

The Impacts of SCFAs on Intestinal Homeostasis, and Glucose-Lipid metabolism

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Abstract. Fiber is anaerobically digested by gut bacteria when it reaches the colon, yielding short-chain fatty acids (SCFAs) by-creation. SCFAs also include acetate, propionate, and butyrate. The interaction of food, intestinal microbiota, and energy metabolism has been the focus of recent SCFA research. Specifically, SCFAs can physiologically stabilize the gut macroscopically and affect metabolism microscopically. This article will specifically explain SCFAs' regulation of SCFAs on glucose and its functions related to the lipid metabolism and mechanisms and effects on weight control. The report also highlights the sequencing effects among diets, SCFAs and intestinal homeostasis. Specifically, the higher the intake of high-fiber foods, the more SCFAs are created, and as SCFAs have regulatory effects on various body parts, so SCFAs will have influence on intestinal homeostasis. SCFAs can mainly help maintain the balance of glucose and lipid metabolism. The formation of SCFAs can be increased by increasing dietary fiber content in diets, which can maintain intestinal homeostasis and control body weight and some gastrointestinal function by binding to GPCRs like FFAR2/3.

Keywords: SCFA, Metabolism, Intestinal Homeostasis.

1. Introduction

According to existing data, intestinal microflora is key to metabolism. In recent decades, fatty acids have evolved into critical intracellular and extracellular signaling molecules, despite their reputation as a simple energy source [1]. Short-chain fatty acids (SCFAs) are also the principal metabolites yielded by the intestinal microbiota acting on indigestible polysaccharides by fermentation, and this is an anaerobic process. Being created in the colon after the dietary fiber is fermented, the three primary metabolites of SCFAs are acetate, butyrate, and propionate [2].

Currently, studies are focused on the production of SCFAs from fermented dietary carbohydrates that cannot be broken down. SCFAs are efficiently absorbed in the large intestine because they are the major anions in the hindgut contents [3]. SCFAs have been proven to impact phagocytosis and chemotaxis in the gut. They also have anti-inflammatory and anti-cancer characteristics and can provide a variety of reactive oxygen species (ROS). Gut homeostasis is also known to be maintained by these substances. SCFAs have a wide range of effects. Their output are decided by diet while they contribute a new foundation for studying their role in glycolipid metabolism, gut homeostasis signaling pathways and even some inflammation [4].

The precise direct control of SCFAs is in glycolipid metabolism and lipids involvement in intestinal homeostasis is unknown. SCFAs, on the other hand, regulate the production of other hormones, such as PYY and GLP-1; therefore, they can have an indirect impact on glucose and lipid metabolism and intestinal homeostasis. By activating AMPK, SCFAs have been found to limit glycogen while facilitating glucose transport and fatty acid oxidation. SCFA controls blood sugar levels via controlling glucagon and insulin production. The research investigates the relationship between SCFAs and diets, as well as their present influence on glycolipid metabolism and intestinal homeostasis. Despite progress in understanding the interaction between intestinal microbiota and human metabolism, the linkage between the two remains unknown. This article aims to comprehensively summarized and analyzed the latest findings related to the link between intestinal microflora and host physiology.

2. SCFAs Definition

A lipid is a collection of substances that contains various chemicals. Most of these substances are fatty acids, valuable tools for studying cellular, molecular, or even macroscopic processes. Aside from being used in multiple domains, such as biology, metabolism research is also fundamental in human nutrition and ecology [5]. Various cell types and tissues release free fatty acids after the lipolysis process (FFAs). These organisms are becoming more involved in biological processes. It has been demonstrated that an uneven SCFA production and composition can result in this group's profile being compromised [1].

Fatty acids are carboxylic acids distinguished by their heavy chain length, double bond presence or absence, and dual bond position. SCFAs are carbon atoms with five or less, MCFAs are carbon atoms with six to twelve, and LCFAs with thirteen to twenty [4]. Because fatty acids are assumed to belong to chains of carbon atoms with carboxyl groups, SCFAs have fewer than six carbon atoms, which are uncommon in fatty acids. SCFAs, like MCFAs and LCFAs, are plasmatic free fatty acids (FFAs), which are an essential source of lipids. During fasting, albumin generated from adipose tissue is transferred to the tissues to give energy. These components were designated to involve in various cellular functions, containing energy metabolism regulation and ion channel function. They are widely consumed, particularly in dairy products [6].

