SHORT-CHAIN FATTY ACIDS: MEDIATORS BETWEEN MICROBIOTA AND HOST

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Abbreviations

AgRP agouti-related protein
AMPs antimicrobial peptides
AMPK adenosine monophosphate-activated protein kinase
CAT catalase
CLDN claudin
FFAR free fatty acid receptor
GIP gastric inhibitory polypeptide
GLP-1 glucagon-like peptide-1
GLUT4 glucose transporter type 4
G6Pase glucose 6-phosphatase
GPCRs G-protein-coupled receptors
GPx glutathione peroxidase
GR glutathione reductase
HbA1c glycosylated hemoglobin
HCA2 hydroxycarboxylic acid receptor 2
HDACs histone deacetylases
H2O2 hydrogen peroxide
Ig immunoglobulin
IL interleukin
MCD microbial activity of carbohydrate degradation
MCT-1 monocarboxylate transporter 1
MUC2 mucin 2
NDCs non-digestible carbohydrates
NIACR1 niacin receptor 1
NPY neuropeptide Y
NRF2 nuclear factor erythroid 2-related factor 2
PEPCK phosphoenolpyruvate carboxy-kinase
PYY peptide tyrosine-tyrosine
ROS reactive oxygen species
RNS reactive nitrogen species
SCFA short-chain fatty acids
SOD2 superoxide dismutase-2
SMCT-1 sodium-coupled monocarboxylate transporter 1
Th2 T helper type 2
TNF-α Tumor necrosis factor alpha
Treg regulatory T cells
Y2R Y receptor type 2
ZO-1 zonula occludens-1

Review

SHORT-CHAIN FATTY ACIDS: MEDIATORS BETWEEN MICROBIOTA AND HOST

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Abstract: A compelling set of links has emerged between the host's diet and the gut microbiota. In this regard, origin, type and quality of food shape the gut microbes and affect their composition. Could these links reflect the relationships that are established with the host's health or illness? A growing body of scientific work shows that metabolites produced from fermentation of dietary fiber by the microbiota influence host physiology. This review has been collected data from a key metabolites generated by the microbiota, the short chain fatty acids (SCFAs), showing that they are capable of modifying the physiology of the host at different levels: appetite regulation, glucose homeostasis, lipid metabolism, gut integrity and anti-oxidative, anti-inflammatory and immuno-modulatory effects. Therefore, the SCFAs could be a potential tool to be more studied and implanted in a future personalized nutrition.

Keywords: gut microbiome; gut microbiota; dietary fiber; short-chain fatty acids; SCFA

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Resum: Ha sorgit un atractiu conjunt de vincles entre la dieta de l'hoste i la microbiota intestinal. En aquest sentit, l'origen, el tipus i la qualitat dels aliments determinen la composició i la funció dels microbis intestinals i afecten la seva composició. Podrien reflectir aquests enllaços les relacions que s'estableixen entre la salut o la malaltia de l'hoste? Un nombre creixent de treballs científics demostren que els metabòlits produïts a partir de la fermentació de la fibra dietètica per part de la microbiota influeixen en la fisiologia de l'hoste. En aquesta revisió s'han recollit dades d'uns metabòlits clau generats per la microbiota, els àcids grassos de cadena curta (AGCC), en què es demostra que aquests són capaços de modificar la fisiologia de l'individu a diferents nivells: regulació de la gana, homeòstasi de la glucosa, metabolisme lipídic, integritat intestinal i efectes antioxidatius, antiinflamatoris i immuno-moduladors. Per tant, els AGCC podrien ser una eina potencial per estudiar i implantar en una nutrició personalitzada futura.

Paraules clau: microbioma intestí; microbiota intestí; fibra dietètica; àcids grassos cadena curta; AGCC

1. Introduction

1.1 The Human Gut Microbiota

The human gut microbiota is the result of a collection of microbes that live in the body. However, the largest and most diverse group of microorganisms inhabit the intestine, as it approaches the large intestine or colon [1]. Approximately 100 trillion microorganisms (bacteria, viruses, fungi and protozoa) exist in the human gastrointestinal tract and, for this reason, the microbiome is now considered as one more organ of the body [2]. The relationship established between the intestinal microbiota and the host is intimate and provides benefits for both, since the host provides a stable environment for microbes while they provide the host with a wide range of functions [1]. However, an aberrant composition of the gut microbiota, called dysbiosis, is associated with several diseases [1,3].

The important role that the intestinal microbiota seems to play in metabolism and, consequently, in human health, has contributed to research on the identification of specific microorganisms involved in different processes and the metabolic pathways in which they participate [3]. For this reason, in recent years, the gut microbiome has been the focus of different research developments that seem promising [4].

1.2 Factors Shaping the Gut Microbiota

Nowadays, it is known that the intestinal microbiota is affected not only by a single factor, but that there are different specific components to each individual, those that are internal (genetic, mode of birth and age) [5], and those that are external (breastfeeding, use of antibiotics, stress, sleep, physical activity and diet), which modulate the composition of the gut microbiota.

1.2.1 Endogenous Factors: Genetic, Mode of Birth and Age

The genetic predisposition to develop a disease plays an important role. However, exposure to a certain environmental factor can exert pressure by increasing or decreasing the risk of suffering from it and with what severity.

