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Signaling Pathways Associated with Metabolites of Dietary Fibers Link to Host Health

Kavita Rani, Jitendra Kumar, Sonia Sangwan,
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Abstract

Food is a basic requirement for human life and well-being. On the other hand, diet is necessary for growth, health and defense, as well as regulating and assisting the symbiotic gut microbial communities that inhabit in the digestive tract, referred to as the gut microbiota. Diet influences the composition of the gut microbiota. The quality and quantity of diet affects their metabolism which creates a link between diet. The microorganisms in response to the type and amount of dietary intake. Dietary fibers, which includes non-digestible carbohydrates (NDCs) are neither neither-digested nor absorbed and are subjected to bacterial fermentation in the gastrointestinal tract resulting in the formation of different metabolites called SCFAs. The SCFAs have been reported to effect metabolic activities at the molecularlevel. Acetate affects the metabolic pathway through the G-protein-coupled receptor (GPCR) and free fatty acid receptor2 (FFAR2/GPR43) while butyrate and propionate transactivate the peroxisome proliferator-activated receptors (PPARγ/ NR1C3) and regulate the PPARγ target gene *Angptl4* in colonic cells of the gut. The NDCs via gut microbiota dependent pathway regulate glucose homeostasis, gut integrity and hormone by GPCR, NF-kB, and AMPK-dependent processes. In this chapter, we will focus on dietary fibers, which interact directly with gut microbes and lead to the production of metabolites and discuss how dietary fiber impacts gut microbiota ecology, host physiology, and health and molecule mechanism of dietary fiber on signaling pathway that linked to the host health.

Keywords: dietary fibe, gut microbiota ecology, host health, signaling pathway, molecule mechanism

1. Introduction

The human gut harbors a plethora of a complex community of micro-organisms that are vital for host development and physiology. This community of microbes inhabiting the gut called "gut microbiota" represents a mutualistic symbiotic relationship with the host [1]. The host creates a stable environment for the microbes while the microbes offer the host with an array of functions such as digestion of complex dietary macronutrients, minerals and vitamins production, pathogen protection, and immune system maintenance. Studies have shown that the gut microbiota comprises of about 3.8×10^{13} microorganisms [2] belonging to a wide

spectrum of about 160 recognized gut bacterial species [3]. Generally, the opus of the gut microbiota is observed to be comparable in all healthy individuals, however the presence of different microbial species is determined by an individual's dietary habits, dietary patterns and lifestyle [4]. Dietary fibers (DFs) are vital modulators of the gut microbiota composition which directly impacts individual biological processes and homeostasis via the metabolites, a consequent of microbial fermentation of nutrients such as, short-chain unsaturated fats (SCFAs) [5]. The gut microbiota plays a key and essential role in the metabolization of DFs including non-digestible carbohydrates (NDCs), proteins and peptides, which has escape digestion by host enzymes in the upper gut and absorption in the lower digestive tract. These dietary constituents, are then subjected to fermentation by the microbiota in the cecum and colon (Macfarlane and Macfarlane, 2012) resulting in the production different metabolites called SCFAs varying in carbon number which includes mainly acetate (60%), propionate (25%) butyrate (15%) and methane (CH_4), carbon dioxide (CO_2) gases [6] which are known to have beneficial effects by behaving as signaling molecules via different pathways. From among the different SCFAs produced Acetate is the most abundant and it is used by many gut commensals to produce propionate and butyrate in a growth-promoting cross-feeding process. Moreover, the SCFA, have been shown a to regulate metabolic activities. Acetate affects the metabolic pathway through the G protein-coupled receptor (GPCR) and free fatty acid receptor 2 (FFAR2/GPR43) while butyrate and propionate transactivate the peroxisome proliferator-activated receptorsγ (PPARγ/NR1C3) and regulates the PPARγ target gene *Angptl4* in colonic cells of the gut. The FFAR2 signaling pathway regulates the insulin-stimulated lipid accumulation in adipocytes and inflammation however peptide tyrosine-tyrosine and glucagon-like peptide 1 regulate appetite. The NDCs via microbiota dependent pathway regulate glucose homeostasis, gut integrity, and hormone by GPCR, NF-kB, and AMPK-dependent processes. Hence in this chapter, emphasis is given to address the effects of dietary fibers metabolites as prime signaling molecules, through different signaling pathways and their link between gut microbiota and the host health.