Except for a small percentage absorbed straightly from dishes, most SCFAs are generated by gut microorganisms through anaerobic fermentation. SCFAs are also the principal metabolites developed by the gut flora from indigestible polysaccharides. SCFAs' primary metabolites are acetate, propionate, and butyrate. Resistant starch could help the colon produce SCFAs after fermentation [2].

Because humans lack the enzymes that break down most dietary fiber, these inedible carbs intactly travel through the upper GI tract and are digested by the anaerobic microbiota in the cecum and large intestine, generating SCFAs [7]. As a result, the creation of SCFAs in the gut is influenced by dietary fiber intake, bacterial makeup, and gut passage time. Colonocytes absorb SCFAs and transfer them to the portal circulation by H^+ or sodium-dependent monocarboxylate transporters (MCT and SMCT in Figure 1), in which they are handled by hepatocytes and the remainder reaches the systemic circulation [2]. The cecum and proximal colon had the greatest amounts of SCFA, whereas the distal colon had the lowest. SCFAs are also engaged in illness and health status regulation. SCFAs can control metabolism and address cancer, gut immunity, asthma, and the nervous system in human health, according to the research [8]. SCFA enters the body and plays various roles in various parts. Because supports for a role in the regulation for SCFAs in regional, intermediate, and peripheral metabolism is growing. SCFAs are a substantial carbon flux from the diet to the recipient via the gut bacteria [9].