In addition, depending on whether the individual is born by cesarean section or vaginal delivery, the composition of the microbiota will vary. In the second case, when the newborn passes through the birth canal it is impregnated with bacteria from the mother's vaginal microbiota [6]. Thusly, the baby's intestinal microbiota is more diverse and healthier compared to babies born by cesarean section and, consequently, this greater diversity in the microbiota is associated with a lower risk of developing certain diseases or conditions [5,7].

In the same way, another important factor that affects the composition of the microbiota is the age. In advanced ages, obvious morphological changes of the intestine appear, such as shortening and atrophy of the intestinal villi and a reduction in the surface of the intestinal mucosa. Hence, the habitable place for the microbiota

decreases and its diversity is reduced, also causing a reduction in the absorptive capacity of nutrients.

1.2.2 Exogenous Factors: Breastfeeding, Use of antibiotics, Stress, Sleep, Physical Exercise and Diet

Human breast milk provides the baby with optimal and complete nutrition, since its composition changes depending on the needs that the baby has to satisfy as it grows [8]. In addition, the variety of nutrients and bioactive molecules which it contains are of special importance for the correct growth and neurological development of the newborn and, therefore, breastfeeding plays a key role in modulating the intestinal microbial composition [5,9].

Several studies have been carried out to investigate the possible adverse effects of the use of antibiotics on the health of the mother and baby during pregnancy or near the time of birth [5]. These findings have shown that the administration of antibiotics has the potential to selectively alter the composition of the microbiota based on the type of antibiotic, the dose and the time it is taken. Consequently, this alteration presents some potential to lead to atopy, asthma, allergy and obesity in childhood [5,10,11].

The effect of stress on the gut-brain axis has been associated with changes in the gut microbiota, alterations in brain-derived neurotropic factor, behavioral changes, and can even lead to anxiety and depression [12]. This evidence highlights that the composition of the microbiota could represent a new strategy for the prevention of mental illnesses [5].

Another factor that modulates the gut microbiota is sleep. Both sleep fragmentation and short sleep duration are associated with the overgrowth of specific intestinal bacteria and lead to intestinal dysbiosis [13]. More specifically, intestinal microbial metabolites influence the expression of central and hepatic clock genes, as well as the duration of sleep in the host, and consequently regulate body composition through circadian transcription factors [14,15].

Exercise is one more factor which shape the gut microbiota. Despite that, the relationship between exercise and the microbiota is complex, because it is dependent on numerous variables like the intensity of exercise. In more detail, it has been observed that in high intensity cases of exercise there is an increase in the permeability of dysbiotic bacteria and toxins in the intestinal mucosa leading to an inflammatory response. On the other hand, in cases of regular exercise this type of inflammatory response has not been observed [16].

A balanced diet meets all the nutritional requirements of carbohydrates, proteins, lipids, vitamins, minerals and water for proper body function, growth, and health. In further detail, carbohydrates are an important part of foods that provide energy and fiber [17]. In this second case, a high-fiber diet, including non-digestible carbohydrates, undergo bacterial fermentation in the gastrointestinal tract, obtaining different metabolites, which play a vital role in signaling pathways to maintenance a healthy gut microbiota. Nevertheless, with the

industrialization of the diet, low-fiber intake, high sugar and protein consumption, known as Western lifestyle, the diversity of the gut bacteria is reduced and their function is altered [17,18,19,20] (Figure 1).

