processes in lymphocytes and non-immune cells that underpin both the positive and harmful effects of microbial metabolites include variations in metabolic signaling and epigenetic states. As a result, histone deacetylase (HDAC) inhibitors, SCFAs, and BAs, which are powerful immunometabolism modulators, have been explored. BAs have also been shown to alter the microbiome as well as adaptive and innate immune systems. We therefore emphasize the important metabolites in liver disease for clinical therapeutic applications. A deep understanding of SCFAs and Bas, as well as their molecular risk, could reveal more about certain liver-disease conditions.

Keywords: short-chain fatty acids; bile acids; liver therapies; metabolomics; metabolic discriminations; biochemistry

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1. Introduction

The trillions of microorganisms that colonize our gastrointestinal (GI) tract are collectively known as gut microbiota. These microbes are mutually linked to the functioning of synergetic cellular metabolism and hence to the host's medical conditions [1,2]. The gut microbiota includes a unique diversity of non-mammalian microbial genes that are required for the synthesis of many microbial molecules such as short-chain fatty acids (SCFAs: acetate, propionate, and butyrate) and bile acids (BAs: primary Bas and, through deconjugation, secondary BAs). These soluble mediators bridge the gap between host cells and commensal bacteria and are required for energy metabolism, shaping the mucosal immune system, and imbalance at the host interface [3,4]. The gut microbiome can be altered through diet, drugs, time, and physiochemical processes. Analysis of intestinal microbiota shows that specific anaerobic gut microbes are significantly required in allogenic stem cell transplantation (SCT) [5,6].

The SCFAs of acetate, propionate, and butyrate are an important type of microbial metabolite. According to the microbial fermentation process, SCFAs are generated in the intestinal lumen through the human microbiota. *Bacteroides* spp. are linked to propionate [7], and acetate synthesis [8]. There are two types of microbial fermentation process: (1) fermentation of water-soluble dietary fibers (i.e., pectin, guar gum, and inulin) and (2) fermentation of insoluble fibers (i.e., resistant starch). The complex microbial molecules pass through the upper GI tract and are digested in the cecum and proximal colon under an anaerobic environment that has maximum amounts of SCFAs [9]. Three SCFAs, acetate, propionate, and butyrate are most prevalent in normally developing mouse microbial

intestines. Furthermore, branched-chain fatty acids (BCFAs) such as valine, leucine, and isoleucine) have been found in much lower amounts in rodent and human GI tracts [10,11].

In contrast to SCFAs and lactate that are also produced by the breakdown of carbohydrates, BCFAs are produced by microbial fermentation. [12,13]. The effects of SCFAs on epithelial cells have been explored and butyrate treatment of epithelial cells has been shown to increase the production of IL-18 by GPR109a. SCFA-associated GPR43 (G-coupled receptor 43) has also been shown to suppress insulin signaling activity, decrease fat accumulation in adipose tissue, and improve energy homeostasis balancing [14]. SCFAs have been implicated in various metabolic dysregulations in human and mice studies and SCFA-associated metabolic phenotypic expression can control GI equilibrium. Gut homeostasis and microbial communication in epithelial tissues, the immune system, *Staphylococcus* epidermidis, and molecular mechanisms are activated by SCFAs via the liver feedback mechanism [15,16].

The microbiota is involved in modulating homeostasis in the human gut. Bacteria influence the development and role of host immune cells, including T helper cells (interleukin 17A and T_H17 cells). Both primary BAs and secondary BAs regulate host and immune responses [17]. SCFAs are the main metabolites and might influence gut–liver crosstalk and gut–brain function. SCFAs are mandatory for gut, body, and brain health.

Notably, in addition to food components, gut microbial bacteria can change host-derived compounds such as primary and secondary BAs. When food is consumed, gallbladder stimulation causes an influx of primary liver-derived BAs into the duodenum, which is responsible for emulsification of nutritional fats [18]. The majority of primary BAs (cholic acid and chenoxycholic acid in humans and cholic acid, α-muricholic acid, and β-muricholic acid in rodents) are generated in the liver and delivered to the liver via the enterohepatic circulation; a lesser proportion is converted into secondary BAs by gut microbiota alteration in the colon [17]. Both primary BAs and secondary BAs have been shown to interact agonistically or antagonistically with a family of nuclear (FXR) and G-protein-coupled receptors, collectively known as BA-activated receptors (BAR), influencing cellular signaling as well as immunological response [19,20]. The secondary BAs of 3-hydroxydeoxycholic acid have recently been found to promote regulatory T cell differentiation via interaction with the farnesoid X receptor on dendritic cells (DCs), indicating a possibility for novel therapies [21].

Therefore, the mechanisms of two significant families of microbial phenotypes in BAs and SCFAs play lead roles in liver metabolism. SCFA and BA phenotypic expression in the clinical domain will enhance diagnostic and therapeutic options.