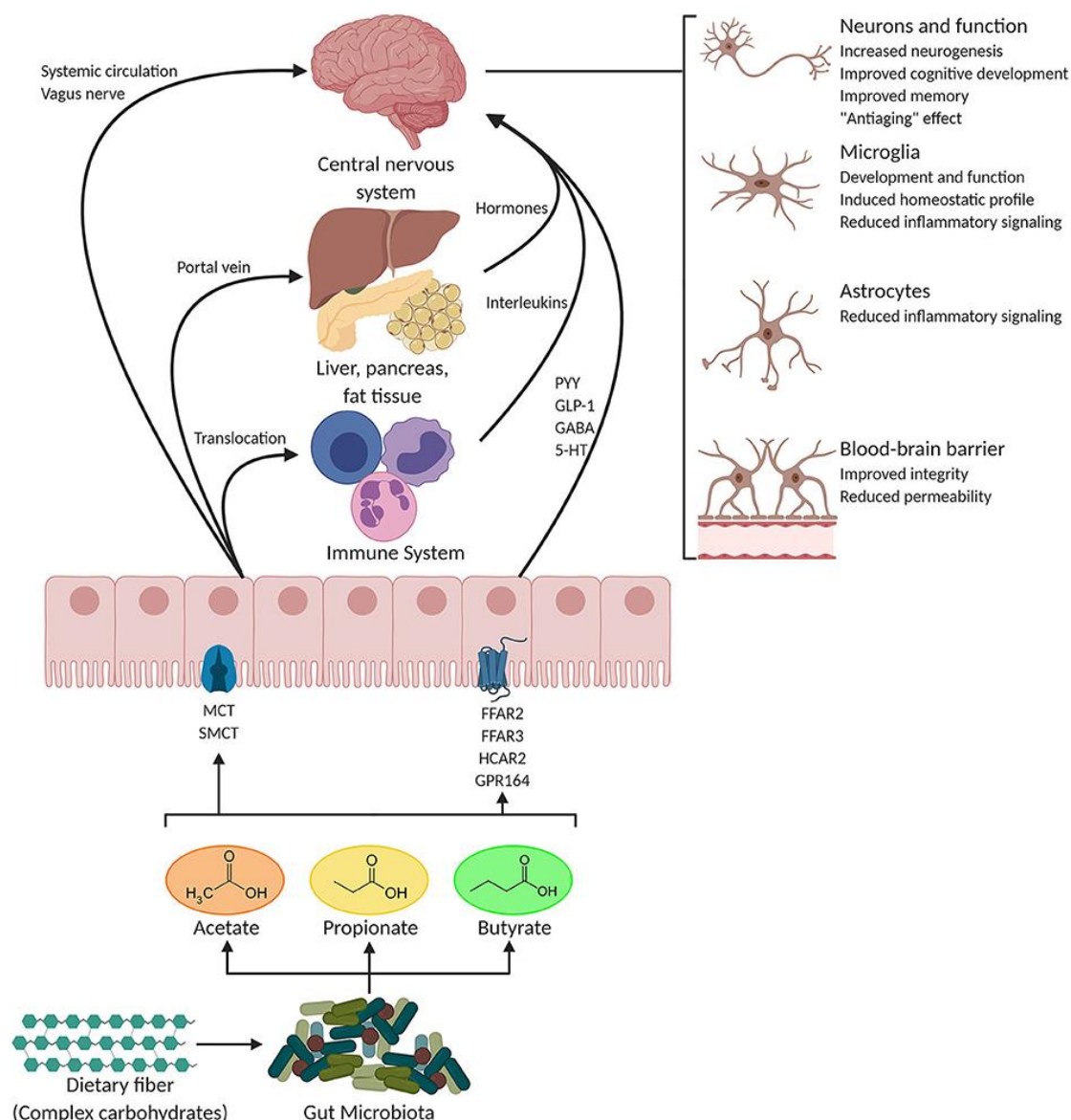


Figure 1. SCFAs are absorbed by colon cells and then transported to other body areas via MCTs or SMCTs. Some of them are connected to FFAR2/3, HCAR2 and GPR164 [2].

3. SCFAs Regulation

3.1. SCFAs on Glucose

The human body's ability to function appropriately relies on tight control over its blood sugar levels. It is achieved through a complex combination of neuropeptides, hormones, and fat tissue released by the pancreas, brain, liver, and muscle tissue. The body's response to low blood sugar levels is controlled by the release of glucagon, which increases the body's natural sugar levels. The insulin is delivered after eating to trigger the uptake of glucose from the bloodstream into the muscles and fat tissue. The interactions between the various tissues and organs of the body can help maintain glucose homeostasis. The pancreas plays a vital role in regulating metabolism and digestion. It also releases various hormones and enzymes to maintain energy homeostasis. Islet cells release hormones such as insulin, amyloid, pancreatic polypeptide, somatostatin, and ghrelin, and they account for around 65 percent to 80 percent of the total islet cells [10].

SCFAs affect several systems and organs of the body, as shown in Figure 1. Through FFAR2 (GPR43) and FFAR3, SCFA can trigger the release of the intestinal hormones PYY and GLP-1. GLP-1 boosts insulin while decreasing pancreatic glucagon creation, whereas PYY stimulates glucose

absorption in muscle, produces a recognition of fullness, and reduces food input. SCFAs have also been proven to inhibit gluconeogenesis in the liver via boosting AMPK action.

As demonstrated in Figure 2, Through the GPR43 and GPR41 receptors, SCFAs can affect glucose levels. By raising insulin production and lowering pancreatic glucagon release, GLP-1 indirectly modulates blood glucose levels. Intracolonic SCFA infusion and fiber consumption grew plasma GLP-1 levels and glucose absorption in adipose tissue.

By stabilizing plasma glucose levels and boosting glucose elimination, SCFAs appear to have a favorable impact on glucose metabolism. It's unclear whether these effects are mediated directly by the AMPK regulatory system in the liver or dependently through the PYY and GLP-1 [11].

