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Review article

Regulation of host energy metabolism by gut microbiota-derived short-chain fatty acids

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Abstract

The gut microbiota is attracting attention as a new target for preventing and improving metabolic diseases, including obesity and type 2 diabetes mellitus. About 100 trillion or more bacteria from at least 1,000 species, most non-cultivable, form multiple interbacterial communities in the human intestinal tract. Recent advances in metagenomic, proteomic, and metabolomic analyses and in mass spectrometry technologies have enabled the identification of gut bacterial strains, those structural components and various metabolites that significantly affect host energy metabolism. Short-chain fatty acids (SCFAs) produced by colonic bacterial fermentation of dietary fiber have been established as essential nutrients that also contribute to maintain host energy homeostasis via immune and epigenome system. Recently, two orphan G-protein-coupled receptors (GPCRs), GPR41 and GPR43, were reported to be activated by SCFAs. In addition to functioning as an energy source, dietary fiber intake plays an important role in determining the diversity and formation of gut microbiota. It is known that appropriate daily dietary habit also reduces the risk of metabolic diseases for improving the intestinal environment in clinical trials. Therefore, the develop of new therapeutic approaches such as gut microbial metabolites including SCFAs is expected for metabolic diseases. In this review, we will focus on the gut microbiota and association between gut microbial SCFAs and host energy metabolism. Findings from previous research, including those from our group, and future prospects will be discussed.

KEY WORDS: gut microbiota, SCFAs, GPCRs, obesity, type 2 diabetes mellitus

Introduction

About 100 trillion or more gut bacteria exist in the human intestinal tract. They include at least 1,000 species and multiple interbacterial communities, and weigh as much as approximately 1.5 kg. The complex of living microorganisms they form is generically called the gut microbiota [1]. Most of the gut microbiota can be classified into four phylum, Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. On analysis at the genus level, these can be further classified into three enterotypes, *Bacteroides*, *Prevotella*, and *Ruminococcus* [2,3]. Recent studies have suggested that the gut microbiota may be closely linked to a range of host diseases, and accumulating evidence suggests that they have an effect on obesity and type 2 diabetes (T2DM) [4-7], inflammatory bowel diseases (ulcerative colitis), Crohn's disease [8,9], and even psychiatric disorders including autism [10].

Recent advances in metagenomic, proteomic, and metabolomic analyses and in mass spectrometry technologies have enabled the identification of gut bacterial metabolites that significantly regulate host energy metabolism. Short-chain fatty acids (SCFAs), for example, are produced by gut microbiota-induced fermentation of dietary fiber. These have been shown to be not only an essential host energy source, but also to act as signaling molecules via G-protein-coupled receptors (GPCRs) in various tissues (***Fig. 1***) [11]. Identification of the physiological activity between microbial metabolites such as SCFAs and their association with these receptors is expected to increase our understanding for metabolic diseases mechanisms. Therefore, the target of gut microbiota

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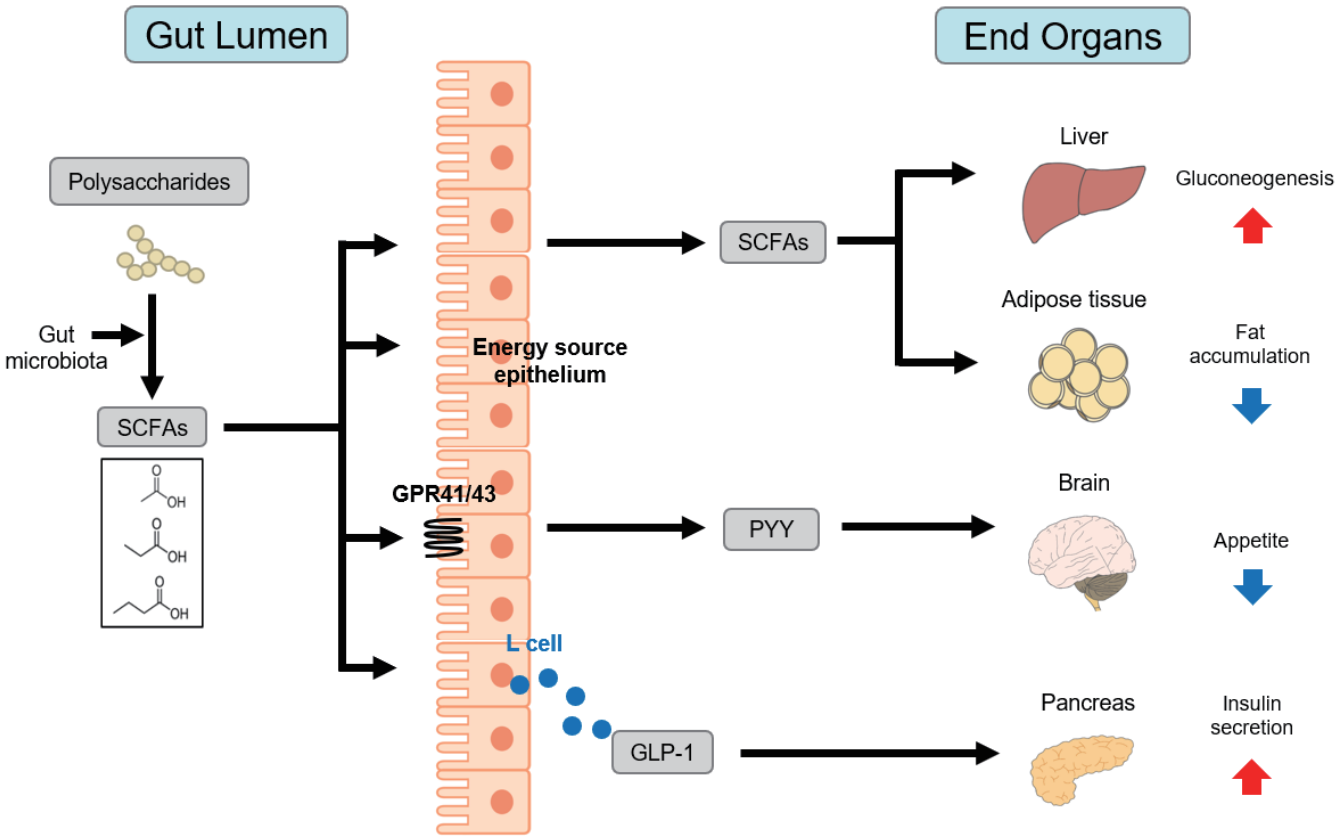

