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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Effects of Short Chain Fatty Acids on the Microbiome

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Received: October 07, 2024; **Published:** November 15, 2024

Abstract

Short Chain Fatty Acids (SCFA) are analyzed, metabolites that generate numerous beneficial processes, including the prevention of colon cancer. It is accepted that the first to discuss the topic were veterinarians and from them, we have learned countless issues about these metabolites. The various functions of fatty acids are evaluated, highlighting the transcendent role in maintaining health and the development of diseases.

Butyric acid is justified as the best fatty acid, as it is the most powerful inhibitor of histone deacetylases, preferred by colonocytes and improves liver disease.

The relationship of SCFA with neuroimmunoendocrinology and their role in the already famous microbiota-gut-brain axis, as well as other organs, are analyzed.

Intestinal dysbiosis and gastrointestinal diseases, as well as extra-gastrointestinal diseases, have their place, including the use SCFA as therapeutics, their adverse effects and the future of fatty acids.

Keywords: *Short Chain Fatty Acids (SCFA); Gut Microbiome (GM); Microbiota (M); Fecal Microbiota Transplant (FMT); Intestinal Microbiota Transplant (IMT)*

Introduction

Short Chain Fatty Acids (SCFA) are metabolites produced by the GM in the cecum and proximal colon, through the anaerobic fermentation of indigestible polysaccharides, such as dietary fiber and resistant starch. They are usually linked to protective functions in obesity, even colorectal cancer. It is well known that specialists in various processes in animals anticipated the conception of SCFA and at this time, gastroenterology tries to achieve these precepts, for the benefit of the health of the patients under its care [1]. Most SCFA are located in the proximal colon, where they are used by enterocytes or transported by the intestinal epithelium into the bloodstream. Two signaling mechanisms have been described: the inhibition of histone deacetylases and the activation of G protein-coupled receptors.

SCFA can unbalance chemotaxis and phagocytosis; inducing reactive oxygen species; changing cell proliferation and function. They have antimicrobial, anti-inflammatory, anti-obesity, anti-diabetes and anti-tumor effects, as well as cardiovascular, hepatic and neurological protection. And not all are positive effects, since they can alter intestinal integrity and, through free fatty acid receptor 2, change the composition of the GM, contributing to colorectal cancer. The most abundant SCFA are butyric acid, acetic acid and propionic acid. Its existence is determined by diet, environmental factors, diseases and the use of antibiotics [2].

Short chain fatty acids (Functions): It has been confirmed that SCFA modify chemotaxis and phagocytosis; drive reactive oxygen species (ROS); they modify cell proliferation and function and generate anti-inflammatory, antitumor and antimicrobial agents; and alter the intestinal membrane. In addition, to the functions already reported, another significant number of functions are listed [3]:

- Play a significant role in maintaining health and developing diseases.
- Regulate inflammation.
- Maintain intestinal and immune homeostasis.
- Inhibit histone deacetylase activity.
- Through enterocytes produce energy.
- Reduce intestinal pH, inhibiting the colonization of pathogens.
- Inhibit the proliferation of enterobacterias.
- Improve the immune response by stimulating the production of cytokines.
- Promote the differentiation of T cells into regulatory T cells.
- Modulate the immune response, through multiprotein inflammasome complexes.
- Repair the intestinal mucosa.
- Modify the host epigenome.
- Regulate digestive and adipose tissue functions.
- Metabolize, produce and absorb.
- Modulate the activation of T lymphocytes and effector responses.
- Use intestinal epithelial cells as a source of ATP.
- Play a crucial role in the health of the symbionts.
- Linked to inflammatory bowel diseases, cardiometabolic disorders and colorectal cancer.
- Effects on tissues and organs beyond the intestine.
- Promote apoptosis.
- Affect the function of immune cells.
- Mediate the communication between the GM and the immune system.
- They are raw materials for the synthesis of sugars and lipids.
- Have an influence by regulating protein molecules, including the inflammasome.
- Contribute to the maintenance of immune homeostasis of the urinary system, respiratory system, the central nervous system and organ of vision.

- Protect epithelial cells.
- Regulate neuroimmunoendocrine functions and the blood-brain barrier and,
- Help explain why changes in the microbiota (M) can contribute to the pathophysiology of human diseases.

On the other hand, it has been described that adding sialilactose increases the number of short chain fatty acids, given by the growth of *Phascolarctobacterium* and *Lachnospiraceae*. Without development of *Bifidobacterium* [4].

What is the best SCFA?

Since butyrate is the most powerful inhibitor of histone deacetylases, preferred by colonocytes, as well as an improver of alcoholic liver disease and probably produced by vaginal and skin bacteria, we could consider it as the best SCFA. Unambiguous sentence. This SCFA provides 60 - 70% of energy needs, improving intestinal barrier function by promoting tight junction coupling. It is worth considering that the existence of butyrate is determined by the type of diet, environmental and immunological factors, intestinal transit time, the use or not of antibiotics and bacterial hydrogen metabolism [5].