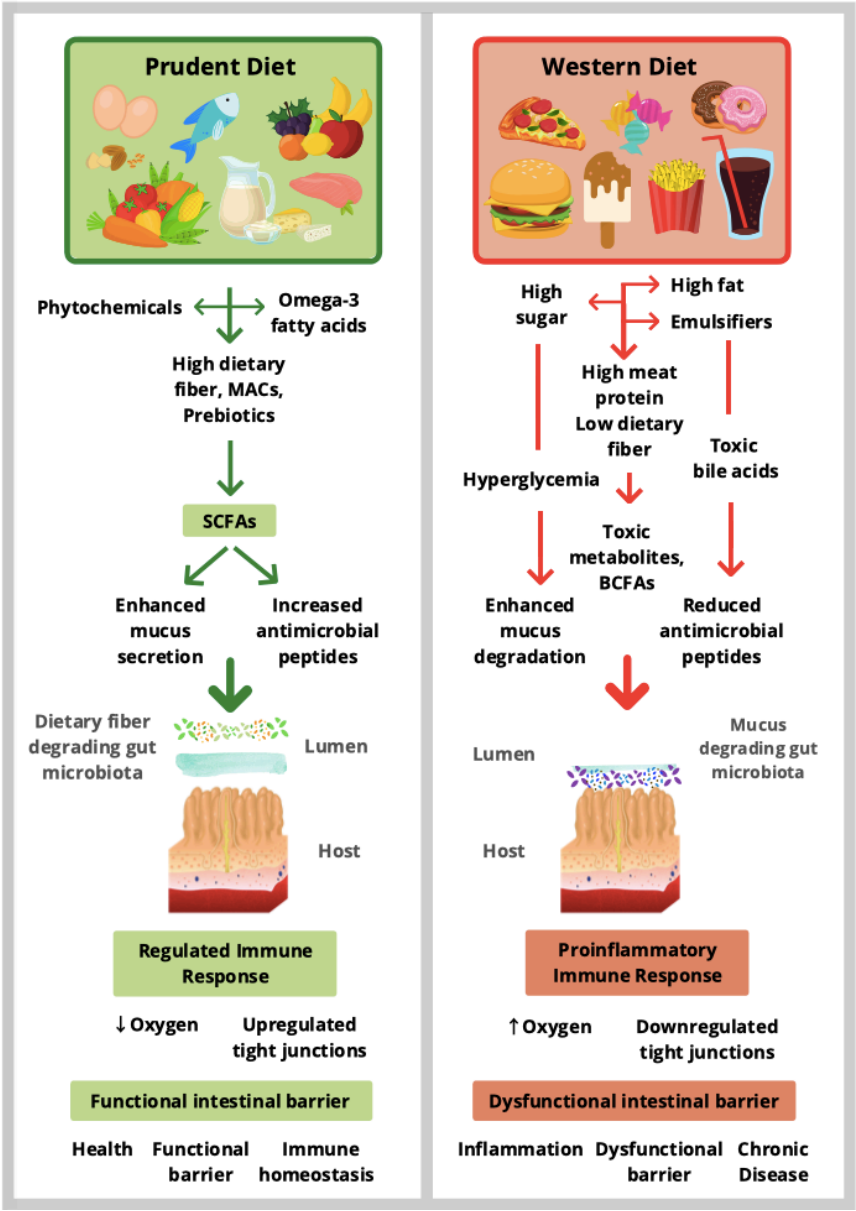

Figure 1. Effect of low- and high-fiber diet on gut microbiota composition, diversity and function in relation to host physiology. Adapted from [18].

1.3 Functions of the Gut Microbiota

The symbiosis that the human organism establishes with intestinal bacteria consists in the fact that the individual provides the residence and the food to survive to the bacteria and, on the other hand, these help to develop a series of essential functions for the organism [3].

The gut microbiota is a key factor in shaping the biochemical profile of the diet and, consequently, its impact on host disease and health [3]. The important role that the gut microbiota appears to play in human

metabolism and health has stimulated research to investigate the functions of the microbiota, which regulates the activation or inhibition of a many metabolic pathways [3].

1.3.1 Intestinal Barrier

The microbiota can prevent the colonization by pathogenic microorganisms (bacteria, viruses, parasites, etc.). In the gastrointestinal tract there are epithelial cells which provide a physical barrier constituted of a single layer of different intestinal epithelial cells [21]. This barrier function is achieved thanks to the ability of bacteria to secrete antimicrobial substances that prevent the growth of potentially pathogenic microorganisms and it is a major line of defense. Therefore, intestinal barrier strongly participates in innate immunity and a dysbiosis on it could be related to increased susceptibility to certain diseases [21,22].

1.3.2 Immune System

Another function that the microbiota performs is to stimulate the immune system [23]. The immune system of the intestinal mucosa is made up of three different mucosal lymphoid structures: Peyer's patches, the lamina propria, and the epithelium [23,24]. This system constitutes the largest immune component of the human being and, together with the intestinal microbiome, establish a close relationship. In this sense, the immune system of the intestinal mucosa is a key factor in homeostasis and host defense. However, once the balance is broken, it appears a dysfunction in host or an abnormal immune response which can lead to the development of intestinal diseases, such as inflammatory bowel disease, rheumatoid arthritis or systemic lupus erythematosus, among others [23].

1.3.3 Vitamin Synthesis

The intestinal microbiota can synthesize different water-soluble vitamins, such as those of B group (thiamine, riboflavin, niacin, biotin, pantothenic acid and folate), critically involved in regular energy metabolism and enzymatic functions important for gene expression [25]. In addition, the intestinal microbiota can synthesize vitamin K (vitamin K2 or menaquinone), a fat-soluble vitamin necessary for coagulation, which the human body is not capable of synthesizing [26].

The effects of vitamins synthesized by the microbiota on the status of systemic vitamins are unclear for the time being. However, studying the interactions between the microbiota and vitamins can help to understand the effects of vitamins on the barrier function and immune system of the intestinal tract [24].

1.3.4 Carbohydrate Fermentation

The gut microbiota helps to digest food and absorb nutrients. The microorganisms are in charge of digesting the foods which the digestive system cannot digest and, in return, they report beneficial substances for

the organism [23]. Dietary fibers, as well as proteins and peptides, which are not digested by host enzymes in the upper intestine, are substrates for the microbiota, especially in the cecum and the colon [1,18]. Thus, most of the soluble fibers are fermented by the microbial activity in the intestine and, once they are metabolized, short-chain fatty acids (SCFAs) and gases are generated [2,3]. More specifically, the main SCFAs produced are acetate, propionate and butyrate, which perform very different but develop highly relevant functions in the human body [2,3]. This process takes place in specific intestinal conditions, where anaerobic bacteria activate certain enzymes and metabolic pathways which allow complex carbohydrates to be metabolized [18]. However, it has been found that the concentration of SCFAs varies throughout the intestine, with the highest levels being in the cecum and proximal colon, while the lowest levels are found in the distal colon [1].

1.4 Gut-Brain Axis

The gut-brain axis corresponds to the bidirectional signaling mechanisms that exist between the gastrointestinal tract and the central nervous system [27]. Such communication can occur through multiple systems including the autonomic nervous system, the enteric nervous system, the immune system, and the neuroendocrine systems [27,28,29].