Fig. 1. **Crosstalk between gut microbiota-derived metabolites and end organs.**

SCFAs, short-chain fatty acids; GLP-1, glucagon-like peptide-1; PYY, peptide YY; GPR 41, G-protein-coupled receptor 41; GPR 43, G-protein-coupled receptor 43.

study has been recognized important as prevention and treatment for metabolic diseases.

This review will focus on the gut microbiota and the association between gut microbial SCFAs and host energy metabolism. Findings from previous research and future prospects will be discussed.

1. Gut Microbiota and Regulation of Host Energy Metabolism

1-1) Effect of Changes in the Gut Microbiota

In 2006, the first obesity-associated composition of gut microbiota was reported. They observed that, compared with lean mice, the gut microbiota of obese mice contained a significantly higher ratio of the phylum Firmicutes to Bacteroidetes, and suggested that the gut microbiota may directly affect obesity and T2DM [12]. Human study also confirmed that the gut microbiota of obese patients whose condition improved after diet therapy was similar to that of healthy individuals, thereby providing proof-of-concept that gut microbiota is a possible indicator of the state of host energy metabolism [12]. Research on the relationship between gut microbiota and metabolic diseases is particularly extensive. For example, an association analysis of gut microbiota and blood metabolomics revealed higher levels of branched-chain amino acids (BCAAs) in obese patients than healthy individuals. Mice fed a high-fat diet containing BCAAs developed insulin resistance [13]. Further, the enzymatic activity of gut microbiota species (*Prevotella copri* and *Bacteroides vulgatus*) with BCAAs synthetase is markedly increased in obese patients, and *P. copri* can induce insulin resistance, aggravate glucose intolerance, and augment circulating levels of BCAAs in high-fat diet-fed mice [14]. Additionally, the results of a large scale cohort study targeting T2DM patients in Europe and China revealed that there is a low percentage of butyrate-producing bacteria of the genus *Clostridium*, but a high percentage of bacteria of other genera in the gut microbiota of all T2DM patients [15, 16]. Moreover, comparison of T2DM patients with healthy individuals in Japan showed that the former had significantly higher levels of *Clostridium cocoides* group, *Clostridium leptum* group, and *Lactobacillus* genus and considerably lower levels of *Prevotella* genus and SCFAs concentrations in feces. These findings suggest the involvement of gut microbiota in T2DM, despite the total number of gut microbiota being similar [17]. It has also been reported the interaction between gut microbiota associating human

genetic factor and body mass index (BMI). Metagenomics analysis of microbiota across >1,000 fecal samples including 416 twin pairs revealed a negative correlation between the abundance of *Christensenellaceae* family and BMI. Furthermore, *Christensenella minuta*, a cultured member of the *Christensenellaceae*, recipient mice reduced weight gain [18].

Recent metagenomics data on the human gut microbiota have revealed a significant difference in the gut microbiota composition owing to differences in the eating habits in each of the regions. For example, the gut microbiota of Americans, who routinely consume western diets, comprise large quantities of *Bacteroides* genus, while the those of African and South American countries, who routinely consume vegetable diets, comprise large *Prevotella* genus [19]. Western diets contain larger quantities of advanced glycation end-products (AGEs), whose accumulation in the body is a risk factor for metabolic diseases such as obesity and T2DM, and cardiovascular disease compared to vegetable diets [20, 21]. AGEs are also known to induce changes in gut microbiota composition; for example, in a trial that compared a high to low intake of AGEs in renal disease patients, the high intake group showed a marked increase in *P. copri* in their gut microbiota [22]. As mentioned above, *P. copri* has been implicated in insulin resistance and deterioration of host glucose intolerance, mediated by BCAAs production. These findings suggest that a high intake of foods containing AGEs may affect gut microbiota composition and associated gut microbial metabolite production profiles, and may be involved in the aggravation of pathological conditions. Therefore, it is expected that low AGEs diet will lead to the prevention or improvement of metabolic diseases via intestinal environment. For example, when dietary fiber, including those from vegetable foods, is consumed as a substitute for meat foods such as high AGEs, SCFAs are produced in the intestine from fermentation by gut microbiota. Studies have shown that gut-derived SCFAs can improve insulin sensitivity by directly regulating insulin secretion at the level of pancreatic β cells thereby contributing to metabolic disease prevention and improvement [23, 24]. However, a high intake of foods containing AGEs also reportedly increases the amount of fecal SCFAs in rats [25]. Therefore, further study required for the association of gut microbiota composition with intake of AGEs and the resulting gut microbial metabolites.