2. Dietary fibers (DFs), gut microbiota and SCFAs metabolites

2.1 Dietary fibers (DFs)

Dietary fibles defined by codex alimentarius commission (2009) are edible carbohydrate polymers with varying monomeric units that are impervious to the host digestive enzymes and thus has escape absorption in the small intestines. These includes, (1) edible naturally occurring carbohydrate polymers present in foods such as fruits, vegetables, legumes, and cereals (2) edible carbohydrate polymers obtained from food raw materials by physical, enzymatic, and chemical means and (3) synthetic carbohydrate polymers. In addition, DFs are further divided either into polysaccharides (non-starchpolysaccharides [NSPs], resistant starch [RS], and resistant oligosaccharides [ROs]) or into insoluble and soluble forms [7]. Soluble fibers are fermented by the gut bacteria giving rise to metabolites such as short-chain fatty acids (SCFAs), insoluble forms of fibers such as cellulose and hemi-cellulose may or slowly digested by the gut bacteria and contributes to a fecal bulking effect, as they reach the colon. Delay absorption of glucose and lipids influencing post-prandial metabolism on the other hand are caused by most soluble NSPs, especially polymers with high molecular weight such as guar gum, certain pectins, b-glucans, and psyllium, are viscous, meaning that they are able to form a gel structure in the intestinal tract that can [7]. Food sources such as legumes, vegetables, nuts, seeds,

fruits, and cereals forms the sources of soluble and insoluble fibers whereas RS can only be found in starchy foods such as legumes, tubers, cereals, and fruitlike green bananas, whereas pectin's are more abundant in fruits and some vegetables, whereas b-glucans are found in cereals [8]. Recently, due to low consumption of DFs in the Industrialized Western world Fortification of foods with extracted or synthesized non-digestible carbohydrates is carried out as a strategy to increase fiber intake. Besides, a wide range of commercial DFs are currently available [9] worldwide, called "prebiotics" on the fact that they exert health benefits by selectively inducing beneficial bacterial populations in the gut. However, contrastingly, studies have reported that irrespective of the types of fibers, virtually all fibers will induce specific shifts in microbiota composition as a result of competitive interactions, and which of these compositional shifts may be beneficial for health, has not yet been established [10]. Furthermore, the mechanisms that have been established to be beneficial to health, is not calculative on the selective utilization of the carbohydrates but on an integrative effect of bacterial fermentation, producing metabolic compounds (e.g., SCFAs) [11], physiological changes (pH lowering), or protection of the mucus layer [12, 13]. Hence, a change in the emphasis of the prebiotic concept away from the selective effect of specific dietary components on gut microbial communities towards the effects of ecological and functional consequences of fiber fermentation, is more significant for host physiology and health [10].

2.2 Gut microbiota

Microorganisms including several species of bacteria, yeast, and viruses make up the Gut microbiota. Out of the different Bacterial phyla, a few phyla represented, by about 160 species [14] composed the gut microbiota. Some of the dominant gut microbial phyla are *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia,* with phyla Firmicutes and phyla Bacteroidetes [15] making up to 90% of gut microbiota. *Clostridium, Enterococcus, Lactobacillus, Bacillus, and Ruminicoccus* are among the more than 200 genera in the Firmicutes phylum. *Clostridium* genera represent 95% of the Firmicutes phyla. Phylum Bacteroidetes consists of Bacteroides and Prevotella as predominant genera. The Actinobacteria a less abundant phylumis mainly represented by the Bifidobacterium genus [15]. Besides, the gut microbiome is to a very large extent affected by dietary administration of fiber, which alters the gut microbiota by providing substrates for microbial growth, and expansion of their populations [7]. The possession of different enzymes, about 130 glycoside hydrolase, 22 polysaccharidelyase, and 16 carbohydrate esterase enzyme families, allows the gut microbiome to switch between different energy sources of fibers depending on their availability [16]. Bacteria such as Firmicutes and Actinobacteria has been found to be prime species, which initiates the degradation of complex substrates [7]. Species such as *Bifidobacteriumadolescentis*, *Ruminoccocusbromii*, *Eubacteriumrectale*, and *Parabacteroides distasonis*play significant roles in degrading resistant Starch [1, 17]. The consumption of galactooligosaccharides mainly induces Bifidobacterium species possessing the enzymatic machinery to utilize the substrate [18]. Reports have also suggested that, degradation of complex substates, occurs in a cascade where, different species will contribute equally at different stages towards production of metabolites [7]. Primary fiber degraders are species that initiate the utilization of a complex fiber through what can be considered a "guild" of species [19] or a keystone species. Although *R. bromii* does not make butyrate, it is considered a keystone species for the breakdown of RS and contributes significantly to butyrate generation in the colon. Other dietary fiber types are expected to have similar keystone species, although they have yet to be discovered.

