SHORT-CHAIN FATTY ACIDS: KEY METABOLITES OF THE MICROBIOTA

AUTHORS:
Dirito Paola [1], Cevasco Eduardo [1], Cassará María Luz [2]
[1]Nutribiota Network , Buenos Aires, Argentina
[2]Pablo Cassará Foundation , Buenos Aires, Argentina
Correspondence: consultas@rednutribiota.com

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SUMMARY

Gut microbiota constitutes a complex metabolic ecosystem whose functional activity decisively impacts systemic homeostasis. Among its main metabolites are short-chain fatty acids (SCFAs)—acetate, propionate , and butyrate—products of the colonic fermentation of prebiotic fibers, which act as key mediators in communication between the gut and multiple organs.
Currently, short-chain fatty acids (SCFAs) are not considered mere energy sources for colonocytes , but rather biological regulators with structural, immunological, metabolic, and epigenetic functions . At the intestinal level, they strengthen the epithelial barrier by stimulating mucin production and reinforcing tight junctions, reducing permeability, and limiting the translocation of endotoxins such as lipopolysaccharide (LPS). They also modulate the immune response by promoting an anti-inflammatory profile and regulating gene expression through the inhibition of histone deacetylases .
The decrease in SCFA-producing bacteria is associated with dysbiosis , increased intestinal permeability, and low-grade chronic inflammation, a phenomenon implicated in the development of metabolic (obesity, type 2 diabetes, dyslipidemia), cardiovascular, renal, neurodegenerative, and immunological diseases.
Modulating the gut microbiota with prebiotics, such as inulin, and probiotics represents a therapeutic strategy aimed at increasing short-chain fatty acid (SCFA) production, restoring the integrity of biological barriers, and attenuating systemic inflammation. Understanding the role of SCFAs allows for the integration of metabolic, immunological, and degenerative alterations within a single pathophysiological framework, highlighting the gut microbiota as a central regulatory axis in human health.
This article constitutes a narrative review of the current scientific evidence on the role of short-chain fatty acids (SCFAs) as key metabolites of the gut microbiota .

KEYWORDS:

microbiota short-chain fatty acids chronic low-grade inflammation intestinal barrier intestinal permeability probiotics prebiotics inulin

INTRODUCTION

The microbiota is defined as the collection of microorganisms (bacteria, viruses, fungi, archaea, and protozoa) that inhabit our bodies. These trillions of microbes live in symbiosis, meaning they benefit each other. It's not just a single microorganism that matters in isolation, but the network they form: a complex metabolic and functional ecosystem.
Microorganisms colonize various anatomical sites, such as the skin, the gastrointestinal tract, the respiratory tract, the urogenital tract, and the mammary gland.
The microbiome is the complete set of genes of the microorganisms that make up the microbiota; in other words, their genetic makeup. Analyzing it allows us to identify which microorganisms are present and to understand their functional potential.
Ninety-five percent of microorganisms reside in the gastrointestinal tract. The large intestine has the highest microbial density and the most complex ecosystem. In contrast, the stomach has a very sparse microbiota due to the extreme acidity and digestive enzymes, which hinder the growth and survival of many microorganisms. The quantity and diversity of microorganisms gradually increase in the small intestine

, reaching their peak concentration in the large intestine.
Microbial density varies along the digestive tract depending on oxygen, pH, and the protective mucus layer:

Oxygen

- It decreases along the gastrointestinal tract.
- The colon is characterized by a predominantly anaerobic environment, a condition that favors the development of bacteria that ferment non-digestible substrates, such as prebiotic fibers.

Intestinal pH

- It gradually rises from the stomach to the colon.
- The acidic pH of the stomach limits microbial growth, while the higher pH of the colon favors greater microbial density and diversity.

Protective mucus layer

- It increases towards the large intestine.
- It plays a key role in protecting the intestinal epithelium and in maintaining and strengthening tight junctions, contributing to the integrity of the intestinal barrier.