While antibiotics are mainly used for the treatment of diseases caused by external invading pathogens, therapeutic antibiotics are also known to have a significant effect on the gut microbiota. Administration of vancomycin, a glycopeptide antibiotic, to obese patients leads to a marked decrease Firmicutes phylum and insulin sensitivity [26]. In contrast, similar treatment with amoxicillin, a β-lactam antibiotic, produces no observable change in insulin sensitivity. A possible explanation for this is that gut microbiota belonging to the phylum Firmicutes may have effects on insulin sensitivity in obese patients. In another study, mice administered antibiotics from age 4 to 10 weeks showed an increase in body weight and fat accumulation compared with untreated mice. Additionally, antibiotics-treated mice showed a significant increase Firmicutes phylum and glucose-dependent insulinotropic polypeptide (GIP) [27], suggesting that there may be a close relationship between gut microbiota and host energy metabolism.

1-2) Effects of Structural Components Derived from Gut Microbiota

Toll-like receptors (TLRs) comprise a family of pattern-recognition receptors that detect conserved molecular products of microorganisms and are critical for the initiation of inflammatory and immune responses. Recent studies showed that TLRs play a key role in maintaining intestinal and microbial homeostasis and contribute to HFD-induced bowel inflammation and subsequent metabolic abnormalities, suggesting that TLRs are responsible for the host energy metabolism as well as immune regulation. For example, TLR2 recognizes lipoteichoic acid, a cell wall component of gram-positive bacteria, and TLR2-deficient mice develop obesity and insulin resistance [28]. Additionally, TLR5 recognizes flagellin, a type of flagella presents on the bacterial cell surface of gut microbiota. TLR5-deficient mice also exhibit hallmark features of metabolic syndrome, including obesity and insulin resistance [29]. In contrast, *Akkermansia muciniphila*, a mucin-degrading bacteria, is decreased in obese or diabetic patients and in the corresponding mouse models. Administration of both live and heat-killed *A. muciniphila* to mouse models of metabolic diseases leads to increases in the intestinal mucosal barrier, goblet cells, and insulin sensitivity. These observations may be explained by the finding that Amuc_1100, an outer cell wall membrane protein of *A. muciniphila* which acts as a ligand for TLR2, increases the expression of tight junctions, including cladudin and occuldin, in the intestinal epithelium [30]. Therefore, therapeutic *A. muciniphila* is currently being examined in clinical trials in Europe [31]. These results suggest that the gut microbiota directly affect hosts and have an effect on host energy metabolism.

2. SCFAs and Regulation of Host Energy Metabolism

SCFAs are produced as gut microbial metabolites and act as signaling molecules via cell membrane receptors. In addition to their role as a host energy substrate, they also contribute to the prevention and improvement of obesity and T2DM by regulating host energy metabolism (***Fig. 2***).

2-1) Roles of SCFAs

SCFAs are saturated aliphatic organic acids with 1-6 carbon atoms (acetate, propionate, butyrate, and valerate) can be directly consumed from daily diet. With oral administration, nutrients such as SCFAs are almost completely absorbed in the small intestine. In recent years, developments in metabolomic analyses have revealed that fermentation of dietary fiber by gut microbiota is a steady source of SCFAs *in vivo* [32]. In fact, certain strains of gut microbiota have been gradually identified, such as producing butyrate in the genera *Clostridium* (*i.e. Clostridium butyricum*) and *Butyrivibrio* (*i.e. Butyrivibrio fibrisolvens*), acetate in the genera *Acetobacter* and *Gluconobacter* [33-35]. These reports suggest that the total SCFAs concentration is approximately 100 mM in large intestine. Thus, detailed studies of gut microbes SCFAs functions in comprehensive