SCFA and immunology: Without a doubt, the immunological role of SCFA is very relevant. We begin with the proven concept that GM is a fundamental basis for immune functions. Modulating neurochemical pathways, through the multi-connected microbiota-gut-brain axis. Even though it has not been fully determined. Signaling from the brain to the gut could affect M, through the immune system or the release of neurotransmitters, motility and immune tone [6]. Below they are analyzed from neuroimmunoendocrinology in relation to SCFA, as well as the brain, microglia, neurons, immune cells and the microbiota-gut-brain axis.

SCFA and neuroimmunoendocrinology: The M is the billions of microorganisms that live symbiotically throughout the human body, highlighting the colon as a habitat. The majority are bacteria, but there are fungi, viruses, and other types of organisms, sharing a mutual effect with pathogens. They have a transcendent role both in modulation and in immune functioning and development, from the moment we are born. Both its homeostatic evaluation and that of SCFA will help us understand the etiology of many diseases [7]. It has been noted that metabolites produced by the colon, such SCFA, affect neuroimmunoendocrine regulation, influencing the blood-brain barrier and blood flow and epithelial functions, through the epithelial neuronal network. Likewise, it has been pointed out that they can have an impact on satiety, stress and mood. The SCFA that pass into the blood vessels can be transported in the blood-brain barrier towards the brain, which gives rise to a series of joint processes, which can invariably make their specific weight felt in health [8]. SCFA are of vital importance in the communication of the digestive system with the nervous system and their significance in the integrity of the blood-brain barrier has been noted in different diseases. It does so by restoring junctional complex proteins, which disrupt its transcription, degradation, and intercellular localization [9]. Yang Which confirms the previously mentioned, by modulating inflammatory processes, SCFA would improve immune responses, both in the intestine and the central nervous system, through the regulatory expression of T lymphocytes and the permeability of the blood-brain barrier, as occurs in Multiple Sclerosis. Likewise, M determines levels of tryptophan in the systemic circulation and therefore, brain serotonin; synthesizing, some microbiota neurotransmitters such as gamma-aminobutyric acid and through its modulation dopamine and neuroepinephrine, as well as brain-derived neurotropic factor, appear.

SCFA and brain: Although it would be more accurate to manifest these lines as brain disorders, here we evaluate the relationship between the brain and SCFA, which is transcendent in this connection. SCFA that are transported by the blood system can do so through the blood-brain barrier and the cerebrospinal fluid. Which can affect the degree of neurotrophic factors, which modify the differentiation and growth of neurons and brain synapses. They also seem to play a role in maintaining the integrity of the blood-brain barrier, generating brain development and maintaining its homeostasis in the central nervous system (CNS). SCFA have different functions through the microbiota-gut-brain axis, and have a positive impact on Alzheimer's Disease and others. Relevant fact is that butyrate, acetate and

propionate have been found in the brain. In summary, they could influence through strengthening the blood-brain barrier in the brain; modulate neurotransmission, promote memory and influence the levels of neurotrophic factors.

SCFA and microglia: Microglia being the resident cells of the brain that regulate brain development, the maintenance of neuronal networks and the repair of injuries, they are also linked to SCFA. Well, they work like brain macrophages, differentiated by the unique homeostatic phenotype and the strict control exerted by the CNS microenvironment. Tyler J and his group [10] determine the following points, related to the linkage of microglia and SCFA: Regulate the functions of microglia; They inhibit the secretion of cytokines; If 2/3 of the mixture is administered, its effect is not blocked; Formate plus non-valerate decreases phagocytic activity and formate plus non-valerate reduces the bursting of microglia-like cells. Concluding that SCFA could improve the functions of microglia that are altered in Alzheimer's Disease. Microglial cells play a relevant role in the elimination of unnecessary synaptic connections, which is convenient in the development of the CNS immune system. A mixture of the three main SCFA improved microglia maturation in mice. Corroborating that SCFA are mediators of the microbiota-gut-brain axis [11]. Caetano-Silva ME, and associates [12], carried out a study in mice, which they fed with inulin, plus lipopolysaccharides, increasing the production of SCFA in the cecum and liver; decreasing tumor necrosis factor TNF-α, without affecting monocarboxylate transporters in microglia, suggesting that SCFA directly regulate microglia, through an epigenetic mechanism. Huuskonen J and her team [13], observe that sodium butyrate is a powerful anti-inflammatory, confirming it with hippocampal sections and neuronal cultures, microglial cells, astrocytes and cerebellar granule neurons. Finally, Yang Y and collaborators [14], seeking the effect SCFA in the microbiota-gut-brain axis, administered a highly specific inhibitor of the colony-stimulating factor 1 receptor and detected links between microglial markers in the brain and the relative abundance of various bacteria, suggesting interference between M and microglia through the microbite-gut-brain axis.