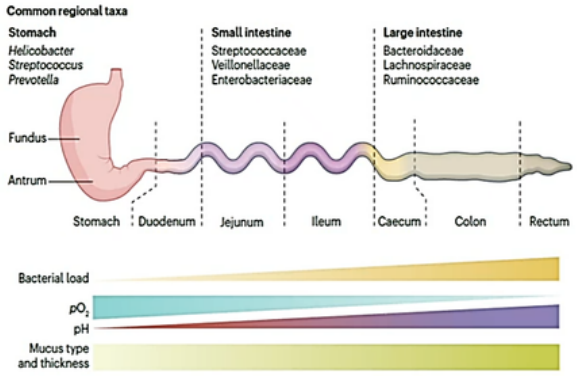


FIG.1:

McCallum, G., & Tropini, C. (2024). The gut microbiota and its biogeography. Nature reviews. Microbiology.

1. Role of the microbiota in health

Gut microbiota constitutes a complex metabolic and functional ecosystem that plays a central role in maintaining health. Many of its benefits derive from its metabolic activity and the substances it produces. Among these are short-chain fatty acids (SCFAs)—acetate, propionate , and butyrate—the main metabolites generated by the colonic fermentation of prebiotic fibers such as inulin.

1.1. Metabolic and digestive functions

It helps break down compounds that the human gut cannot process on its own. It is responsible for the fermentation of fibers and indigestible carbohydrates, producing short-chain fatty acids (SCFAs), which are key for colon health and energy metabolism.

1.2. Elimination of toxic compounds Many gut bacteria possess enzymes capable of metabolizing toxins, and some bacteria can physically bind to heavy metals, mycotoxins , or bacterial toxins, preventing their intestinal absorption. For example , Lactobacillus rhamnosus can bind to aflatoxins , reducing their bioavailability.

1.3. Protection against pathogens

Through exclusion mechanisms, it limits its growth by competing for nutrients and ecological niches. It also produces bacteriocins and organic acids with antimicrobial effects.

1.4. Immunological modulation

It stimulates the development of the innate and adaptive immune system, influencing both the maturation of immune cells and the production of cytokines, and also prevents excessive inflammatory responses.
Innate lymphoid cells (ILCs), located in the intestinal epithelium, are involved in maintaining appropriate immune responses to various microorganisms, enhancing adaptive immunity, and regulating inflammation and tissue repair in the intestinal mucosa. ILC functions are also regulated by the gut microbiota.
Interactions between the gut microbiota and cells of the innate immune system occur through microbial pattern recognition receptors (TLRs, NODs inflammasomes , etc.) or metabolites (tryptophan, indoles , butyrate) produced by the microbiota. These stimuli activate both the barrier functions described above and the synthesis of other mediators (cytokines, co -stimulatory molecules, etc.) that regulate the response of specialized immune cells in the gut-associated lymphoid tissue, coordinating their actions to prevent pathogen invasion and promote the development of tolerance to harmless antigens.

1.5. Maintenance of the intestinal barrier The gut microbiota exerts a trophic effect on the intestinal epithelium, promoting the proliferation of epithelial cells and the maintenance of tight junctions. The microbiota is also key to the production of the mucus layer that protects the intestinal epithelium, thus promoting its integrity.

Bioactive and neuroactive compounds

The intestinal microbiota actively participates in the synthesis of essential bioactive compounds , such as B complex vitamins and vitamin K, which are fundamental for coagulation and metabolism.

Furthermore, it is involved directly or indirectly in the synthesis of neuroactive compounds , including various neurotransmitters (serotonin, dopamine, γ-aminobutyric acid [GABA], etc.) that influence brain functions, behavior, metabolism, and immunity.

The influence of the gut microbiota on serotonin synthesis is particularly relevant, as up to 90% of this neurotransmitter—which performs key functions both centrally and peripherally—is synthesized in the gut. At the level of the central nervous system, serotonin regulates mood, appetite, and cognitive functions; at the intestinal level, it regulates inflammation and motility. The gut microbiota can be involved both in reducing serotonin levels, through its ability to metabolize tryptophan, which acts as a precursor, and in its production, by stimulating the expression of the genes (tryptophan 1- hydroxylase) involved in its synthesis. Microbial modulation of serotonin biosynthesis and the expression of its receptors mitigates intestinal inflammation and depressive symptoms.