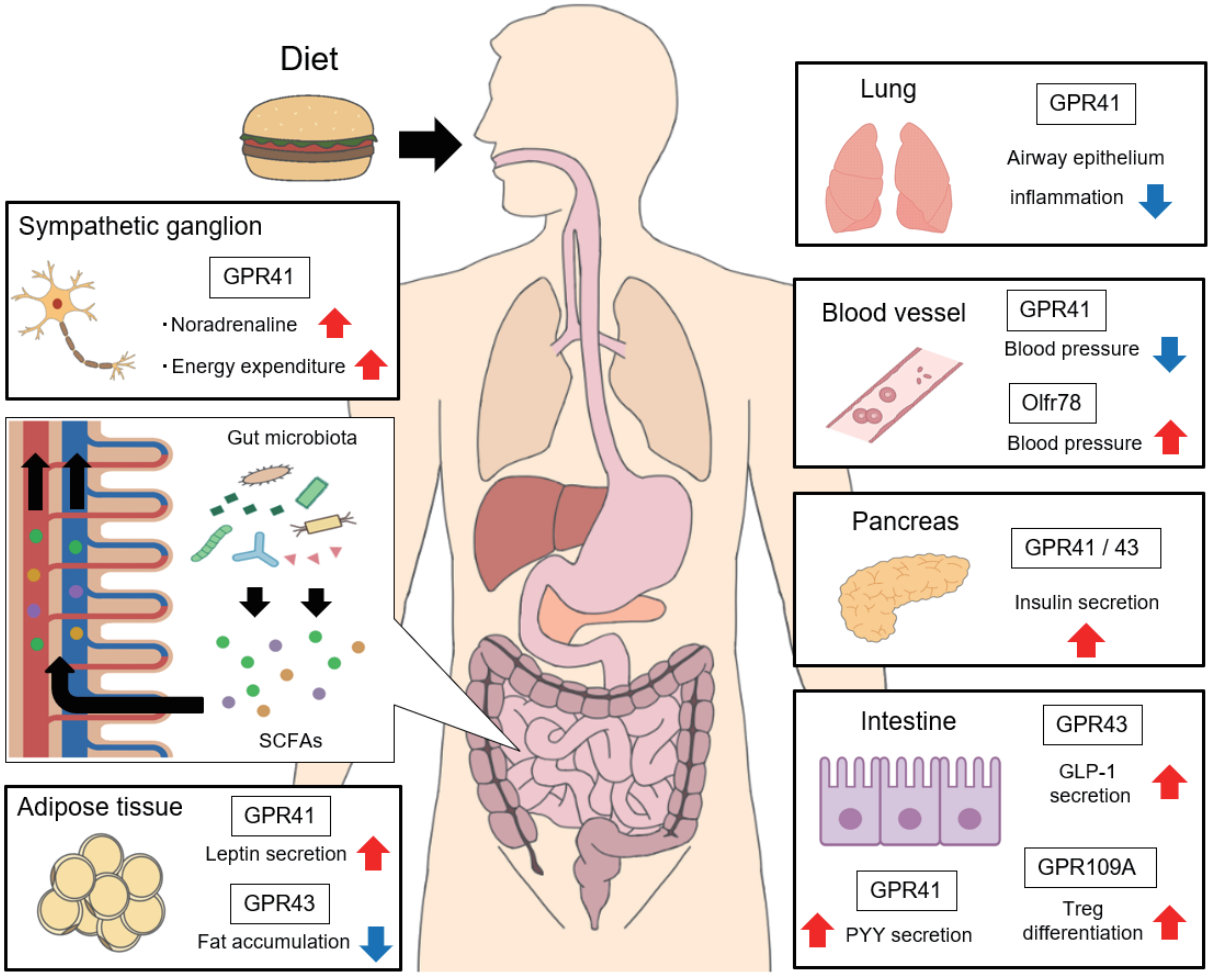

Fig. 2. **SCFA receptors regulate host energy homeostasis.**

SCFAs, short-chain fatty acids.

evaluation will require on the connections between dietary fiber-gut microbiota-SCFAs and energy homeostasis.

2-2) Absorption and Recognition Mechanism of SCFAs

Over 95% of SCFAs produced by gut microbiota are rapidly absorbed into colonocytes, during which time hydrogen ions are removed and bicarbonate ions are simultaneously secreted followed by preventing intestinal tract acidification. Thus, SCFAs contribute to the regulation of host homeostasis in the intestinal environment. Gut microbiota-derived SCFAs are also thought to play an important role by acting as an energy source and contributing to the growth of epithelial cells in the large intestine, mucus secretion, absorption of water and minerals, and acting the synthesis of fat in peripheral tissues like the liver.

Recent studies have identified that SCFAs act as signaling molecules via GPCRs and elucidation of the function of various GPCRs is rapidly progressing. Among the various SCFA receptors, GPR41 and GPR43 have been identified to be involved in energy regulation in response to SCFAs produced by gut microbiota. These receptors are activated by SCFAs with 50% effective concentrations (EC50) values of μM order under physiological conditions. This is because the concentration of SCFAs, as well as several hundred μM levels of acetate and dozen μM levels of propionate and butyrate acid in peripheral blood, at least doubles SCFAs concentration after meal consumption. GPR41 is activated equally by propionate and butyrate, whereas GPR43 is equally by propionate and acetate rather than butyrate [36,37]. GPR41 and GPR43 is reported to couple with Gi/o protein. Stimulation of GPR41 and GPR43 by SCFAs inhibits cAMP production and promotes activation of mitogen-activated protein kinase (MAPK) cascade. GPR43 is also known as dual-coupling GPCR that binds the pertussis toxin-sensitive Gq increasing intracellular Ca^{2+} levels. In addition to GPR41 and GPR43, Olfr78 and GPR109A have also been identified by SCFAs, and the studies are in progress to determine their functions. Olfr78 is a known olfactory receptor, although it has also been found to be expressed in blood vessels, where it is involved in blood pressure regulation by promoting renin secretion through SCFAs [38]. Furthermore, niacin and the ketone body ß-hydroxybutyrate are known ligands of GPR109A, a receptor that is also activated by butyrate, and maintain the mucosal environment by strengthening the induction of immunotolerance in the small intestine via butyrate, and the anti-food allergy effect by oral

immunotolerance [39]. These studies demonstrate the detailed molecular mechanisms and multifaceted bioregulatory actions of SCFAs as ligands of GPCRs, and are expected to lead to the complete elucidation of the relationship between gut microbiota and host homeostasis.