Specifically, the enteric nervous system, which corresponds to the part of the autonomic nervous system in charge of controlling the digestive system, is recently known as the "second brain", because of its capability in acting as an independent entity of the central nervous system [30]. However, it is in constant communication with the autonomic nervous system (sympathetic and parasympathetic systems) [31]. In this regard, the enterochromaffin cells of the intestinal mucosa and the neurons of the enteric nervous system synthesize 50% of dopamine and 90% of serotonin, both of which modulate behavior [30,31]. Hence, a large number of studies report that SCFAs can participate directly or indirectly in communication through the gut-brain axis due to their neuroactive properties and the effects they exert on the signaling pathways that act on the endocrine and immune systems [27]. Thereby, the intestinal microbiota is an object of study to understand the close relationship that exists between intestinal health and mood, anxiety or depression, among others [27,30,32].

2. Objectives

The main objective of this work is to do an in-depth review to examine and summarize the available data on the influences of SCFAs synthesized by the gut microbiota on human health.

In order to do so, more concrete aims will be achieved:

a) To investigate what are SCFAs and to know their different pathways of metabolism.

b) To do a deep examination of how SCFAs become the link to connect dietary fibers and gut microbiota to intestinal health.

c) To discuss the potential use of dietary fiber to modulate the microbiota, as well as the concept of personalized nutrition, like a new perspective for the future.

3. Materials and Methods

An extensive bibliographic search was carried out for the most reliable and up-to-date articles, reviews and books on the topic. To be able to accomplish that, PubMed®, developed by the National Center for Biotechnology Information (NCBI), was the aim resource in which this work is based, jointly Scopus®, the largest abstract and citation database of peer-reviewed literature. However, for this search it has been used other bibliographic databases ("Cerca-bib" of the University of Barcelona and Google Scholar) and books on the subject written by recognized scientists.

In all databases, the search strategy included these terms: "gut microbiota" [AND] "short-chain fatty acids", "gut microbiota" [AND] "SCFA", "gut microbiota" [AND] "diet", "gut microbiota" [AND] "dietary fiber".

Thus, on September 4th 2020, the search for the articles began. Using each search strategy, approximately 2,600-10,500 articles were found. Of these, the search was narrowed by applying the filter of "publication date" to 5 years and the filter of "article type" to review. As a result, the number of articles found ranged from 90-700 and applying the filter of "publication date" of 5 years and the one of "article type" of meta-analysis, up to 30 articles were obtained in total.

Once a general overview of the different topics was made, a more specific search was attained, joining the different sections and subsections of each topic. Thusly, having selected the information to be treated, the next step was to read it and to highlight the most relevant aspects to be discussed in this work, in order to present it in a summarized mode.

Finally, Mendeley® was used to reference all the bibliography which appears in this this bibliographic research.

4. Results

4.1 SCFAs: Biosynthesis, Absorption and Distribution

To break down carbohydrates into simpler sugars, humans have salivary α-amylase, an enzyme found in the oral cavity, and some other enzymes for the complete digestion of digestible carbohydrates acting in the intestinal lumen: pancreatic α-amylase, maltase, sucrase, galactose and lactase [17,33]. However, in the case of non-digestible carbohydrates (NDCs), they are metabolized by the microbial activity of carbohydrate degradation (MCD), obtaining the SCFAs as a result products [1]. Thus, dietary fiber which contains 10 or more monomeric units cannot be hydrolyzed by digestive enzymes and it is a substrate susceptible to bacterial fermentation in the colon, mostly producing (≥95%) acetate (C2), propionate (C3) and butyrate (C4), with a molar ratio of 60:20:20 in human feces, respectively [34,35] (Figure 2). In more detail, different

anaerobic microorganisms produce different proportion of SCFAs; however, Bacteroidetes (Gram negative) mainly produce acetate and propionate, while Firmicutes (Gram positive) generate butyrate as the metabolic end products [35].

Firstly, acetate is absorbed and transported by the portal vein [1]. It is the most abundant SCFA in the peripheral circulation and it has the ability to cross the blood-brain barrier [17]. In addition, in rat liver it is involved in cholesterol metabolism and lipogenesis and may play a role in central regulation of appetite [2,36].