2.3 SCFAs metabolites

Dietary fibers, are metabolized by the microbiota in the cecum and colon [20] resulting in the formation of major products such as particular, acetate, propionate, and butyrate [21]. However, studies have reported that, microbes can utilize amino acids from dietary proteins and triglycerols from fats [22, 23] to facilitate diminished supply of dietary fermentable fibers resulting in reduced fermentative activity and formation of SCFAs as minor end products [24]. Although, protein fermentation was observed to the SCFA pool but, however dietary proteins mostly give rise to branched-chain fatty acids such asisobutyrate, 2-methylbutyrate, and isovalerate, [25] which are may have a concerning effect as a result of insulin resistance [26].

Acetate (C2) is a major SCFA metabolite produced from pyruvate. Many gut bacteria produce Acetate from pyruvate via acetyl-CoA or the Wood-Ljungdahl pathway, which produces acetate via two branches: (1) the C1-body branch (also known as the Eastern branch) via CO_2 reduction to formate and (2) the carbon monoxide branch (also known as the Western branch) via CO_2 reduction to CO, which is then combined with a methyl group. Propionate is created when succinate is converted to methylmalonyl-CoA through the succinate pathway. Furthermore, propionate, can also be synthesized from acrylate using lactate as a precursor via the acrylate pathway [27] and via the propanediol pathway using deoxyhexose sugars as substrates [28]. Butyrate, the third main SCFA, is produced by the condensation of two molecules of acetyl-CoA and subsequent reduction to butyryl-CoA, which can then be converted to butyrate by phosphotrans butyrylase and butyrate kinase via the classical pathway [29]. The butyryl-CoA: acetate CoA-transferase enzyme can also convert butyryl-CoA to butyrate [30]. Besides, reports have also shown that some microbes can use both lactate and acetate to synthesize butyrate. Butyrate can also be produced from proteins via the lysine pathway, according to a recent analysis of metagenome data [31], implying that microorganisms in the gut can adjust to dietary changes in order to sustain the synthesis of important metabolites like SCFAs. SCFA levels vary along the length of the gut, with the highest concentrations in the cecum and proximal colon and decreasing towards the distal colon [21].

3. Dietary fibers metabolites signaling mechanism and their health implications

3.1 Molecular mechanism of dietary fibers (DFs) and its metabolites

The metabolites of dietary fibers (DFs) are SCFAs that play a significant role in metabolic diseases prevention and treatment along with some contradictory research finding [32]. The SCFAs formate, lactate, acetate, propionate, and butyrate are produces by the saccharolytic fermentation of the dietary fibrous [33] which have a significant role in the maintenance of health by reducing the chances of development of different disease.

World Health Organization have recommended daily intake of dietary fiber 20 g per 1000 kcal consumed for adults human being and this (20 g per 1000 kcal) quantity of dietary fiber is full filled by the daily consumption 400 g per day of fresh vegetables, fruits and grains (https://www.who.int/news-room/fact-sheets/detail/healthy-diet). Modern life style, dietary pattern, seasonality, stress, habitat, consumption of antibiotics and disease cause a drastic change in dietary pattern of individual's finally leads to gut microbial alteration [34] that influence production of SCAFs. The various physiological functions in the gut (including adding the energy to colonocytes, maintaining their mobility, blood flow, and regularize the movements

of electrolytes and nutrients within the lumen) activate and modulate by SCAFs [35]. Colonic cell proliferation, differentiation and integrity mentioned by butyrate along with the major and preferred metabolic substrate for colonocytes 60–70% energy requirement [36]. Propionate maintains glucose homeostasis by gluconeogenic pathway [37]. The expression of leptin has enhanced by propionate and acetate. Leptin is a potent anorectic hormone, in adipocytes [38]. Acetate is a lipogenic SCFAs, reduced levels of acetate would result in decreased lipogenesis [37]. In the rat hepatocytes, acetate act as de novo lipogenesis and cholesterol synthesis, and these two pathways are to be inhibited by propionate [39]. The increased levels of propionate SCFAs would assist in the inhibition of acetate conversion into lipid in adipose tissue and the liver. The DFs via gut microbiota increase the rate of acetate synthesis while reducing the level of propionate in cells [40]. Acetate SCFAs is inversely related to plasma insulin levels [41] and acetate also activates leptin secretion in murine adipocytes [42].