2. SCFAs—Associated Metabolic Expression and Biomarker Modelling

The GI tract has a rich and condensed microbial environment, making it the sole site of host–microbiota crosstalk. Metabolic disturbance of host–microbe and microbe–microbe interactions has been linked to inflammatory illnesses (e.g., inflammatory bowel disease and colitis-associated carcinogenesis [22]. To maintain the gut immune system, microbial communities require a balance between pathogen protection and tolerance to commensals and dietary antigens. As a result, the microbiome genome scale plays a role in controlling the immunological response, including effects on intestinal epithelial cells, activation of anti-inflammatory cells, neurological disorders, and reduction of the inflammatory response [23].

New research has found that SCFAs have a variety of impacts on epithelial cells. Injection of SCFAs has been shown to enhance retinoic acid (RA) in intentional epithelial cells. Vitamin A derivative compounds are formed via aldehyde dehydrogenase which is related to signaling and growth of peripheral T-regs (pT-regs) during an immunosuppressive response [24–26]. Furthermore, butyrate treatment of epithelial cells boosted IL-18 production via a GPR109a-mediated pathway, promoting stomach homeostasis and defending against colorectal carcinogenesis [27–29].

In addition, binding of SCFAs to GPR41 and GPR43 increased the production of antimicrobial factors such as RegIIIγ and β-defensins in IEC via increased mTOR and STAT3 signaling, while animals lacking the receptors had a poor immunological response to *C. rodentium* infection [30,31]. The regulation of antimicrobial molecules in epithelial cells could lead to an increase in metabolic signaling information. Acetyl-CoA regulates genes for plasma-cell differentiation and IgA antibody development. IgA is more important for gut homeostasis maintenance [32]. Microbial bacteria-derived SCFAs are required for gut homeostasis, mucosal integrity, and IgA production [33,34].

3. Modulatory Role of SCFAs

Propionate and butyrate regulate gene expression by directly inhibiting histone deacetylases (HDACs). HDAC is responsible for transcriptional gene silencing. HDAC inhibitors in liver disease are key to exploiting specific therapeutic strategies. The second route for SCFA actions is signaling via G-protein-coupled receptors (GPR: GPR41, GPR43, and GPR109A) [1]. In addition, GPR43 expression was found in immune cells as well as in the GI tract. The presence of GPR43 and GPR109A in immune-system neutrophils, macrophages, and dendritic cells (DCs) suggests that SCFAs play a role in immunological reactions [35,36].

The anti-inflammatory activity of GPR43 has been discovered in colitis and arthritic mice [26]. SCFAs have been shown to improve body weight by activating the expression of GPR41 and GRP109A [37]. GPR43 and GPR41 have a 43% amino acid sequence identity and may bind to acetate, propionate, or butyrate [38]. Butyrate has been the most efficient activator for GPR109A, which is an individual state in the human microbiome, whereas propionate is more discriminating for GPR41 and GPR43 [39]. It is worthwhile investigating remedies that target these receptors or their signaling pathways to impact SCFAs for liver therapeutic interventions and metabolic disease.

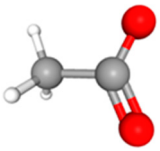
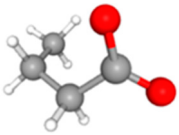
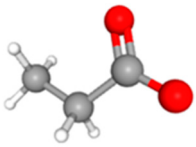
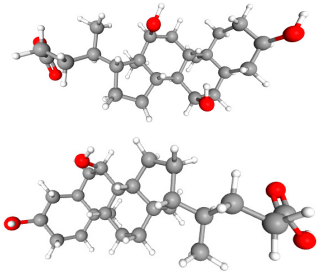
4. Liver Disease

The impact of SCFAs on liver cirrhosis has been studied in both animals and humans. Butyrate induces T-reg differentiation. It could play a role in the control of inflammation. Butyrate provides energy and maintains the integrity of colonocytes, improving barrier function [40]. Acetate and butyrate supplementation has protected against nicotine-induced excess hepatic steatosis, and Western-style-diet-induced non-alcoholic steatohepatitis (NASH) [41,42]. In human studies, SCFA levels were observed to be decreased in non-obese non-alcoholic fatty liver disease (NAFLD) patients compared to non-obese healthy individuals [43]. Table 1 shows the metabolite-producing flora for SCFAs and BAs.

In addition, SCFAs help to inhibit the progress of NAFLD in a variety of ways: Firstly, SCFAs have important impacts on fatty-acid metabolism and visceral adipose tissue (VAT), both of which are important in the development of NAFLD. Excessive VAT accumulation has been linked to an increase in the release of free fatty acids (FFAs) into the liver [44]. Because they activate NF-kB, FFAs are thought to play a major role in the development of NAFLD [45]. Furthermore, VAT generates an imbalance of pro-inflammatory and anti-inflammatory adipokines, leading to systemic inflammation, including liver inflammation. Acetate could inhibit hormone-sensitive lipase (HSL) phosphorylation in human multipotent adipose-tissue-produced stem adipocytes in GPR [46].