SCFA and neurons: Although knowledge about the nutritional and environmental regulation of the enteric nervous system is little, knowledge has been developing, due to the cascade of articles on the matter, such as that butyrate regulates the homeostasis of the colonic mucosa, and can modulate excitability neuronal. Observing it in rats that received resistant starch diet or intracecal perfusion of SCFA. Likewise, searching for the pathways through which SCFA remotely carry out eating behavior and probably other brain functions. Chayon Goswami and his collaborators [15], identify vagal input as a new route. Concluding that vagal afferents could participate in the suppression of feeding by SCFA found in the intestine. On the other hand, there is reorganization in GM metabolites associated with the pathophysiology of several neurological processes, such as anxiety and depression, as well as stress, Alzheimer's disease, Parkinson's, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Autism, Vascular Dementia, Schizophrenia, Stroke, and Neuromyelitis Optica Spectrum Disorders.

SCFA and immune cells: The most abundant immune cells are lymphocytes: T cells (Tregs), B cells, NK cells, neutrophils and monocytes/macrophages. All of them are related to free fatty acids, belonging to receptors coupled to the G protein. By inhibiting histone deacetylase, they generate anti-inflammatory balance. Its relationship with the GM is continuous, although indirect. Thus we see that butyrate is mediated through direct influences on the discrimination of intestinal epithelial cells, B cells, phagocytes, plasma cells and regulatory T effectors.

Now, which example is the most important in this connection: "It has been determined that SCFA drive the proliferation of Tregs. Those that include FoxP3+ T cells, which prevent inflammation by generating IL-10".

On the other hand, SCFA can generate Tregs and consequently the release of IL-10 through other cells.

B cells require glycolysis, palmitic acid synthesis, and oxidative phosphorylation in the processes of proliferation, differentiation, and antibody secretion. These processes are determining factors for the survival of germline B cells and SCFA. Oxidative phosphorylation helps

differentiate B cells and stimulates them to produce antibodies. Finally, SCFA promote the differentiation of B cells and the generation of antibodies, by increasing glycolysis in them. To conclude, natural killer cells can confront virus infected cells, especially with the production of cell destruction and generation of pro-inflammatory cytokines. They belong to the group of three lymphocytes, forming part of the innate immune system and the first line of defense.

SCFA and brain disorders: There is alteration of GM, SCFA, permeability and inflammation in Parkinson's Disease, the relationship between them being unknown. In the study by Aho VTE and his group [16], report that although more evidence is required, calprotectin increased and SCFA decreased in feces. The diversity and constitution of M was related to levels of SCFA, inflammatory factors and zonulin in feces. Intestinal inflammatory responses and reductions in fecal SCFA occur and are related to M and disease onset, and are not reflected in plasma inflammatory profiles.

There are many benefits that SCFA generate in neurodegenerative diseases, associating themselves with GM, preserving healthy mitochondrial function, stimulating the maturation of microglia, canceling cognitive deterioration, intervening in oxidative stress and inflammation. They are being considered for their ability to correct the alteration of M, which appears in numerous undesirable chronic processes. The modulatory effect that SCFA exert on learning and memory is considerable, confirmed through alterations in the metabolome.

It has been pointed out that both GM and its SCFA have significance in patients with autism spectrum disorders. Low levels of fecal acetic acid and butyrate and high levels of fecal valeric acid are usually determined. Likewise, a decrease in butyrate-producing taxa (*Ruminococcaceae, Eubacterium, Lachnospiraceae* and *Erysipelotrichaceae*) and increase in bacteria associated with valeric acid (Acidobacteria). Suggesting that GM contributes to constipation and that through the modulation of M, it could be used as an appropriate strategy.