High-fat diet-fed rats have increased acetate (C2) production due to gut microbiota that leads to ghrelin secretion and glucose-stimulated insulin secretion by activation of the parasympathetic nervous system (PNS), apart from these high calorically dense diet through gut microbiota-brain-β-cell axis promotes obesity and health complications by regimenting glucose and lipids homeostasis [43].

New study finding by many researchers groups have suggested that [44, 45] the loss of gut microbiota species from the colonic microbiota is associated to consumption of the high-fat, low-dietary fiber diets and other nutrient intake and diversity of gut microbiome [46, 47]. The fermentable dietary fibers directly govern the diversity of the gut microbiota [48], SCFAs regulate the different physiological activity of host. The majority of SCFAs transported across the mucosa by active transport, mediated by two receptors. The monocarboxylate transporter 1 (MCT-1) and the sodium-coupled monocarboxylate transporter 1 (SMCT-1) receptors. Direct inhibition of histone deacetylases HDACs to directly regulate gene expression and SCFA also effects signaling through G-protein-coupled receptors (GPCRs), this may influence host physiology by modulate biological responses of the host.

3.2 SCFAs sensing signaling pathway

All physiological activities occurring in the body are gut metabolites driven and SCFAs are connecting the link between the gut immunity with microbiota. The crucial role of SCFA has been signified in shaping and regulating both local and peripheral immune systems that respond to host metabolism via inflammatory pathways. Therefore, SCFAs modulate functions of the different systems including the enteric, nervous, endocrine, and blood vascular system serving as a key factor to regulate metabolic disorders and immunity. The dietary fibers metabolites exerted effects via their receptors, like the G protein-coupled receptor (FFAR3/GPR41 and FFAR2/GPR43 and GPR109a) through the inhibition of histone deacetylases and the activation of G-protein coupled receptors [32, 49].

3.3 SCFAs sensing signaling pathway in immunological responses

Gut bacteria produced SCFAs from indigestible saccharides diet precursors and SCFAs transported across the mucosa by active transport mediated by two receptors, monocarboxylate transporter 1 (MCT-1) and sodium-coupled monocarboxylate transporter 1 (SMCT-1) receptors which influence host physiological functions and modulate biological responses of the host. The main mechanism is direct inhibition of histone deacetylases (HDACs) to directly regulate gene expression. HDACs remove acetyl groups (deacetylation) from lysine residues of histones [50]. Transcription of genes is enhanced through inhibition of HDACs function by increasing histone

acetylation. Dietary fibers SCFAs inhibit HDACs activity and therefore suppress expression of gene in different cells. Butyrate (C4) SCFAs is the most potent inhibitor of HDACs activity and induces gene activation by facilitating the access of transcription factors to promoter region, such kind's activity of C4 known as an epigenetic modification of chromatins [51]. The SCFAs-mediated HDACs inhibition, acts as an anti-inflammatory immune response mediated by less production of inflammatory cytokines IL-8, IL-6, and TNFα [52]. Apart from these butyrate and propionate reduced NF-kB activity and inflammatory cytokines [53], showing that the anti-inflammatory effects of SCFAs are mediated through the modulation of NF-kB signaling pathway. Beside this the SCFAs also affect signaling through GPCRs. The SCFAs activate different GPCRs e.g. propionate (C3) is a most potent activator of GPR43. The expression of GPR43 has been reported in the entire gastrointestinal tract (GIT) along with cells of the immune and nervous systems. In GIT, GPR43 is highly expressed in endocrine L-cells of the ileum and colon of intestinal PYY and GLP-1 [54] producing cells as well as on colonocytes and enterocytes. The order of potency was reported as like propionate >butyrate>acetate for GPR41 receptor [55]. The SCFAs control the body weight through the release of leptin in adipose tissue by the expression of GPR41 [56]. The SCFAs play crucial role in metabolic functions of hepatic cells through the FFAR3 signaling pathway without influencing the intestinal environment [57]. Niacin receptor 1 (GPR109a) is activated by C4 at low concentration while highly expressed in adipocytes with a lesser extent is also expressed on immune cells. Activation of GPR109a in adipocytes suppresses lipolysis and the lowering of plasma-free fatty acid levels (FFAs) [58]. Through epigenetic mechanisms via histone acetylation acetate also increases fatty acid synthesis [59]. Therefore these finding could helpful to promote the development of functional foods using SCFAs or dietary significance of non-digestible carbohydrates fiber.