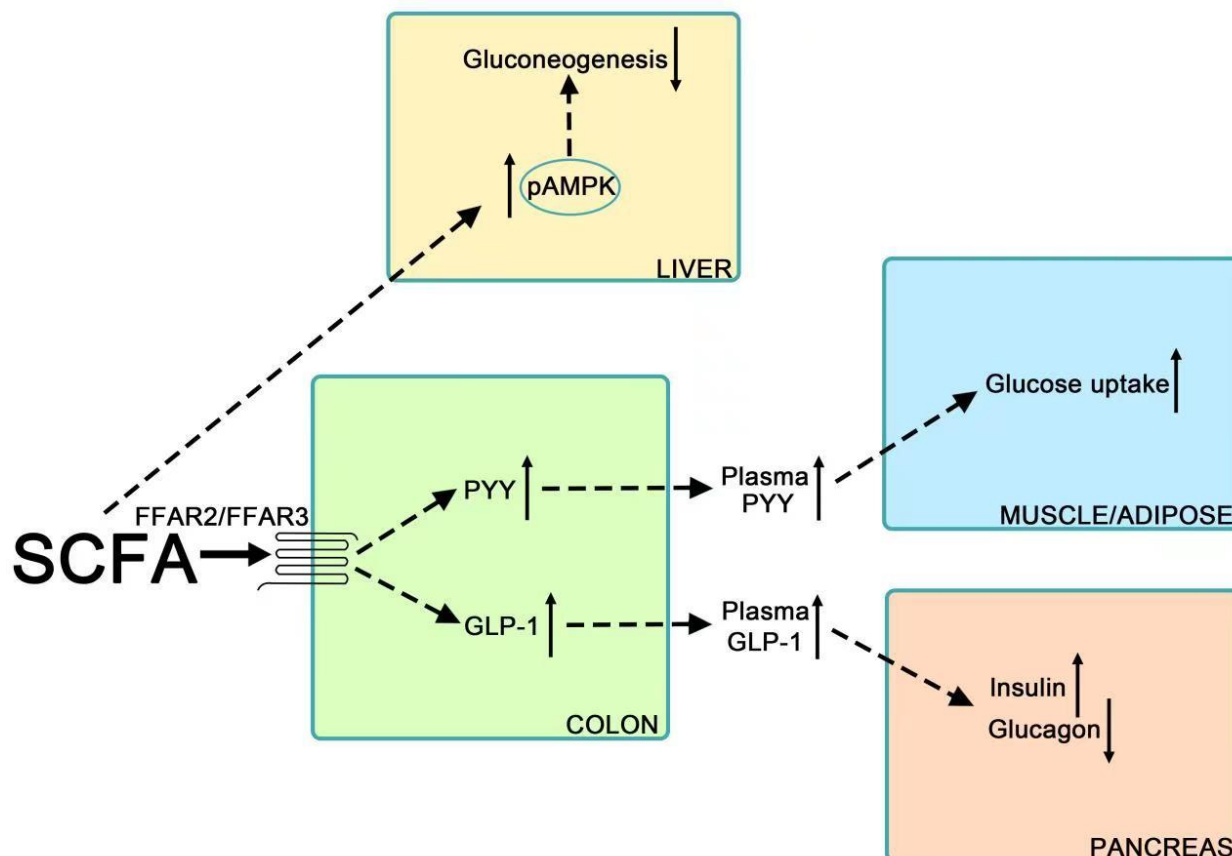


Figure 2. The activation of FFAR3 by SCFA has been found to enhance PYY and GLP-1 release, which raises the glucose intake in muscle and insulin in the pancreas. SCFAs also increase the AMPK resulting in gluconeogenesis decreasing.

3.2. SCFAs on Lipids

Because they provide a substrate for lipid synthesis, SCFAs can influence lipid metabolism. Acetate and butyrate are dietary fibers that the anaerobic cecal and colonic bacteria ferment, according to the preceding description of SCFAs. These two chemicals are also the primary de novo lipogenesis substrates of colonic epithelial cells from rats. Colonocytes use citrate to move acetyl units out of mitochondria to the cytoplasm and SCFAs and ketone bodies into lipids, to a lesser extent. The experiments suggest that the SCFA carbons utilized by colonocytes to manufacture lipids are unlikely to be carried into the cytoplasm as citrate [12].

Both lipid and glucose metabolism are affected by AMPK signaling (Figure 3). AMPK activation has been shown to increase PGC-1 expression in skeletal muscle and adipose in previous studies. PGC-1, a 91-kDa transcription factor that stimulates the activity of many genes, controls lipids, etabolism and long-chain fatty acid oxidation pathways [13].

In lipid metabolism, uncoupling proteins (UCPs) are essential. Three primary isoforms in adipose tissue—UCP1, UCP2, and UCP3—reduce lipid deposition by limiting ATP synthesis, increasing

thermogenesis, and allowing fatty acid oxidation. In brown adipose tissue, SCFA can boost PGC-1 and UCP-1 protein expression [11].

SCFAs influence lipid metabolism in general by lowering lipid accumulation and boosting fatty acid oxidation.