SCFA and microbiota-gut-brain axis: Communication in the microbiota-gut-brain axis can occur through the autonomous nervous system, the immune system and the neuroendocrine system, with SCFA playing a determining role, generating alterations in this axis, neurological development disorders and neurodegenerative diseases. This bidirectional communication occurs through various mechanisms, among which the biochemical messengers, produced by M, are very significant. SCFA could affect psychological physiology through interactions with G protein-coupled receptors or histone deacetylases and influence their effects on the brain, through direct humoral means, indirect hormonal and immune pathways, and neuronal routes. It is good to know that current research covers the systemic circulation from the intestinal lumen, the cerebral circulation; the same in the blood-brain barrier and the incidences in acute and chronic processes in the function and structure of the brain. There is a series of events that clarify the action of the microbiota-gut-brain axis, such as: The microorganisms of the intestine are capable of interacting and activating the vagus nerve, exerting actions in the CNS, even when it has not been determined. Whether this nerve acts by bacterial interaction or through microbial components. The indication from the brain to the intestine can make M act, through the immune system or through motility itself, the release of neurotransmitters or intestinal immune tone. This alteration of the M is induced by brain signals or by changes in the GM. Modifications in diet, use of antibiotics, infections or stress itself generate changes in GM, with repercussions on the brain and behavior. Diseases of the intestine that affect the permeability and translocation of bacterial products could produce cytokines, affecting the blood-brain barrier. Finally, SCFA and other bacterial byproducts are indicated as mediators of back-and-forth communication. Xiao W and her team [17], point out that bilateral obstruction of the common carotid artery in rats produces cognitive impairment, depressive-like behavior, decreased SCFA, decreased intestinal motility, and compromised intestinal barrier. And when fecal microbiota transplantation (FMT) is carried out, rats recolonized with balanced GM presented a higher level of SCFA in the hippocampus, and a decrease in neuroinflammation, when exposed to lipopolysaccharides. Furthermore, FMT improved intestinal motility, cognitive impairment, depressive behaviors, and intestinal barrier functions; by inhibiting hippocampal neuronal apoptosis.

SCFA and gut microbiome: The healthy GM, almost forgotten organ, it is essential to maintain health. This set of microorganisms: bacteria, fungi, viruses and their genes, live naturally in our bodies. And, it can be affected by numerous circumstances such as stress; or by the decrease in SCFA, by producing: *Anaerostipes, Butyricicoccus, Coprococcus* and *Parabacteroides*, and increasing *Odoribacter*. GM produces metabolites, neurotransmitters and immune molecules, as well as SCFA. These fatty acids bind to receptors on enteroendocrine cells, determining hormones such as glucagon-like peptide 1 and peptide YY, which regulate appetite and insulin sensitivity. The intestinal surface is the largest in the human body and extends approximately between 200 and 300m^2. 100 billion bacteria live in it in symbiosis, in which both the potentially pathogenic and the healthy ones receive various satisfiers. All of these microorganisms are related to numerous external stimuli, producing bioactive metabolites, generated by bacterial degradation, linked to receptors, which activate signaling cascades and modulate various metabolic pathways. Within these products, SCFA appear, affecting the health of the host at the tissue level and of different devices and systems, through processes that interact with the intestinal tract, immunomodulation, glucose homeostasis and obesity. M, although exposed to various pressures, is usually stable, because microbial communities are resilient and resistant to change. Resilience: "To adapt to a disruptive agent or an adverse state or situation". Recent studies reveal plasticity of M in our biology. Evaluating the imperative of the various metabolic and immunological needs, at different ages, linking them with diets, lifestyle and physiological stage. GM has a transcendent role in health, but its alterations can generate various conditions. Therefore, it is very convenient to understand these changes and avoid or minimize them, in order to maintain a healthy life.

SCFA and Dysbiosis: Considering dysbiosis as an imbalance between the organisms present in the GM, which is considered to contribute to poor health, it is worth delving deeper into it. The plasticity of the GM stands out, to maintain health. Dysbiosis is linked to different conditions, affecting the physiology of the host, through the generation of bioactive metabolites. Among those that stand out are SCFA, those that affect through the nervous, metabolic and immune systems; Dysbiosis alters the production of fatty acids, affecting signaling that produces cellular dysfunction. Almost all research has been directed towards the relationship of M with dysbiosis. Since it is more necessary to establish eubiosis than to maintain dysbiosis, through specific protocols. Considering the alterations within neuroimmunology is to determine the knowledge of the physical and psychological modifications, since dysbiosis generates alterations in dopamine, serotonin, GABA and norepinephrine, which can deepen depression, anxiety, schizophrenia, mood disorders, psychotic and personality. There are numerous conditions that exemplify dysbiosis as an adjuvant in them, one more example is systemic lupus erythematosus, in which there is an increase in SCFA in the blood. Furthermore, the correlation of *Firmicutes/Bacteroidetes* decreases in patients with lupus. Qin Zeng and his team [18] study multiple sclerosis (MS) in Chinese patients and find that intestinal microorganisms are involved, increasing *Streptococcus* and decreasing *Prevotella*, with minimization of acetate, propionate and butyrate. They conclude that in Chinese patients with MS there is intestinal dysbiosis and lack of SCFA, which could be related to an aberrant immune response; This relationship may have diagnostic and therapeutic value for patients with MS [19].

SCFA and intestinal dysbiosis: Although dysbiosis occurs in numerous systems, the one that appears in GM is transcendent, due to its multiple incidences. De la Cuesta and his collaborators [20] analyzed what happened in 441 adults, through sequencing of the 16S rRNA gene and concentration of SCFA in feces, through gas chromatography/mass spectrometry, concluding that greater excretion of SCFA was associated with evidence of intestinal dysbiosis, intestinal permeability, excess adiposity and cardiometabolic risk factors.