2-3) Regulation of Host Energy Metabolism by SCFAs

GPR41 is abundantly expressed in intestinal tract and sympathetic ganglion, promoting secretion of the anorectic hormone peptide YY (PYY) in endocrine L cells. Germ-free mice led to significantly lower PYY levels [40, 41], while *Gpr41*-deficient mice expressed similar PYY levels compared with wild-type mice, suggesting that PYY secretion by promoting gut microbiota-derived SCFAs regulate food intake and control energy metabolism [41]. Furthermore, *Gpr41*-deficient mice had reduced energy consumption and sympathetic nervous system dysfunction, compared to wild-type mice [42]. Noradrenaline secretion and sympathetic activity by SCFAs stimulation involve MAPK pathway via the Gi/o signal. These effect are abolished in *Gpr41*-deficient mice. These results indicate that gut microbiota-derived SCFAs promoted the energy consumption followed by activating sympathetic ganglion via GPR41, and contribute to maintaining energy homeostasis *in vivo* [43]. The expression of GPR41 in peripheral nerves is reportedly involved in the intestine-brain axis, and gut microbiota-derived SCFAs improve metabolic function by controlling glucose metabolism via the central nervous system [44].

GPR43 is abundantly expressed in the intestinal tract, adipose tissue, and immune system. GPR43 is also highly expressed in endocrine L cells stimulating the release of PYY and glucagon-like peptide-1 (GLP-1) secretion. Conversely, *GPR43*-deficient mice decrease GLP-1 secretion followed insulin secretion and insulin resistance [45]. SCFA-mediated secretion of gut hormones (PYY and GLP-1) has also been confirmed in human studies. Further, PYY and GLP-1 secretion following propionate administration significantly suppresses body weight and fat accumulation in obese patients [46]. It is reported that *GPR43* expression was greater in the white adipose tissue (WAT) in high-fat diet (HFD) induced obesity mice compared with normal chow-fed mice [47]. To clarify the function of GPR43 in adipose tissue, the effect of HFD induced obesity using *GPR43*-deficient mice and adipose-specific overexpression of *aP2-GPR43* [adipocyte protein 2 (aP2)] was investigated. *Gpr43*-deficient mice induced symptoms of obesity, while *aP2-Gpr43*-transgenic mice were lean under normal conditions. Raised under germ-free conditions or after antibiotics treatment, both phenotypes of mice have abolished [48]. Furthermore, SCFA- mediated GPR43 activation suppressed adipose insulin signaling via adipocyte-specific Gi/o, leading to inhibition of fat accumulation in the adipose tissue [48]. Moreover, SCFAs are involved in controlling insulin sensitivity by directly regulating insulin secretion from pancreatic β cells via GPR41 and GPR43 [23, 24]. These results show that the conventional molecular mechanisms of dietary fiber are initiated by the actions of gut microbiota-derived SCFAs via GPCRs. This suggests that these SCFAs and their receptors are promising therapeutic targets for the treatment of metabolic disorders such as obesity and T2DM.

3. Physiological Effects of SCFAs

3-1) GPCR-mediated Immunoregulation by SCFAs

In addition to their regulation of metabolic function, studies on the physiological effects of SCFAs-mediated GPCRs have also focused on their role in immune function. Intestinal immunoglobulin A (IgA) has a crucial role in maintenance of intestinal homeostasis and protecting inflammation. It is reported that acetate derived gut microbiota promoted B-cell IgA class switching and IgA production via GPR43 [49]. Additionally, dietary fiber and diet-derived SCFAs promote the survival of mice with influenza by changing the hematopoietic effects of bone marrow and enhance the function of effector CD8-T cells [50].

Recent studies have demonstrated GPR41 expresses in dendritic cells and lung tissue, and indicated that propionate controls airway epithelial inflammation via GPR41 [51]. Additionally, GPR41 activation leads to increased expression of autoimmune regulators, and fetuses born to mothers fed rich dietary fiber during pregnancy and lactation show enhanced differentiation of regulatory T cells (T reg) derived from the thymus [52]. Additionally, the SCFA receptor GPR109A reportedly suppresses the expression of IL-6 in macrophages and dendritic cells in the colon, and increases the production of IL-10 and retinoic acid. It also contributes to the maintenance of Treg homeostasis and the suppression of colitis and colon cancer [53, 54]. Analysis of the GPR43 in immune cells of adipose tissue has shown that SCFA-mediated activation via GPR43 induces the expression of inflammatory cytokine TNF-α in M2 macrophages, which are responsible for adipose tissue repair, partially clarifying the remodeling mechanism of adipose tissue [55]. In addition, SCFAs induce intestinal inflammasome activation via GPR43 or GPR109A on intestinal epithelial cells, and acetate enhances the barrier function of colonic epithelial cells, leading to suppression of pathogenic infections [39, 56]. Recent studies have also revealed that supplementation with rich dietary fiber and diet-derived SCFAs increase bone mass and suppresses post-menopausal- and inflammation-induced loss of bone mass [57].