Furthermore, several gut bacteria encode tyrosinases capable of transforming tyrosine into L-dihydroxyphenylalanine (L-DOPA), which in turn leads to the synthesis of catecholamines such as dopamine, norepinephrine, and epinephrine. Dopamine plays an important role in the reward system, which is involved in regulating eating behavior and mood.

GABA, on the other hand, is produced by various intestinal bacteria through the decarboxylation of glutamate by the enzyme glutamate decarboxylase , which is involved in tolerance to acidic pH and the maintenance of bacterial intracellular homeostasis. GABA is an important neurotransmitter with inhibitory effects in the brain, and its dysfunction is implicated in diseases such as autism and schizophrenia.

2. Short-chain fatty acids: key metabolites of microbial fermentation

Although for years SCFAs were considered simply as an energy source for colonocytes , today they are recognized as key mediators in the communication between the gut microbiota and the organism, playing a central role in the maintenance of local and systemic homeostasis.

2.1. Role of SCFAs on the intestinal barrier

The intestinal mucosa is lined with a mucus layer rich in mucins that acts as a physical barrier against bacteria and viruses, bile acids, digestive enzymes, and dietary irritants. This layer keeps bacteria separate from the epithelium, limits pathogen adhesion, reduces the translocation of bacterial endotoxins such as lipopolysaccharide (LPS), and decreases unnecessary inflammatory activation.

Butyrate is the main energy substrate for colonocytes and the most potent regulator of mucus secretion, contributing to the reinforcement of tight junctions. Without this mucus layer, the epithelium would be highly vulnerable to injury and erosion. The production of secretory immunoglobulin A (IgA) represents another key defense mechanism, as it limits bacterial access to the mucosa by neutralizing them and promoting their elimination. Likewise, macrophages phagocytize and eliminate any microorganisms that may penetrate the intestinal epithelium. Together, this structural and immunological network maintains the functional integrity of the intestinal barrier.

In addition to maintaining the structural integrity of the intestinal barrier, SCFAs help lower luminal pH , creating a less favorable environment for pathogenic microorganisms. They also stimulate intestinal motility and actively modulate the immune response, reducing the production of pro-inflammatory cytokines and promoting an anti-inflammatory immune profile.

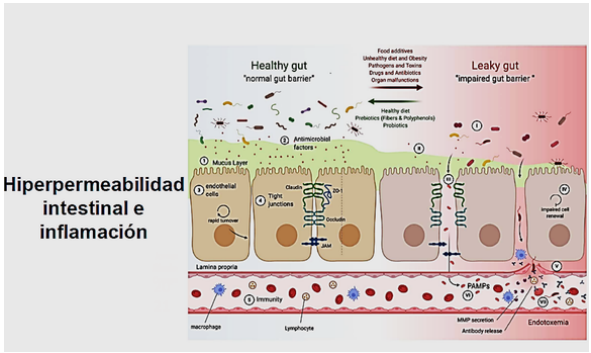


FIG. 2: Journal of Endocrinology 248, 2; 10.1530/JOE-20-0473

2.1.1. Impact on Intestinal Permeability

When the number of SCFA-producing bacteria decreases, this defensive network weakens. The epithelial barrier loses cohesion, its integrity is compromised, and the immune response becomes dysregulated, increasing intestinal permeability and facilitating the passage of bacteria and their components into the systemic circulation.

Among these components, LPS, a molecule that forms part of the outer membrane of Gram-negative bacteria , activates recognition receptors on immune cells, promoting the production of pro-inflammatory cytokines . This process favors metabolic endotoxemia and the establishment of a persistent, low-grade systemic inflammatory state.

This type of chronic, low-grade inflammation is associated not only with metabolic alterations but also with biological aging. Chronic inflammation can affect physiological processes such as muscle protein synthesis, contributing to sarcopenia and frailty, and constitutes a common pathophysiological axis in multiple chronic diseases.

Taken together, the alteration of SCFAs constitutes a central mechanism linking intestinal dysbiosis to the development and progression of highly prevalent metabolic, immunological, and degenerative diseases. From this intestinal starting point, multiple systemic clinical manifestations can be understood.