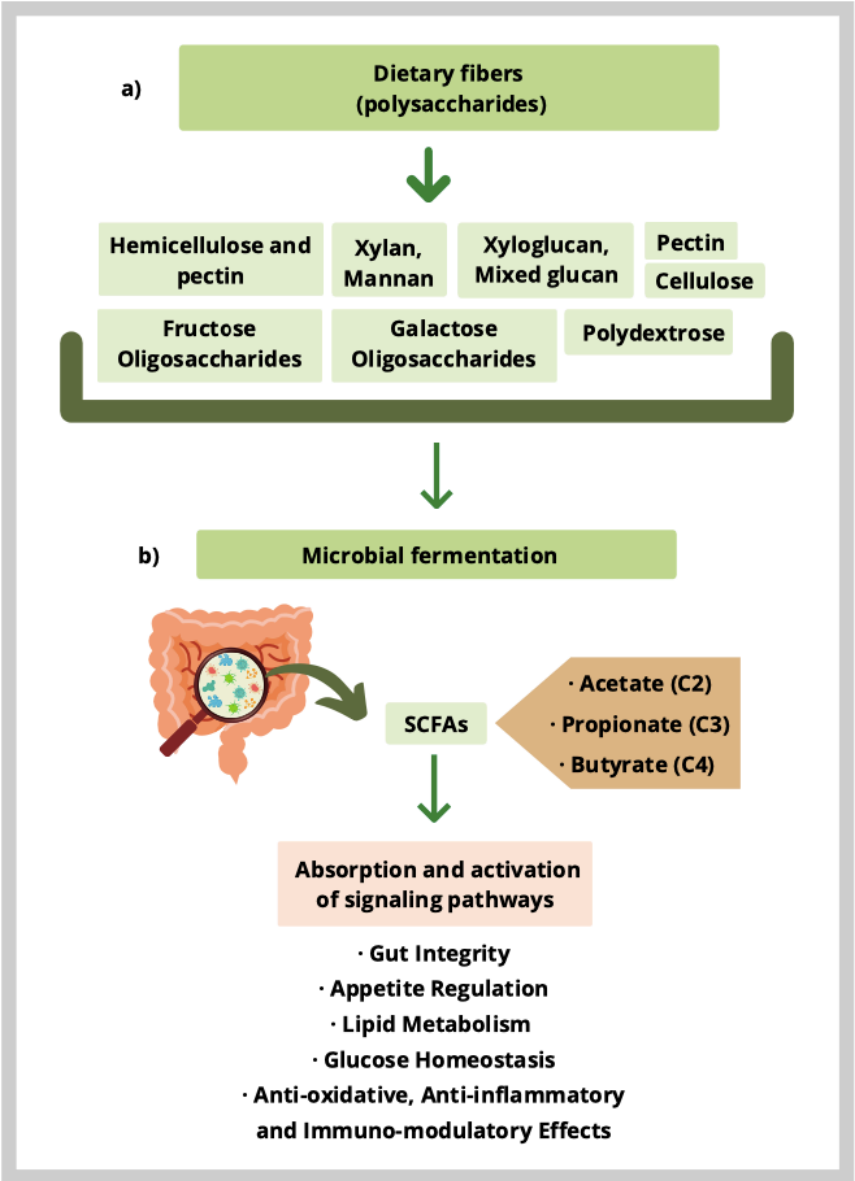

Figure 2. a) Graphical abstract of dietary fiber and indigestible carbohydrates, which are made up of natural polymers [17]; **b)** Fermentation process of dietary fiber in the colon by the intestinal microbiota, indicating the metabolites produced (short chain fatty acids, SCFAs) and their main physiological functions. Modified from [17].

Secondly, propionate is absorbed and transported by the portal vein, as acetate too [1]. Furthermore, it is metabolized in the liver and, therefore, its concentration in peripheral organs is very low. Besides, it is able to regulate the state of satiety and the gluconeogenesis, through interaction with gut fatty acid receptors [2,37].

Thirdly, butyrate turns out to be the preferred energy source for colonocytes and is consequently consumed locally, maintaining oxygen balance in the gut and preventing gut microbiota dysbiosis [2]. Different studies show the important role that butyrate plays in the proliferation, differentiation and integrity of rat colon cells [17,38]. Furthermore, it can induce apoptosis of colon cancer cells, and can activate intestinal gluconeogenesis, having beneficial effects on glucose and energy homeostasis [2].

Hence, SCFAs have been the subject of many studies, since they directly and indirectly affect peripheral organs by activating signaling pathways which regulate the hormonal and nervous systems, modulating the physiology of the host [1] (Figure 3).

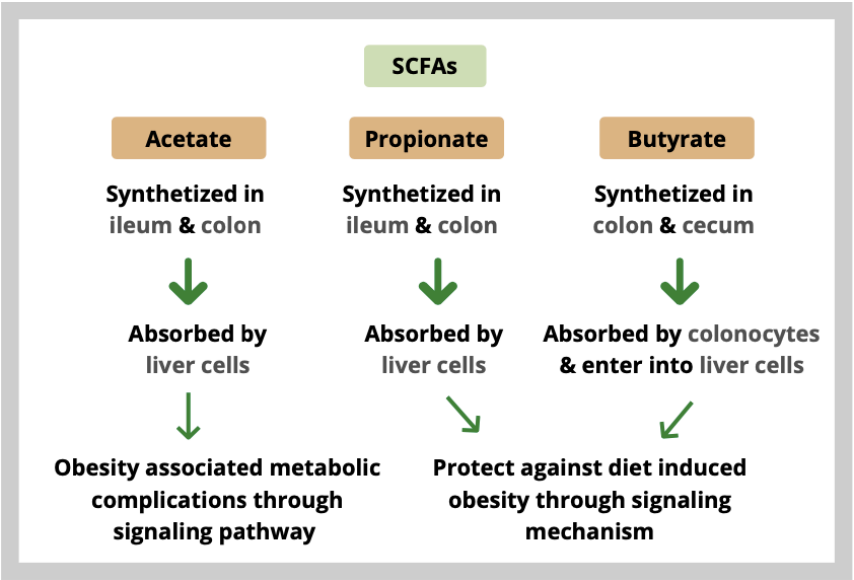

Figure 3. Formation process of SCFAs and their physiological importance. Obtained from [17].