These findings suggest that SCFAs play an essential role in maintaining homeostasis by regulating immune responses via GPCRs, indicating that these receptors may be promising therapeutic targets.

3-2) Epigenetic Control by SCFAs

Recent studies indicate that SCFAs can induce epigenetic modifications. Butyrate treatment suppresses neurodegeneration and prevents neuronal cell death in Huntington's disease model mice via inhibition of the histone deacetylase (HDAC) activity [58]. Additionally, suppression of the HDAC activity by butyrate is involved in mucosal immune response including control of antimicrobial peptides and mucins, gut peptides, chemokines, and cytokines in the intestinal tract [59]. Germ-free mice, compared with Specific Pathogen- Free (SPF) mice, have reduced immune function in the gut mucosa, including decreased antimicrobial peptide and IgA production in the intestinal tract, and reduced the frequency of T cell. However, administration of butyrate to germ-free mice promotes the differentiation of naive T cells

to T reg through the epigenetic modifications [60]. These findings are confirmed that histone modifications such as acetylation and methylation have been observed in germ-free mice that were fed SCFAs [61]. It is also reported that various diets (a normal diet, low dietary fiber diet, and high-fat diet) fed mice are different in gut microbiota composition, SCFAs concentration in intestine, and histone modification (acetylation, methylation).

Thus, it has revealed that dietary environmental factors, including gut microbiota and SCFAs, associate not only regulating the endocrine and immune systems via various pathway, but also involved in regulation of epigenetic gene expression. Therefore, clarification of the detailed molecular mechanisms via SCFAs is expected to be a wide range of clinical prevention, such as cancer and neurodegenerative diseases.

4. Possible Clinical Applications

4-1) Evidence for Diet Therapy

Gut microbial metabolites, including SCFAs, are closely related to those consumed in the diet, and are thought to be directly involved in the regulation of biological functions through circulating in the plasma. Recent studies have clarified the effect of diet-derived gut microbiota metabolites on host energy metabolism and their mechanisms in molecular level.

Trimethylamine-N-oxide (TMAO) produced by gut microbiota from carnitine and phosphatidylcholine in shrimp, eggs, and red meat is known to cause lipid accumulation in arteriosclerotic plaques by promoting macrophage-derived foam-cell formation, thereby causing cardiovascular disease [62]. Using apolipoprotein E knockout mice (*apoE*-KO mice), an arteriosclerosis mouse model, fed a diet containing choline showed an increase in arteriosclerotic plaques compared with those of normal diet. Conversely, inhibition of the effect of gut microbiota by antibiotic treatment also inhibited the increase in arteriosclerotic plaques. Administration of *A. muciniphila* to *apoE*-KO mice led to the inhibition of TMAO formation and an improvement in arteriosclerosis [63, 64]. Human study also showed meat diets consumption increase the genera *Ruminococcus* and *Streptococcus* in the gut microbiota composition and detected higher TMAO concentration [65]. In contrast, those who consume a diet consisting mainly of vegetables and grains exhibit an increase in genera *Prevotella* and *Lachnospira*, and intake of dietary fiber leads to high concentrations of SCFAs [66]. These findings indicate that diet is a significant determinant of the composition of the gut microbiota and its metabolites.

A recent study discovered that gut microbiota metabolites, such as long-chain fatty acids, present in edible oils, affect host energy metabolism. During metabolism of the essential fatty acid linoleic acid, a ω-6 polyunsaturated fatty acid, to oleic acid, a monounsaturated fatty acid, the gut microbiota produces various intermediate metabolites in the intestinal tract [67]. For example, certain *Lactobacilli* metabolize linoleic acid to 10-hydroxy-cis-12-octadecenoic acid (HYA) is reported to have a protective effect against pathogenic *Escherichia coli* infection and enterocolitis via a strengthening the barrier function of intestinal epithelial cells [68]. Additionally, when ω-3 polyunsaturated fatty acid (α-linolenic acid) and its *Lactobacilli* metabolites (13-hydroxy-9(Z), 15(Z)-octadecadienoic acid, 13-oxo-9(Z), 15(Z)-octadecadienoic acid) were administered to wild-type mice, there was an improvement in insulin sensitivity and suppression of adipose tissue inflammation. Further, the number of anti-inflammatory M2 macrophages in the intestinal tract was increased, suggesting that the metabolites also exhibit anti-inflammatory action in the intestine and contribute to improving host homeostasis. Indeed, it has revealed that the involvement of these metabolites in the differential regulation of M2 macrophages occurs via GPR40 [69]. Although some aspects regarding the functionality of various intermediate metabolites produced from metabolism of unsaturated fatty acids by gut microbiota remain unexplained. Therefore, these metabolism by gut microbiota is expected to have an important effect on host homeostasis. The above observations suggest that changes in the intestinal environment resulting different daily diet intake, such as those in gut microbiota composition and differences in metabolite profiles, may be associated with the onset of metabolic diseases in hosts. This strongly suggests that the quality and variety of an individual's daily diet may be a useful tool for preventing or improving metabolic disorders such as obesity and T2DM.