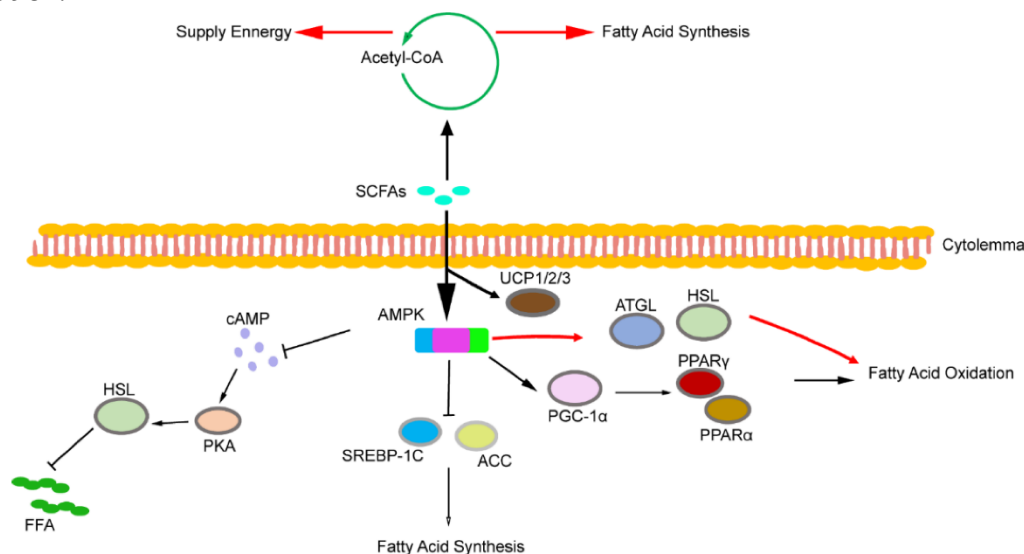


Figure 3. The pathways of how SCFAs affect lipid metabolism [11].

3.3. SCFAs on Weight

SCFAs are also involved in weight regulation because of the influence on appetite control [14].

Microbial acetate formation from H_2+CO_2 is usually the predominant H_2 depletion response in the hypoxic gut environments [15]. The data suggest that acetate has beneficial effects on energy and substrate metabolism via increasing the release of GLP-1 and PYY. By influencing systemic lipolysis, pro-inflammatory cytokine levels, energy expenditure, and fat oxidation, acetate influences hunger [14].

Specific GP receptors (GPRs), which regulate lipid and glucose metabolism, detect SCFA concentrations. SCFA receptors GPR41 and GPR43 are two different kinds. SCFAs increase oxidation of fatty acids while decreasing synthesis and lipolysis once more, by which help the body maintain a healthy equilibrium. As a consequence, the plasma concentration of free fatty acids decreases, as does body weight [7].

Studies suggest that, like acetate, propionate may potentially have a function in appetite control. Furthermore, weight gain among obese persons is prohibited by raising colonic propionate levels. Previous research suggested that administering propionate will enhance GLP-1 and PYY secretion while restricting calorie and weight overrun in obese people. A novel inulin-propionate has been created, which distributes propionate to the colon selectively. The effect of propionate inulin on calorie consumption and GLP-1 and PYY levels was studied in randomized controlled research. A randomized controlled experiments involving 60 obese persons explored the impact of propionate inulin on weight growth. The experimental results found that compared with the observation group, supplementing with 10g/day inulin propionate markedly lowered weight gain and body fat gain within 24 weeks. The generation of PYY and GLP-1 was shown to be substantially stimulated by propionate, and their level were increased after an acute ingestion of propionate inulin, the energy intake were also decreased in the same time [16]. In overweight to obese males, prebiotic inulin improved fat oxidation and stimulates SCFA synthesis. Generally, substituting fermentable inulin for digestible carbohydrates may benefit substrate metabolism in humans [17].

Butyrate protects against obesity caused by a diet through a mechanism that is not dependent on FFAR3 [18]. Therefore, it is not difficult to find that SCFAs are essential for appetite regulation and weight suppression. In mammals, SCFA propionate enhances glucagon and FABP4 synthesis, limiting insulin action. Previous experiments demonstrated that propionate increases glucagon and

rich acid-binding FABP4 plasma concentrations by stimulating glycogenolysis and hyperglycemia in mice. Propionate may cause insulin resistance and hyperinsulinemia via activating catecholamine-mediated increases in insulin counterregulatory signaling, which can lead to obesity and metabolic problems over time. [19].

4. Relationship Between Intestinal Homeostasis and SCFAs

The intestinal microflora is made up of various microorganisms such as bacteria, yeast, and viruses [20]. Firmicutes members are known to produce SCFAs, as seen in Figure 4. Firmicutes are anaerobic bacteria with different cell sizes depending on the species. They can only thrive in environments with no oxygen. As a result, they're commonly discovered in people in places like the cecum and large intestine. The proximal colon hosts most bacterial activity due to the abundance of a substrate [7].