Bojović K and his team [21], delve into the topic and report that GM is different in healthy children than those with neurodevelopmental disorders, including autism; less diversity of beneficial microorganisms appeared (*Enterococcus faecalis* ($P < 0.05$), *Enterococcus gallinarum* ($P < 0.01$), *Streptococcus pasteurianus* ($P < 0.05$), *Lactobacillus rhamnosus* ($P < 0.01$) and *Bifidobacteria* sp.) and, a greater number of pathogens, the presence of intestinal dysbiosis being, therefore, frequent in many of them. This same premise appearing in other investigations. The authors suggest that M should be analyzed, if possible, at an early age, since its incidences in the future are many.

Likewise, more studies are required in neurodevelopmental disorders related to intestinal dysbiosis. Since the current ones focus on the link between autism and intestinal dysbiosis.

SCFA and gastrointestinal diseases: SCFA are affected in their production by the source of the substrate, the composition of the microbes, the pH of the colon, the intestinal transit time and the fermentation process. The liver is significant for its metabolism, since 40% of the acetate and 80% of the propionate are absorbed by the portal vein and metabolized in the gland. The above contributes to the appearance of digestive disorders.

SCFA are valuable fuels for intestinal epithelial cells and represent the dietary carbon flux, broken down by GM. They play significant regulatory functions in local, intermediate and peripheral metabolisms. It has been pointed out that both gastrointestinal and inflammatory diseases result in altered homeostatic interactions between M and the host. They become worse with stress and, in laboratory mice, have been shown to change its composition. The increased risk of colorectal cancer (CRC) is associated with altered GM, as well as decreased production of SCFA. Discussing the relationship between GM and SCFA, the genes and proteins linked to the signaling pathways measured by SCFA, and their correlation with the onset and development of CRC. Therefore, pointing to SCFA transformers to regulate their generation is exciting. And we see a promising future in the use of SCFA, GM and some natural compounds for the management of CRC. Inhibition of HDAC by regulating gene expression produces subsequent negative effects. Our understanding of SCFA-mediated HDAC inhibition is still in its infancy. SCFA alter chemotaxis, phagocytosis; induce reactive oxygen species (ROS); change cell proliferation and function; and they have anti-inflammatory, antitumor and antimicrobial effects, as well as alter intestinal integrity. These findings highlight the role of SCFA as a transcendent part in the maintenance of intestinal and immune homeostasis. Due to the effects of SCFA and the fact that their levels are regulated by diet, they provide new basis to explain the higher prevalence of inflammatory diseases in Western countries.

There are numerous gastrointestinal conditions generated by changes in M, so we see, for example, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), also due to alterations in bacterial diversity, in addition to changes in SCFA concentrations, which can be verified histologically. The above is determined by Raul M, Rehman A, and their collaborators [22]. Patients with NASH were characterized by a greater presence of *Fusobacteria* and *Fusobacteriaceae*. People with NAFLD had higher levels of fecal acetate and propionate, the taxonomic differences of fecal bacteria were dominated by SCFA producing bacteria. They conclude that, patients with NASH are characterized by different IM with higher levels of SCFA in feces and greater abundance of SCFA producing bacteria in NAFLD. These alterations are associated with immunological processes of disease progression. It has been proposed that Ulcerative Colitis (UC), a chronic inflammatory condition of the colon, can be caused by a metabolic deficiency in the oxidation of SCFA in the large intestine, and can be remedied through supra-physiological luminal ranges of SCFA. Clinical trials published to date suggest that these acids applied topically provide effective primary and/or adjunctive treatment in patients with mild to moderate distal UC. They suggest: acetate 80 mmol, propionate 30 mmol and butyrate 40 mmol; twice a day, with substantial cost savings and without significant side effects. Talley NA and her group [23], sought to determine whether topical butyric acid enemas (40 mmol) relieve symptoms and improve macroscopic and microscopic findings in chronic radiation proctitis. They conclude that butyric acid enemas do not appear to be superior to placebo in the treatment of chronic radiation proctitis.

Finally, Mortensen PB and Clausen MR [24], report that SCFA are important for understanding the physiological function of dietary fiber and its possible role in colon neoplasia. The production and absorption of SCFA are linked to the nutrition of the colonic mucosa, the absorption of water and sodium, and the mechanisms of diarrhea. People with severe malabsorption compensate by fermenting osmotically active saccharides SCFA, which are easily absorbed and used as energy fuel in the body. The effect of butyrate enemas on UC is through the oxidation of SCFA in colonocytes.

SCFA and metabolic disorders: Among the morbid metabolic processes that are related to SCFA in type 2 diabetes mellitus (T2DM), Obesity, alone or associated with high blood pressure and coronary artery disease. As well as Gaucher Disease, hemochromatosis, phenylketonuria and mitochondrial disorders.