Regarding the uptake of SCFAs, they are transported through the intestinal mucosa thanks to an active transport chiefly mediated by two receptors: the sodium-coupled monocarboxylate transporter 1 (SMCT-1) and the monocarboxylate transporter 1 (MCT-1). In such a way, it is possible to directly inhibit histone deacetylases (HDAC) and consequently, by regulating gene expression and host physiology, to signal the effects of SCFA through G-protein-coupled receptors (GPCRs) [17].

4.2 Mechanisms of Action

In the first place, it is necessary to emphasize that the vast majority of physiological activities that take place in the body are directed by intestinal metabolites. For this reason, SCFAs have been the subject of numerous studies in which it has been possible to demonstrate the key role that they exert by modulating the function of different systems, such as the intestinal, endocrine, nervous and blood systems, and, as a consequence, regulating metabolic disorders and immunity (Figure 3). Nevertheless, most of these effects have been shown *in vitro* and *ex vivo* studies and, therefore, convincing evidence in humans is still lacking [39].

4.2.1 Appetite Regulation

In different studies carried out in humans on the participation of NDCs, the modulating effect which it presents on energy consumption and appetite has been demonstrated [40,41]. In this sense, it has been observed that propionate produced in the intestine is capable of regulating food intake through peptide tyrosine-tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) [42]. More specifically, the PYY participates both in the regulation of food intake and in satiety, through the activation of central Y receptor type 2 (Y2R) coupled to the G protein in neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons, which are located in the arcuate nucleus of the hypothalamus [17]. Consequently, a signaling cascade is initiated, which inhibits appetite-stimulating NPY neurons and finally, satiety is induced [43].

Other studies in mice have shown that the intake of oral probiotics, which are able to produce certain SCFAs such as sodium butyrate, increases transiently the secretion of GLP-1 and GIP (Gastric inhibitory polypeptide) [17,44]. In the case of GLP-1, there are studies in which is demonstrated that this hormone can increase insulin, inhibiting the secretion of glucagon located in the pancreas as well as gastric emptying and influencing both satiety and food intake [17,45,46]. Additionally, there is evidence that acetate can regulate appetite both through central hypothalamic mechanisms and by controlling satiety through acetate-induced vagal activation or intestinal hormones [47].

Appetite regulation is coordinated by nutrients, like fiber, and microbial metabolites, as SCFAs do, through the central nervous system circuitry and circulating hormones from peripheral tissues [47]. Therefore, an impaired of this process it could have some significant implication in the development of obesity or certain metabolic diseases [17].

4.2.2 Glucose Homeostasis

SCFAs act in concert to contribute to glucose and lipid homeostasis in the liver, through adenosine monophosphate-activated protein kinase (AMPK). Thereby, AMPK activation reduces the gene expression of glucose 6-phosphatase (G6Pase) and

phosphoenolpyruvate carboxy-kinase (PEPCK), both of enzymes playing an important role of gluconeogenesis [35].

Other studies have shown that the activation of free fatty acid receptor 3 (FFAR3) by SCFA can stimulate the secretion of intestinal hormone PYY in endocrine cells [35]. As a consequence, it is an improvement of glucose absorption in adipose and muscle tissue, producing satiety and the food intake is reduced [48]. Regarding glucose transporter type 4 (GLUT4), a speed-limiting protein that allows glucose to enter muscle cells, SCFAs can increase its expression and translocate it to the cell membrane. As a result, the uptake of more glucose by myoblasts is promoted [35]. Furthermore, SCFAs can stimulate the production of GLP-1, by activating free fatty acid receptor 2 (FFAR2), which increase insulin secretion and decrease pancreatic glucagon, indirectly regulating blood glucose levels [35]. More specifically, different findings have observed a possible association between butyrate and insulin sensitivity, a fact which indicates that there is a relationship between the characteristics of the individual's intestinal microbiota and their glucose metabolism [1,49]. Hence, there is evidence that shows that SCFAs are capable of influencing insulin receptors, since a high-fiber diet modulates the intestinal microbiota and, as a consequence, there is an improvement in glucose metabolism in patients with type 2 diabetes mellitus [50,51]. Similarly, a deficit in the production of SCFAs has been related to an increased risk of type 2 diabetes mellitus, by interfering with the levels of glycosylated hemoglobin (HbA1c) [52].

However, leptin plays an important role to balance blood glucose, as glucagon and insulin do [35]. It has been demonstrated that SCFAs can increase leptin secretion by activating FFAR2, both *in vivo* or *in vitro*. As follows, there is evidence indicating that this hormone promotes glucose uptake in brown adipose tissue and the soleus muscle. Moreover, leptin can directly promote the synthesis of glycogen in liver and muscle blood glucose uptake [35].