Secondly, through modulating GI motility, SCFAs may increase energy yield, improve nutritional absorption, and accelerate hepatic lipogenesis. The molecular metabolism for this is that activation of GPR41 and GPR43 stimulates the production of 5-hydroxytryptamine (5-HT), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1), which may block intestinal transit and decrease gastric emptying, diet intake, and intestinal motility [47].

Table 1. Human gut microbiota produces SCFAs and bile acid metabolites.

Class	Metabolites	3D Structure	Fabricating Flora
SCFAs	Acetic acid (Acetate)		*Bacteroides*, *Lactobacillus*, *Streptococcus* and *Bifidobacterium*)
	Butyric acid (Butyrate)		*Clostridium*, *Spirillum*, *Bacillus* and *Ruminococcus*
	Propionic acid (Propionate)		*Bacteroides*
Bile acids	Primary BAs (cholic acid and chenoxycholic acid). Secondary BAs		*Lactobacillus*, *Bifidobacterium*, *Clostridium*, and *Bacteroides*

Thirdly, SCFAs may help to defend the colonic barrier. Acetate, propionate, and butyrate could trigger the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in the gut, increasing IL-18 release and improving intestinal barrier integrity [48]. GPR41 and GPR43 influence genetic responses through two primary signaling pathways, as shown in Figure 1. Finally, SCFAs enter the liver directly through the portal vein, where they suppress inflammation and hepatic steatosis.

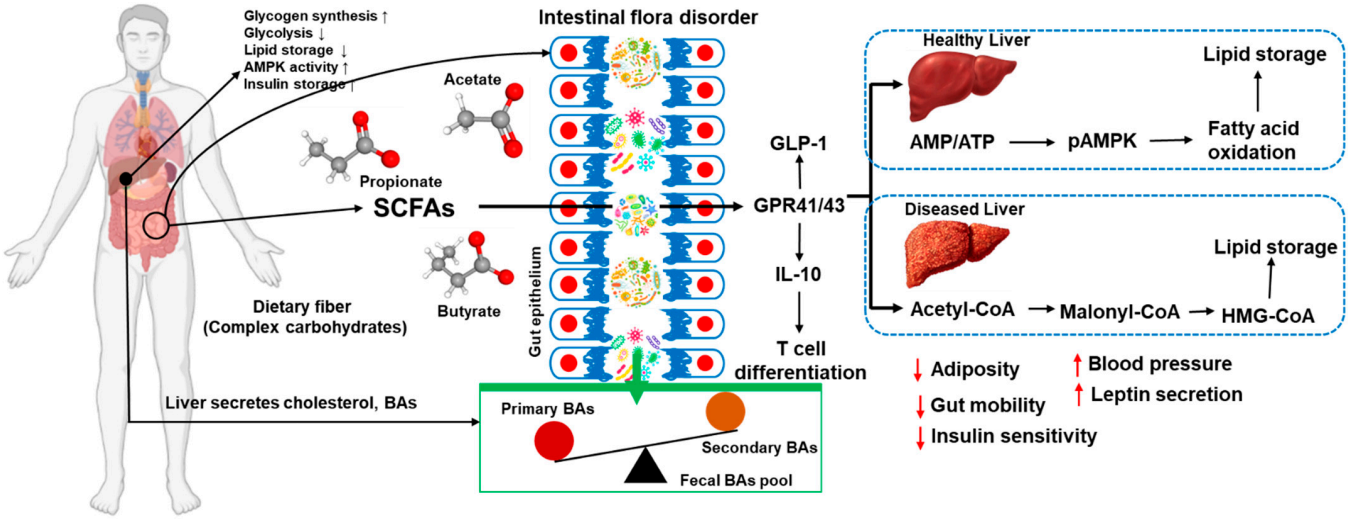


Figure 1. Gut microbiota and host. The role of SCFAs in human microbiome communication in healthy liver and disease. This dysbiosis is associated with fluctuations in bacterial metabolites such as SCFAs and BAs. GPR41/43, IL-10, and GLP-1 control the metabolic activities of fatty acid oxidation, lipid storage, insulin production, and acetyl-CoA synthesis.

Acetate, propionate, and butyrate have been shown to alleviate hepatic steatosis by activating AMP-activated protein kinase, expressing a fatty-acid oxidation gene, and inhibiting macrophage proinflammatory activation [49]. SCFAs also play an epigenetic function in NAFLD development. As histone deacetylase inhibitors, propionate, acetate, and butyrate play an important role in NAFLD by decreasing chromatin-bound acetyl groups [50,51]. The multi-omics data sets and clinic databases must be linked, as this will set the tone for future systems.

5. Conclusions

In conclusion, SCFA and BA metabolites promote human liver health and research into them allows a deeper understanding of the role of host–microbiota networks. HDAC inhibitors are new anti-cancer drugs in apoptosis and liver cancer cell-cycle arrest. We believe that SCFAs, Bas, and HDAC biotransformation offer us opportunities to devise therapeutic interventions for liver metabolic diseases, including fatty liver, hepatitis, and cancers. In the future, metabolic compounds such as SCFAs and BAs will receive significant attention in clinical and translational research.

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