Most of these alterations can be postponed with fiber intake, which changes the composition of the GM, increasing the production of SCFA. In T2DM, changes are observed in the composition of M, with species that produce little butyrate.

Sanna S and her team [25], study normoglycemic people, with genotype, intestinal metagenomic sequence and SCFA levels, detecting that good butyrate production is associated with a better insulin response, after an oral glucose tolerance test, as well as how propionate production is linked to a higher risk of T2DM. While in obese patients, a lower diversity of bacteria is observed, as well as higher concentrations of SCFA in stool samples.

SCFA can regulate immune responses and GM composition. This determines its importance in a variety of chronic inflammatory diseases. Preclinical evidence reiterates their role as modulators.

Yao Y and her group [26], add some processes carried out by SCFA, such as key energy for the colon and ileum, impact on the intestinal epithelial barrier, defense functions, by regulating genetic expression. Regulation of innate immune cells, such as macrophages, neutrophils and dendritic cells; regulation of T and B cell differentiation, as well as antigen-specific immunity. Finally, they are raw materials for the synthesis of sugars and lipids.

It has been pointed out that there is an association between SCFA and metabolic syndromes, so they should be included in all processes, already considered. Likewise, it has been concluded that SCFA modulate metabolic health through a variety of specific mechanisms, related to appetite, glucose homeostasis, energy expenditure and immunomodulation. Remembering that the studies carried out are mainly in animals.

SCFA and extra-intestinal conditions: Many inflammatory diseases are potentiated by unfavorable interactions of the host with the resident GM. There are numerous bacterial metabolites generated by the decomposition of dietary fiber that cannot be processed, and produce pathophysiological alterations, which can be severe. Likewise, GM manages to convert cholesterol into secondary bile acids, which can modulate microorganisms and SCFA fight diseases and improve health [27]. All of this must be delved into in depth to undertake therapy in the different morbid processes that occur, such as the various extra-intestinal conditions, where SCFA play a transcendent role and are extremely beneficial. Thus we see that these acids, as microbial bioactive metabolites, if they are deficient, are linked to brain inflammation, as a fundamental process of neuropsychiatric alterations. Therefore, constant reports point towards this relationship such as Alzheimer's disease, autism spectrum disorders, anxiety, depression, schizophrenia, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, vascular dementia, cerebral vascular accidents, etc. The multi-cited intestinal bacterial dysbiosis can generate various pathologies and disrupt the formation of bacterial metabolites, which produce deregulation of the metabolic and immune system. Another point that must be further explored is the relationship between COVID-19 and various neuropsychiatric complications, where the presence of dysbiosis and imbalance of the microbiota-gut-brain axis is evident [28]. And it is not only neuropsychiatric processes that have been linked to M. There are also renal and other processes. In relation to kidney disease, Felizardo RJF and his team [29], point out: "Chronic kidney disease is linked to GM, with a reduction in SCFA".

SCFA and autoimmune conditions: There are nearly a hundred autoimmune diseases, the following stand out:

- Addison's disease
- Autoimmune vasculitis

- Chronic inflammatory demyelinating polyneuropathy
- Dermatomyositis
- Graves' disease
- Guillain-Barré syndrome
- Inflammatory bowel disease (Crohn's and Ulcerative Colitis)
- Psoriasis
- Psoriatic arthritis
- Reactive arthritis
- Celiac Disease
- Diabetes type 1
- Hashimoto's thyroiditis
- Multiple sclerosis
- Myasthenia gravis
- Pernicious anemia
- Sjogren's syndrome
- Systemic lupus erythematosus.

Autoimmune conditions affect 19% of the population and continue to increase. They all have a self-destructive system and terrible physiology [30]. M has been included among the triggering factors, which include the environment, infections and epigenetic factors. Conventional antirheumatic treatment has good results, although with a good number of side effects, ranging from mild high blood pressure to fatal organ failure. For this reason, both the microbiota-gut-brain axis and the GM have been included, since it has enormous responsibility in immune regulation, since it groups two thirds of the immune cells, determining that the pathogenesis of autoimmunity is associated with intestinal dysbiosis. Process activated by SCFA; those that restore the counterbalance of pro and anti-inflammatory vectors. And, they are considered specific therapy in autoimmune diseases [31].

It is accepted that GM determines immune responses and interacts in autoimmune diseases [32]. It does this through its metabolites. As an example, in multiple sclerosis there is a reduction in *Clostridia* groups IV and XIVa, reducing the release of SCFA. Current research highlights the immunomodulatory potential of SCFA in several autoimmune processes, such as type 1 diabetes, multiple sclerosis and rheumatoid arthritis [33].

The impact that SCFA have on both glycemia and adiposity should be delved into, and with this, the use of these acids in type 1 diabetes should be reiterated. Igudesman D and his team [34] detected that fecal propionate influenced the decreased blood glucose and SCFA-producing microorganisms were useful for adiposity.