4.2.3 Lipid Metabolism

As members of the fatty acids group, SCFAs can be a substrate for a lipid synthesis in the organism. Hence, they exert their actions through their receptors, such as the GPR41 (FFAR3), GPR43 (FFAR2) and GPR109A, due to an activation of G-protein-coupled receptors and the inhibition of HDAC [17,53,54]. There is evidence which shows that acetate is a precursor in the synthesis of palmitate and stearate [55]. Thereby, the SCFAs are converted into acetyl-CoA, as a precursor in the synthesis of other triglycerides. Nevertheless, SCFAs are not only a substrate involved in lipid metabolism; they also can be a factor to regulate lipid metabolism [35]. Concerning to GPR41, there is evidence showing that the potency order of activation for this receptor is propionate firstly, butyrate secondly and acetate thirdly [56]. In more detail, through this receptor, SCFAs can control leptin release in adipose tissue and, to some extent, regulate body weight [17]. In this regard, propionate has been shown to be able to reduce fat deposition in the liver

and visceral organs [42]. Regarding GPR109A, also known as the niacin receptor 1 (NIACR1) or hydroxycarboxylic acid receptor 2 (HCA2), it has been found that it is mostly expressed in adipocytes activated by butyric acid, a fact that occurs in the immune cells as well [17]. The result of its activation is the suppression of lipolysis in adipocytes and, consequently, plasma levels of free fatty acids are reduced [57]. Moreover, butyrate can increase both the oxidation of fatty acids in brown adipose tissue and promote the browning of white tissue [58]. Besides, it can increase the number of multicellular adipose cells, reduce the size of adipose cells and improve the insulin resistance and the obesity caused by diet [35]. However, it must be taken into account that acetate is capable of increasing the synthesis of fatty acids through the acetylation of histones [59]. Furthermore, SCFAs have also been shown to participate in the metabolic functions of the liver through the FFAR3 signaling pathway [17,60].

4.2.4 Gut Integrity

The barrier function of epithelial cells is the first line of defense in the intestine, separating the intestinal luminal contents from the host to ensure intestinal integrity [39]. The evidence concludes that SCFAs are the most important components to maintain the integrity of the intestinal barrier and they turn out to be the substrate to nourish the colonocytes, being butyrate the main source of energy used by colonic cells [61]. Nonetheless, the effect of SCFAs may be concentration-dependent [39,62,63].

SCFAs act mainly through the modification of the expression of tight junction proteins to regulate paracellular permeability, as well as the transport of solutes through channels between intestinal cells [64,65,66]. More specifically, butyrate appears to be the most important regulator of tight junctions, through the positive regulation of genes responsible for encoding tight junction proteins [39,67]. In this respect, a study has shown that butyrate improves the expression of tight junction proteins, such as claudin-1 (CLDN1) and zonula occludens-1 (ZO-1) and moreover, it is capable of suppressing the interleukin 10 (IL-10) receptor-dependent expression of claudin-2 (CLDN2) to promote epithelial barrier function [39,68]. In addition, it can contribute to increase the expression of mucin 2 (MUC2), which is expressed on the surface of the intestinal mucosa and strengthens the mucosa layer to prevent the entry of luminal pathogens, and it also induces antimicrobial peptides (AMPs) production [69,70,71].

SCFAs have been shown to help relieve gastrointestinal disorders, such as inflammatory bowel disease (Crohn's disease and ulcerative colitis) [53,72]. Particularly, these intestinal disorders are more frequently localized in the western part of the world, as a consequence of drastic changes in eating habits and lifestyle patterns [17]. In this regard, it has been demonstrated that the reduction in the flow of SCFAs predisposes to the appearance of intestinal disorders at the molecular level.

In another study, it was observed that those mice which were fed with a high-sugar diet and a high-fat diet finally presented an alteration in intestinal integrity [73]. Thereby, the expression of GPR43 was found to be decreased in people with Crohn's disease [74] and, thus, the addition of SCFAs and prebiotic fibers in food was recommended for treatment, because of SCFAs participate in the regulation of the tight junctions in the intestinal epithelium [73]. Using the C57BL/6 mouse model, it was observed that dietary fiber shifts the gut microbiome toward an increased butyrate production [75]. As a result, a positive regulation of the microbiota and of gene expression dependent on AMPK was found, a fact that led to an improvement in intestinal integrity [75].

4.2.5 Anti-oxidative Effects

SCFAs can influence the inflammatory process as well as carcinogenesis. In both, there is a situation of oxidative stress due to an imbalance between the oxidizing substances found in the body and the endogenous antioxidant system of the host [39]. In such situations, there is scientific evidence which shows that SCFAs, mainly butyrate, are capable of modulating oxidative stress [39,76]. Hence, it has been observed that incubation of rat or human colonocytes with butyrate significantly reduces the levels of DNA damage produced by hydrogen peroxide (H2O2) [39]. In this line, it is suggested that the antioxidant function of SCFAs takes place thanks to the regulation of oxidoreductase [39,77]. Furthermore, butyrate has been shown to significantly increase the activities of different antioxidant enzymes, such as glutathione reductase (GR), glutathione peroxidase (GPx) and catalase (CAT), to induce apoptosis in MCF-7 human breast cancer cells [39]. More evidence in *in vitro* studies indicates that antioxidant enzymes, such as superoxide dismutase-2 (SOD2) and CAT, increased after butyrate treatment [70]. Moreover, butyrate can suppress oxidative stress induced by a high-fat diet in the rat liver, through the nuclear factor erythroid 2-related factor 2 (NRF2) pathway and mitochondrial function [78]. In healthy humans, locally administered butyrate at physiological concentrations has been shown to increase antioxidant glutathione and probably decrease reactive oxygen species (ROS) production, due to a decreased in uric acid production [39]. In short, in a broad sense, SCFAs prevent the production of ROS and reactive nitrogen species (RNS) [39].