Symbiotic gut bacteria work together with the host to assist the body in digesting nutrients from food while also creating a class of metabolites. The health of the host is affected by many guts' microbial metabolites. SCFAs are significant participants in altered immunological processes, metabolic balance management, and neuroprotection versus neuroprotection, according to data on a large class of bacterial metabolites implicated in SCFAs [21]. Intestinal homeostasis is characterized as a delicate equilibrium of metabolites, bacteria, the epithelial barrier, and the immune system all working together to keep infections at bay, resulting in a healthy intestinal environment [22].

According to earlier research, proteins can be used as substrates for gut bacteria to generate SCFAs during amino acid metabolism, resulting in fatty acids such as isovaleric and is butyric acid. Dietary carbohydrates are the essential substrates for many bacterial species and aid in the synthesis of SCFAs in the colon. These compounds enable balanced microbial dynamics by limiting the development of various bacteria at low pH, which is essential for host gut homeostasis. As a result, SCFAs impact the host gut and the immune systems of several organs. SCFAs, in particular, are hypothesized to operate as intermediates in the immune system's interaction with the gut microbiota. FFARs, which are members of the GPCR family, carry their signals to immune cells. SCFAs have a complicated influence on improving epithelial barrier function and immunological tolerance. It promotes intestinal homeostasis through multiple mechanisms, including increased mucus production by intestinal goblet cells, inhibition of NF- κ B, activation of inflammasomes, and interleukin 18 shows; increases the release of secretory IgA from B cells [23].

Acetate can be thought of as a nutrient. It can be used to support the metabolism of acetyl coenzyme A. This is a vital component of protein acetylation [24]. When acetate in SCFA supports the metabolism of acetyl-CoA (Ac-CoA), and increased concentrations of Ac-CoA promote protein acetylation, which interferes with metabolic processes and energy homeostasis. Therefore, SCFAs affect Intestinal Homeostasis [20].

The researchers looked at stool samples from allo-HCT patients to see if there was a link between allo-HCT and cGVHD. In comparison to the control group, plasma samples from individuals with cGVHD included microbe-derived propionate and butyrate. SCFA regulates the immunological homeostasis of gastrointestinal patients, as previously stated. The salt concentration in the blood is low. The findings show that, at least in part due to regulated SCFA synthesis, the intestinal microbiota may have an immunomodulatory effect in allo-HCT patients [25].

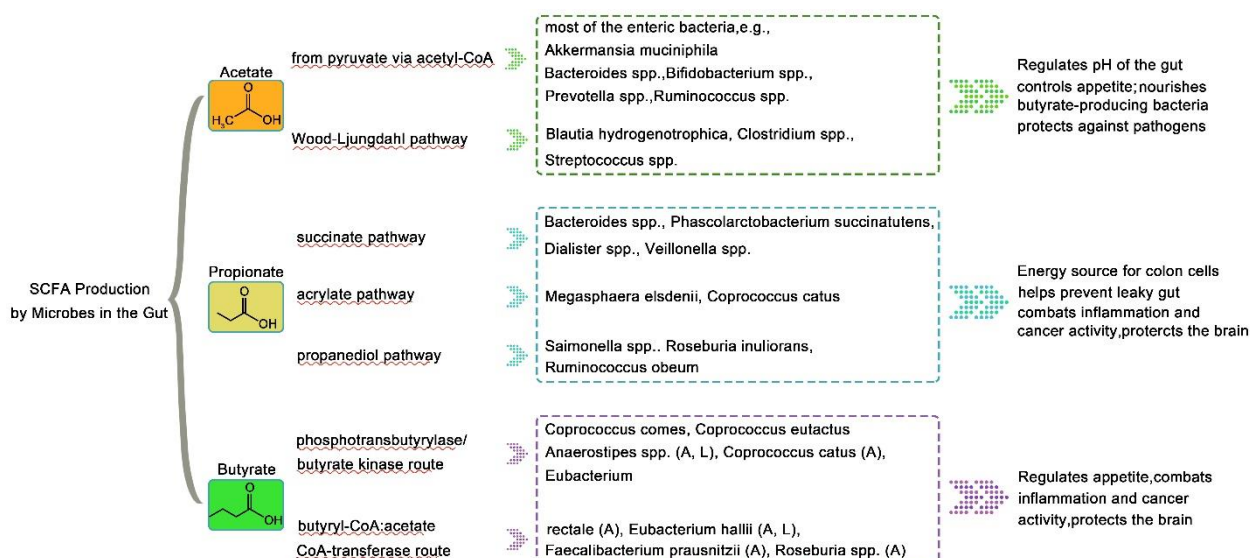


Figure 4. The acetyl-CoA or Wood-Ljungdahl routes are used by gut bacteria to produce acetate from pyruvate, and succinate pathway transforms propionate from succinate to methyl malonyl-CoA. Propionate can be produced from acrylates using lactic acid as a precursor and deoxyhexose as a substrate in the acrylate and propylene glycol pathways. The condensation and subsequent reduction of two acetyl-CoA molecules to butyryl-CoA produces the third main SCFA, butyrate [8].