4-2) Probiotics and Prebiotics

Probiotics are defined as living microorganisms that yield beneficial effects for the host by improving balance in the gut microbiota. In particular, the administration of probiotics of the genera *Lactobacillus* and *Bifidobacterium* reportedly improves energy metabolism in the host, induces changes in gut microbiota composition via an increase in *Bifidobacteria* species and decrease in *Enterobacteria* species. Studies have reported some mechanisms of probiotics, including inhibition of lipid absorption in the intestinal tract [70, 71], suppression of the accumulation of fat in adipocytes through lipoprotein lipase (LPL) inhibition via induction of *Fiaf*/*Angptl4* expression [72], lipolytic promotion by activation of sympathetic nerves [73], and maintenance of the balance in Treg/Th17 (T helper 17 cells) [74]. However, there is currently no clear consensus that the intake of probiotics improves metabolic diseases. Further multifaceted investigation is needed to confirm the role of probiotics in the treatment of obesity and T2DM.

Prebiotics, such as oligosaccharides and inulin, are defined as non-digestible food ingredients that provide beneficial effects to hosts by selectively promoting the growth and activity of gut microbiota in the distal intestinal tract and contribute to change in gut microbiota, in particularly promoting *Bifidobacteria* species. It was reported an increase in the abundance of phylum Actinobacteria, including those of the genus *Bifidobacterium*, in the intestine and SCFAs production in mice fed a diet supplemented with whole grain barley flour containing high levels of ß-glucan as well as purified barley ß-glucan, whereas germ-free mice fed a diet supplemented with whole grain barley flour abolished gut hormone secretion and improvement in insulin sensitivity. It is suggested that the metabolic improvement by barley flour was exerted through the SCFAs production by gut microbiota, which uses ß-glucan as a substrate (***Fig. 3***) [75].

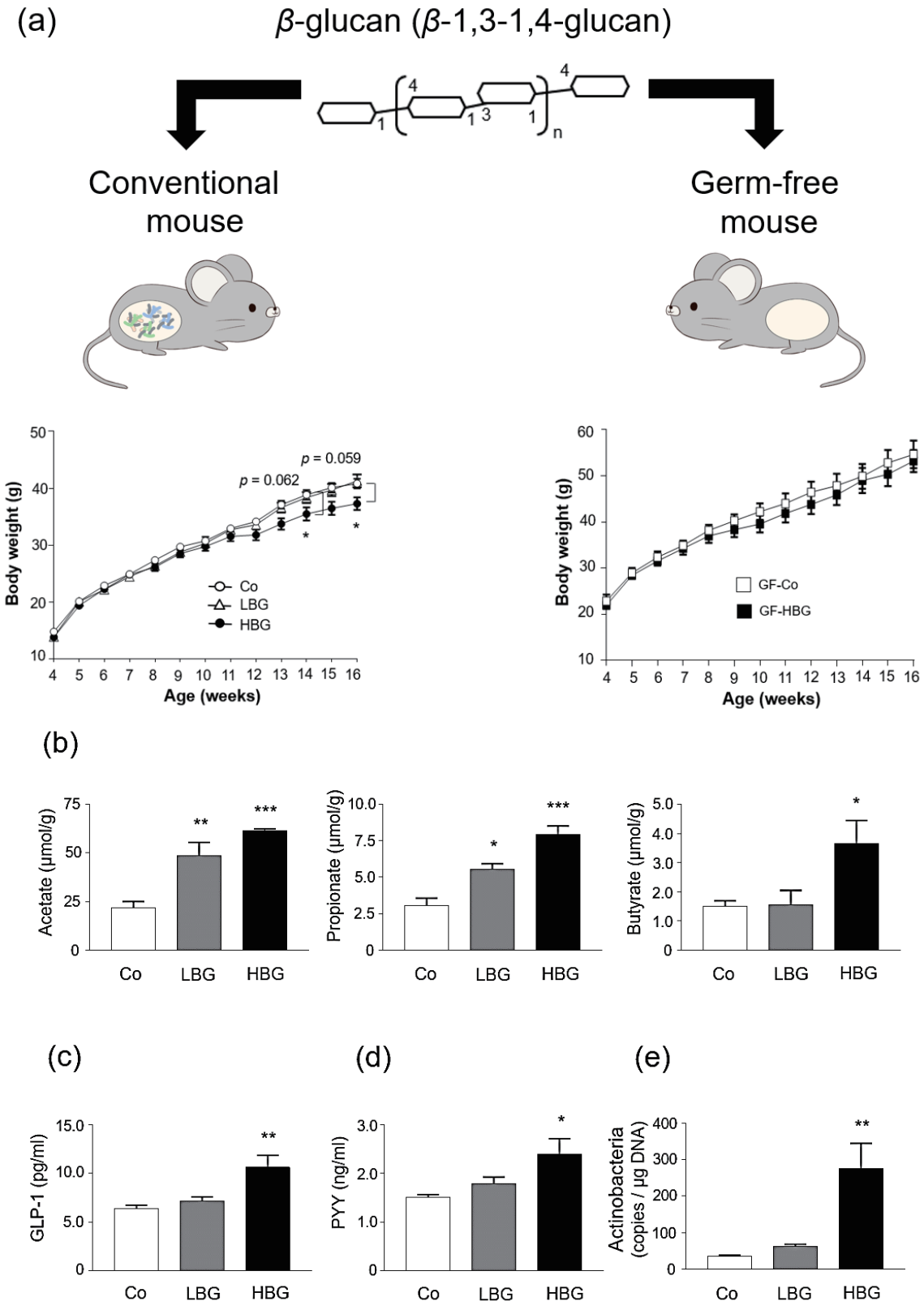

Fig. 3. **Barley β-glucan improves metabolic condition via production of gut microbial SCFAs.**