4.2.6 Anti-inflammatory and Immuno-modulatory Effects

The anti-inflammatory and immuno-modulatory effects of SCFAs involve both the activation of GPR41 / FFAR3, GPR43 / FFAR2 and GPR109A receptors, and moreover, inhibiting HDACs activity [79]. Particularly, in reference to the immuno-modulatory effects, different findings have demonstrated the capacity of SCFAs to configure and modulate the immune system, in its local and peripheral form, regulated through inflammatory pathways [17]. In this regard, the evidence that exists on the subject shows that SCFAs can have a strong impact on the modulation of both the innate and adaptive immune systems [79]. In this

sense, a study carried out in mice showed that those which were deficient in GPR43 developed arthritis, colitis and asthma. Thus, a direct action of SCFA on the T regulatory (Treg) cells of the colon was demonstrated, through the increase of the gene expression of GPR43 [79,80].

On the one hand, butyrate can modulate the activity of GPR109A, regulating the pro-inflammatory activities of phagocytic cells in the colon. Moreover, it is known that it contributes to the differentiation of Treg cells, as well as to the production of anti-inflammatory cytokines such as IL-10 and decreases the colonic epithelial secretion of IL-6, IL-18, and tumor necrosis factor (TNF-α), which are pro-inflammatory cytokines [79].

On the other hand, propionate and acetate are capable to improve Treg cells function too. In more detail, it is probably that commensal bacterial species in the gut promote inducible Tregs cells through SCFAs release [79]. Furthermore, it has been shown that propionate increases the phagocytic capacity of dendritic cells in the bone marrow and is able to limit their capacity ability to trigger a T helper type 2 (Th2) response in the airways, through its binding to GPR41 [79,81].

In general, it has been shown that SCFAs increase the immunoglobulin A (IgA) response at the intestinal level and immunoglobulin G (IgG) at the systemic level and, probably by promoting the differentiation of plasma B cells is promoted. Thusly, studies carried out with mice exposed to a low-fiber diet and, consequently, a low synthesis of SCFA, have shown to induce an imbalance of antibodies and, as a result, they have been more susceptible to suffering from infections [82].

5. Discussion

In this manuscript, the numerous beneficial effects of dietary fiber consumption have been reported, especially due to the SCFAs generation. However, there may be a wide range of situations in which caution is warranted in making generalizable recommendations on fiber intake to the general population [18]. More specifically, in cases of people with irritable bowel syndrome, the intake of fiber can cause undesirable side effects, such as bloating, flatulence, stomach pain, constipation and diarrhea [18]. In this line, different investigations using animal models suggest that the metabolites which are generated after fiber ingestion can have a strong negative impact on health in people suffering from colitis or colorectal cancer [83,84]. However, it should be noted, that tolerance to dietary fiber depends on the individual and, in most cases, improves with time as higher doses of fiber are ingested thanks to an adaptation by the gastrointestinal tract and the microbiota [85].

Hence, the main problem that must be solved in the development of this approach is that, many studies, *in vitro* (cells) and *in vivo* (animal models), have been conducted, but research in humans is still scarce [39]. In addition, most of the current studies focus on a single SCFA, and do not consider the synergistic effects of all SCFAs and exposure times used. Nevertheless, this limitation could be overcome by the combined

application of different administrations of acetate, propionate and butyrate at different times [39]. Thus, the lack of deep and detailed knowledge about the functioning of the bacterial consortia which are part of the human intestinal microbiota is another challenge to overcome, as well as the high amount of dietary fiber that would be necessary to produce significant results in the host [39]. Moreover, the wide variability in the response to dietary modification due to the resistance to change of certain microbial strains is another limitation, along with the need to develop new forms of dietary fiber supplements which are tolerable and palatable when were ingested in effective amounts [86].

However, precision, personalized, preventive and predictive medicine based on epigenetics, microbiomics and metabolomics may not be far off to be the medicine in the more or less near future. Science and technology will have advanced enough so that people can go to a health center and submit their saliva, skin, blood, breath and stool samples. Thusly, said samples will be analyzed in automated machines by standardized protocols that will check what microorganisms the individual has *in situ* and which metabolites they produce. In addition, the complete genome will already be sequenced, and it will be known how it is associated with the human microbiome [87]. Based on these results, hand in hand with artificial intelligence and big data, through complex algorithms based on systems medicine, the computer will allow the preparation of a report with the dietary recommendations for the individual, simultaneously informing of the bacterial consortia the host need. Besides, itself will carry out an exhaustive analysis of the health risks linked to a series of detailed advice so that the individual can know and apply [87]. As follows, specific types of fiber could be used individually combined with the host's own microbiota profile to reduce the severity of side effects, while providing a beneficial physiological effect to the body [18]. In this manner, if there were the ability to identify some key bacteria and their metabolites related to the appearance or generation of a disease or protection against it, the microbiota of the affected individual could be precisely treated [39].

6. Conclusions

The intestinal microbiota has been the focus of researchers in recent years. Dietary fiber is considered a key compound to preserve gut health thanks to the SCFAs, which the microbiota produce during the fiber fermentation process and they play important roles in homeostasis and regulation of host physiology. For a better understanding of the interactions between diet and microbiota, it would be necessary to develop a personalized nutrition approach. It would more efficiently reduce the incidence of many of the diseases currently present and serves as a diagnostic tool. Therefore, given the different current gaps which exist on this topic, more scientific evidence is required that can be translated into clinical practice, since the field of microbiota research presents enormous potential.

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