Treatment of diseases with SCFA and diet: One of the most important factors that influence health is diet. The type of diet to be implemented is discussed in the literature, although there is no fully defined criterion, I consider that the most significant thing is, first of all, the intake of sufficient SCFA precursors. Likewise, influence processes that trigger damage to the GM such as stress, lack of physical exercise, ingestion of antibiotics, and other medications, as well as temporarily ingesting biotics that protect our health. Understanding the ecological component of microorganisms and their various metabolites, as well as the engineering of butyrogenic bacteria, management with fiber and SCFA can be supported.

Dietary fiber works as a SCFA-generating substrate: They are carbohydrate polymers and oligomers that encompass monosaccharides linked to different molecules, of various sizes. They are classified into soluble dietary fibers (such as pectin and inulin) and insoluble dietary fibers (different resistant starches). They can be made of cellulose, hemi-cellulose or lignin, which process dough. We must remember that if fiber intake is reduced, M metabolizes proteins or amino acids: leucine, isoleucine and valine. It is a fact that dietary fibers are the most important source of SCFA. Zhang S and his collaborators [35], carry out an excellent review of a common condition that involves the liver, with numerous evolutionary morbid processes, and point out between SCFA, a physiologically relevant concentration, GM and host metabolism.

Likewise, it is noted that the presence of a good number of SCFA prevents the growth of pathobionts in the intestine and increases the capacity to absorb minerals such as calcium and others. Therefore, the intake of peas and lentils, corn flour, potatoes and pasta is suggested. The Cleveland Clinic group [36], mentions that we should consume whole fruits and vegetables, rich in prebiotic fiber, as well as fermented foods: yogurt, pickles, millet soup or sauerkraut, rich in probiotics.

Healthy sources of fats, such as fish, nuts, and vegetable oils, which are anti-inflammatory.

Brown K and his colleagues [37], point out: "The usual routines, education, diets, socioeconomic level, genetics from the host, medical care and factors environmental can contribute to the composition of an individual's M".

An example of a key environmental factor that can cause negative outcomes is nicotine consumption.

The dysbiosis that diet can produce is usually a cause that motivates inflammatory responses. The M was considered a stable organ, but it is not, since dysbiosis usually affects aberrant immune responses.

Side effects of SCFA: Although SCFA have numerous health benefits, such as anti-inflammatory, anti-obesity, anti-diabetes, immunoregulatory, hepato-cardiovascular and neurological.

They also generate various side effects, which depend on the health of the hosts:

- Accelerate the differentiation of 3T3-L1 adipocytes and promote lipid accumulation [38].
- Intestinal acetate could increase the presence of hepatic lipids [39].
- Alter choline metabolism and elevate endogenous ethanol levels [40].
- Alter the intestinal barrier through metabolic reprogramming in T cell-mediated acute inflammation [41].
- Induce deterioration of brain neurochemistry [42].
- Propionate increases glutamate level and glutamate/glutamine ratio, decreasing gamma aminobutyric acid (GABA), glutamine and GABA/glutamate ratio [43].

High-quality, large-sample epidemiological studies will be required to verify the effects of SCFA in humans.

SCFA and biotics: Many GM studies in patients with inflammatory bowel disease indicate a decrease in *Clostridium* groups IV and XIVa, which include butyrate producers such as *Faecalibacterium prausnitzii* and *Roseburia intestinalis*. This knowledge is basic to institute adequate therapy, based on new generation probiotics (promoters of B cell differentiation and antibody production), considering the decrease in microorganisms. The benign effect of *F. prausnitzii* is not only the production of butyrate. Likewise, *Clostridium tyrobutyricum*, also a butyrate producer, improves colitis in mice and has an anti-diabetic and neuroprotective effect in mice with vascular dementia [44].

Lactobacillus and *Bifidobacterium* increase the levels of IgA (plays an irreplaceable role in the regulation of mucosal immunity) and IgG in feces and serum, but decrease IgA in germ-free mice treated with antibiotics. It has also been pointed out that if the effect of probiotics and dietary fiber is combined, the production of SCFA can be regulated. The primary activity of probiotics appears to be through the modulation of immune responses (immunomodulations) and the colonization and competitive protection of pathogens.

The good effect of probiotics has been pointed out by Hashempour-Baltork F and colleagues [45], who analyze diabetes, acne, colon cancer, cardiovascular disorders, urinary tract infections, atopic eczema syndrome, food allergies, obesity and fibrocystic disease of ovaries and the improvement in the use of pharmacological treatment with probiotics has led to the emergence of resistance problems to the use of medications.