Barley β-glucan suppresses HFD-induced obesity via SCFAs. Body weight change **(a)**, fecal SCFAs **(b)**, plasma GLP-1 **(c)**, and plasma PYY levels **(d)** were measured in male mice that were fed Co, HBG, or LBG diets for 12 weeks. **(e)** Actinobacteria in feces were measured using quantitative real-time PCR from mice fed Co, HBG, and LBG diets for 2 weeks. Values are expressed as mean ± SEM, n = 4 ± 8, $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$, compared with Co (Tukey-Kramer test). SCFAs, short-chain fatty acids; HFD, high-fat diet; Co, control; LBG, general barley; HBG, β-glucan-rich barley; GLP-1, glucagon-like peptide-1; PYY, peptide YY; PCR, polymerase chain reaction; SEM, standard error of the mean.

4-3) Treatment to Promote Changes in Gut Microbiota

Although diet and exercise therapies are applied to improve blood glucose levels in early onset obesity and T2DM, drug therapy is selected for patients with severe insulin resistance. For example, the biguanide drug metformin, improvement of blood glucose levels by inhibiting gluconeogenesis in the liver and glucose absorption in the intestinal tract, is typically used to treat T2DM. In recent studies, administration of metformin to T2DM patients in Europe and China has led to improvements in insulin resistance [76]. In animal studies, administration of metformin led to an increase in *A. muciniphila* and goblet cells, which are essential for intestinal mucosal barrier function. Additionally, changes in gut microbiota composition have been suggested to partially contribute to the metformin-induced improvement in insulin resistance.

Gastric bypass surgery (Roux-en-Y gastric bypass: RYGB) is an effective treatment for severe obesity or T2DM patients. The surgery induces changes in the transit time of consumed food, a lowering of the gastric secretion of ghrelin, improvement of insulin resistance, and increasing GLP-1 and GIP secretion. As a result, RYGB lead to weight loss and a subsequent reduction in obesity. Also, RYGB surgery showed significantly lower ratio of the phylum Firmicutes to Bacteroidetes in gut microbiota composition in short-term changes. Interestingly, these changes are reportedly retained long after surgery [77]. By colonizing germ-free mice with stools from the RYGB surgery patients, the surgically altered microbiota promoted reduced fat deposition in recipient mice [78]. Even T2DM patients who have undergone RYGB surgery have demonstrated an increase phylum *Bacteroidetes* and *E. coli*, a decrease in *Lactobacillus* and *Bifidobacterium* species, and an overall increase in gut microbiota diversity [79]. These observations suggest a close relationship between pathology of metabolic diseases and gut microbiota composition.

Fecal microbiota transplantation (FMT) has recently received attention as a new alternative that can be directly applied to change the gut microbiota composition and has the potential to significantly change the recipient's intestinal environment. FMT was significantly more effective for the treatment of recurrent *Clostridium difficile* infection than conventional therapy [80]. The effect of FMT has also been confirmed in intestinal inflammatory bowel diseases (ulcerative colitis and Crohn's disease) [81]. FMT is currently being trialed in Europe and the United States, even in patients with metabolic diseases such as T2DM. In Japan, however, clinical application of FMT has delayed for reasons related to safety, restriction to fecal donors who are second degree relatives or a spouse, and FMT resistance in patients. FMT may be a promising new therapeutic potential. Future work should focus on precisely defining the optimum treatment and the role of donor-recipient matching based on microbial profiles.

Conclusion

Metabolic disorders such as obesity and T2DM are becoming one of the major health-care problems. The strategy for therapy of metabolic disorders has become an urgent need. Scientific evidence-based elucidation that the gut microbiota directly affect the pathology of metabolic diseases has led to recognition that the quality and variety of the diet can significantly change gut microbiota composition and metabolite production. SCFAs produced from the fermentation of dietary fiber by gut microbiota are an essential energy source in the host and act as signaling molecules via the G-protein coupled receptors GPR41 and GPR43. It has become clear that SCFAs can contribute to the maintenance of host energy homeostasis and affect the epigenetic control. Recently, Olfr78 and GPR109A, in addition to GPR41 and GPR43, were identified as SCFA receptors. Regulation of the host energy metabolism or immune system has been suggested to contribute to the prevention or improvement of obesity and T2DM. The development of prebiotics including polysaccharide and probiotics is expected as an effective increasing SCFAs production in the intestine. Identification and functional analysis of gut microbial metabolites, including SCFAs, and their target receptors develop new therapeutic agents in the prevention and treatment for various diseases.

Conflict of Interest Statement

The authors have no conflict of interest.

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