3.4 SCFAs sensing signaling pathway in hormone regulation

Gut microbes regulates the host metabolism by secretion of gut hormone. Gut microbiota induced signal to nearby intestinal enteroendocrine cells through microbial metabolites of DFs. These enteroendocrine cells release metabolically active hormones like GLP-1, PYY, GIP, 5-HT, and CCK which influence feeding behavior, glucose metabolism, insulin sensitivity and adiposity. Dietary components also impact on the composition of gut microbiota which may have further downstream consequences on gut hormone secretion and host metabolism. Enterochromaffin cells (EC) of the gut are the main source of serotonin (5-HT, 5-hydroxytryptamine). The EC is dispersed throughout the GI tract of the host and constitutes about half of all enteroendocrine cells. The gut microbiota influences 5-HT levels in the host. The antibiotic-treated mice study showed that significantly lower levels of EC cell-derived 5-HT when compared to antibiotic free animals. The EC cells can sense microbial metabolites by FFAR2 and FFAR3 signaling mechanisms [60]. PYY (Peptide tyrosine-tyrosine) regulates food intake and satiety through activation of central G protein-coupled Y2 receptors on neuropeptide Y (NPY) and AgRP neurons in arcuate nucleus of hypothalamic part of brain [61]. This is the relay of signaling cascade where by appetite-stimulating NPY neurons are suppressed that allowing for the activation of the satiety-inducing a-MSH / pro-opiomelanocortin (POMC) pathway [62]. The ability of gut microbiota to influence PYY secretion, therefore, gut microbiota has significant implications for the development of metabolic disease and obesity. Study reported that oral administration of C4 increased circulating PYY level [63] by FFAR2/3 signaling. Glucagon-like peptide 1 (GLP-1) augments insulin and inhibits glucagon secretion from the pancreas cells. GLP-1 inhibits gastric emptying and influences satiety and food intake [64, 65]. Orally

administrated sodium butyrate in mice has been shown to transiently increase GIP and GLP-1 secretion and GIP level were associated with adiposity reported the ileal infusion of acetate, propionate, and butyrate during feeding in pigs, increased plasma CCK levels and paradoxically inhibit pancreatic secretion [66]. SCFAs are influence insulin function via their receptors [67, 68]. Glucose homeostasis in type 2 diabetes mellitus patients managed by fiber reaches diet that alters the gut microbiota. The deficiency in SCFAs production in host has associated with type 2 diabetes by interfering HbA1c levels in circulation [69]. Diet plat a major role in gut microbiota composition and gut microbiota regulates metabolism via metabolites produces by plant-based diets and intake of probiotics increases secretion of carbohydrate-active enzymes [70] in luminal of GIT.

4. Conclusion

Dietary fibers and its gut microbial metabolite SCFAs have been known to exert metabolic benefits to the host [71]. Various health benefits have been reported whereby Dietary fibers via SCFA increase plasma SCFA levels to active FFAR3 which has been shown to improve hepatic metabolic conditions. Furthermore, Dietary fibers consumption reduced HFD-induced liver weight growth and hepatic TG accumulation, as well as a shift in hepatic lipid metabolism. Dietary SCFAs consumption improved hepatic metabolic conditions via the FFAR3 signaling pathway. Besides, Dietary fibers were reported to shift the gut microbiome towards the production of more butanoate which is accompanied by up-regulation of microbiota and AMP-activated protein kinase (AMPK)-dependent gene expression which contributes to intestinal integrity and homeostasis by affecting metabolism, transporter expression. In addition, microbial metabolite SCFAs derived from microbial fermentation of dietary fibers are likely to have more broad impacts on various aspects of host physiology including health. Hence, Diet plays a pivotal role and is key as they have a significant impact on the composition, variety, and richness of the gut microbiota which directly determines the formation of essential SCFAs metabolites. Different aspects of the diet have a time-dependent effect on gut bacterial ecosystems. Long-term dietary patterns, particularly high protein and animal fat intake, have been demonstrated to diminish the number of beneficial microorganisms, which has been linked to host health.

Conflict of interest

The authors declare no competing interest.

Author contributions

The authors' responsibilities were as follows- Kavita Rani, Jitendra Kumar, S. Sangwan, Nampher Masharing, M.D. Mitra and H.B. Singh conceived and designed the chapter. Draft was completed by Kavita Rani, Jitendra Kumar, Nampher Masharing.

Notes/thanks/other declarations

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