The most studied species include: *Lactobacillus, Bifidobacterium* and *Saccharomyces*. And they are effective in: acute infectious diarrhea, that associated with antibiotics and that associated with *Clostridioides difficile*, hepatic encephalopathy, chronic nonspecific ulcerative colitis, irritable bowel syndrome and necrotizing enterocolitis. Butyrate and propionate affect cell apoptosis, cell differentiation, and growth arrest of cancer cells. Various research mentions that SCFA alter the composition of GM and prebiotics and dietary fibers reduce the risk of colon cancer through various processes.

Nagpal R and his group [46], evaluate the composition of the GM and the fecal levels of SCFA and lactate in three animal models compared to human subjects and find that, based on β diversity, the human GM seems to be located closer to non-human primates, than in rats and mice, while in rats, GM appears to be closer to humans.

SCFA and diet: Intermittent fasting improves intestinal health and weight control, modulating GM, weight, body composition and digestive tract function. It is said that an intermittent fasting diet generates significant alterations in the microbial constitution and body composition. Interactions between M and diet influence health and disease and we see modifications in the microbial profile. 21 articles are reviewed and an intimate relationship between M and diet is observed. From this union, pathological processes appear, including metabolic diseases and immunological processes, related to the microbiota-gut-brain axis [47].

M plays a determining role in the maintenance of the host's normal physiology, in immune development and homeostasis, being crucial in protection against infectious diseases.

Gastrointestinal, including bacterial and viral infections. Polysaccharide diet can change not only the members of the microbial community but also its function.

It is advisable not to ingest less than 25g of fiber daily, since otherwise microorganisms metabolize proteins or amino acids, which through fermentation produce SCFA.

The production of a greater number of SCFA occurs if we ingest fiber of plant origin; ground cereals being more useful. And it is also better to eat plants than animals. Finally, unground cereals also generate a greater number of fatty acids as well as starch.

Do not forget that the GM is a microbial organ, which works symbiotically, inside the host. Possessing the possibility of self-replication, for the purpose of its maintenance and repair. Likewise, the degradation of GM from nutrients produces bioactive metabolites, which bind to receptors, accelerating signaling and modulating host metabolism [48]. Diet is one of the most powerful modulators of the composition and function of the GM and has a significant effect on diseases. If the diet is rich in omega-3 and fiber, the production of SCFA increases, which improve membrane integrity, lipids, the immune system, the inflammatory response, glucose metabolism and blood pressure.

SCFA and intestinal microbiota transplantation: When IMT is performed, GM modulation can improve intestinal dysbiosis, as well as depressive behavior and cognitive impairment.

This criterion is indicated as preferential in the management of sepsis, since what antibiotics generate is damage to the microbiome. It is observed that *Proteobacteria* in septic patients increase, while *Firmicutes* decrease. It was described that mice with GM disorder were at risk of dying and IMT and SCFA could reverse the process, adjusting the abundance of bacteria such as *Firmicutes, Proteobacteria, Escherichia, Shigella* and *Lactobacillus*.

Lactic acid and fecal propionic acid decrease in chronic cerebral hypoperfusion, which are reintegrated after the administration of FMT and SCFA [49].

In relation to obesity and the impact that SCFA and GM have on obesity, there are diverse results. Meta-analyses indicate that obesity is associated with high levels of SCFA, but not with the abundance of GM.

Therefore, more studies are required to determine this process.

SCFA and retention enemas: In the use of therapies based on SCFA and biotics, in which some aspects are not clear, it is necessary to delve into numerous concepts. It is noted that rhubarb enema can increase the level of SCFA in nephrectomized rats, improving the damage of the intestinal barrier, and the presence of proteins in the intestinal tight junctions, reducing inflammation.

SCFA and its future therapeutic use: We will see in the future the use of biotics that, by modulating GM, and increasing SCFA (metabolites of M), will treat diseases. We must remember that SCFA adapt most of the immune cells of the intestine, in terms of their function and development. Fecal concentrations and the type of SCFA will be determined, to use those with greater possibility, together with FMT to treat autoimmune and infectious diseases; Clarifying to what extent the GM changes are a cause or consequence of the same disease. We will move from research in animals to protocols in humans, to determine the real context of the IMT, based on the discovery of microorganisms, which have not yet been discovered. Large-scale research on SCFA will increase as a therapeutic for diseases, especially neurological processes, achieved through international cooperation.

Knowledge of the mechanistic particularities of how SCFA act in different cells and organs will increase.

Conclusion

- The use of SCFA in the colon, together with diets, prevents diabetes in non-obese diabetic mice.
- In pregnancy, SCFA can protect against allergic airway disease.
- A tablespoon of psyllium plantago with water, on an empty stomach, not only helps improve constipation, but also generates SCFA.
- SCFA are capable of restoring imbalances in lipid and glucose metabolism.
- Butyrate and propionate regulate various functions in immune cells and can counteract the low-grade inflammatory state of the affected endothelium.

Conflicts of Interest

The authors declare that do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

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Volume 11 Issue 8 August 2024