5. Diets and SCFAs

SCFAs are formed due to complex interactions between gut bacteria and food. The scientists determined intestinal microflora in persons who consumed a low-fat, high-fiber diet. In another study, rural Africans consumed a Western-style diet high in fat and low in fiber. The composition, SCFAs, and bile acids changed significantly in fecal water. Butyrate-producing bacteria and butyrate production were both increased in the guts of the low-fat, high-fiber group. Another group had a higher number of intestinal lymphocytes, indicating more severe inflammation. Weight gain, consumption of food, glucose tolerance, and insulin sensitivity are all found to benefit from dietary fiber. Fiber traveling through the upper gastrointestinal tract is primarily composed of polysaccharides and resistant starch. They are indigestible and then will be degraded by anaerobic bacteria in the intestine [10]. The intestinal microbiota was enriched in Bacteroidetes, Verrucobacterium, and Proteobacteria after RYGB gastric bypass surgery, with comparatively high propionate and acetate production, suggesting that the intestinal microflora made a contribution in the decrease of weight gain and obesity [9]. Nutrition, intestinal microflora, and metabolism are all connected in the research.

Gut microorganisms can produce two separate SCFA metabolic pathways using amino acids obtained from the breakdown of ingested carbohydrates and proteins. The ecophysiology of propionate and butyrate bacteria, including growth requirements and sensitivity to environmental conditions, is influenced by dietary manipulation of intermediate metabolites among different gut bacteria [14].

SCFAs affect lipid metabolism and adipose tissue in a variety of ways. Adipose tissue produces leptin, a homeostatic signal-regulating energy balance, and appetite. SCFAs appear to influence short-term appetite regulation via a process mediated by PYY and GLP-1, according to a study that used targeted modification of human colonic propionate. In only a few human intervention studies, fermentable fiber has been associated with improved appetite regulation [9]. According to epidemiological research (IBD), a fiber-rich diet reduces the incidence of colon cancer. According to epidemiological research (IBD), it provides a considerable therapeutic effect in people with inflammatory bowel disease, according to epidemiological research (IBD). The metabolite-sensing

receptors FFAR3 and FFAR2, found in the intestinal epithelium and immune cells, allow SCFAs to communicate [26]

6. Conclusion

The intestinal microflora can consume SCFAs, the principal end product of indigestible carbohydrate fermentation. SCFAs, which are present in various cell types, including enteroendocrine and immunological cells, are natural ligands for FFAR 2/3. SCFAs have been found to have several positive effects on several elements of energy metabolism, as well as helping to maintain intestinal homeostasis.

The paper also clarified any possible relationships between SCFAs and food, as SCFAs are the predominant carbon flow from the diet to the host via the microbiota.

Food consumption, intestinal microflora composition and function, and their effects on human health are being explored recently. Because once high-fiber diets have been shown to promote health over time, they may be used as long-term epidemiological evidence. Scientists can modify people's energy metabolism and intestinal health through relatively easy and cost-effective therapies. However, inadequate information is currently to guide suitable, evidence-based clinical or public health treatments using SCFA formulations with well-defined outcomes. Although SCFAs have substantial metabolic effects, their regulatory mechanisms are partly unknown due to present research methods and methods' limitations. There are some limitations to the current investigation. Although experimental animals such as mice are employed as model animals to see if they apply to humans, it is unclear whether the data collected from these animals is genuinely transferable to humans. Since in vivo assessment of SCFA production is challenging, most human research has used pre-existing mature cell lines or in vitro with gut or fecal microbiota. Furthermore, the diversity of microbiota throughout the separation process varies substantially due to changes in fermentation in vitro and in vivo, and products accumulate are also different during fermentation. Finally, most current research has been on butyrate, which may not accurately represent SCFA.

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