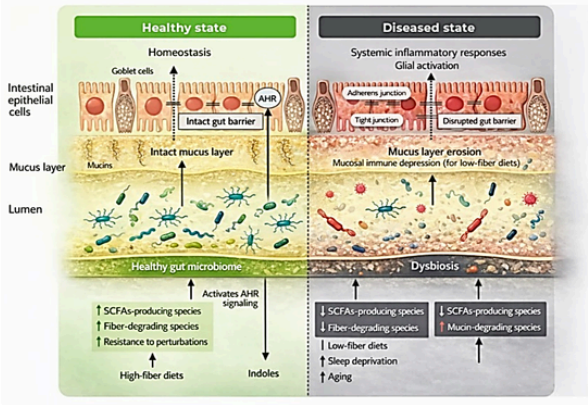


FIG. 3: Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, Yeow SH, Foo JB, Ong YS, How CW, Khaw KY. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduct Target Ther . 2024 Feb 16;9(1):37. doi :10.1038/s41392-024-01743-1. PMID: 38360862; PMCID: PMC10869798

Gut microbiota functions as a dynamic ecosystem whose stability depends on the quantity and diversity of its microbes, and particularly on the production of short-chain fatty acids (SCFAs). When this balance is disrupted, a state of dysbiosis develops, characterized by the loss of beneficial bacteria and a reduction in key metabolites. This not only compromises the integrity of the intestinal barrier but also promotes permeability and the translocation of bacterial components, in addition to activating systemic inflammation. From this point of intestinal disruption, a biological environment conducive to the development of highly prevalent metabolic, immunological, and degenerative diseases begins to take shape.

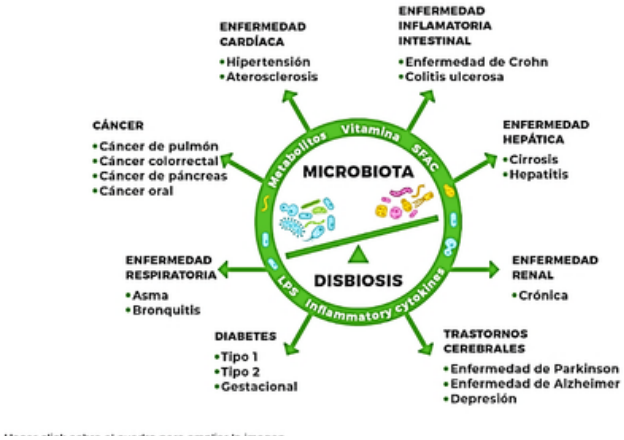


FIG. 4: Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, Zhu D, Koya JB, Wei L, Li J, Chen ZS. Microbiota in health and diseases. Signal Transduct Target Ther . 2022 Apr 23 ;7(1):135. doi : 10.1038/s41392-022-00974-4 . PMID: 35461318; PMCID: PMC9034083)

2.2. Role of SCFAs on metabolism

Dysbiosis , characterized by a reduction in SCFA-producing bacteria, promotes a systemic inflammatory environment that simultaneously impacts metabolic regulation and cardiovascular function.

The sustained reduction of these metabolites is associated with the development and progression of obesity, type 2 diabetes, dyslipidemia , fatty liver, hypertension, atherosclerosis and cardiovascular disease, creating a scenario in which metabolic and vascular alterations coexist and reinforce each other.

Role of the AGCC:

- They stimulate the secretion of incretin peptides , such as Glucagon-like peptide-1 (GLP-1) which improves glucose-dependent insulin secretion, slows gastric emptying and reduces postprandial blood glucose, and Peptide YY (PYY) which increases satiety and helps reduce calorie intake.
- They modulate hepatic gluconeogenesis, contributing to the regulation of glucose production in the liver and promoting the maintenance of blood glucose levels within physiological ranges.
- They promote the oxidation of fatty acids, which promotes better use of fatty acids as an energy source, contributing to greater metabolic balance and less lipid accumulation.

- They regulate lipolysis and the metabolism of adipose tissue, participating in the control of the release and storage of fatty acids, helping to maintain an adequate energy balance.
- They contribute to the regulation of cholesterol, promoting its hepatic uptake from the bloodstream and reducing its plasma levels.
- When the production of SCFAs decreases, this regulatory framework is altered, favoring insulin resistance, expansion of inflamed adipose tissue, metabolic dysregulation, and amplification of the systemic inflammatory state.

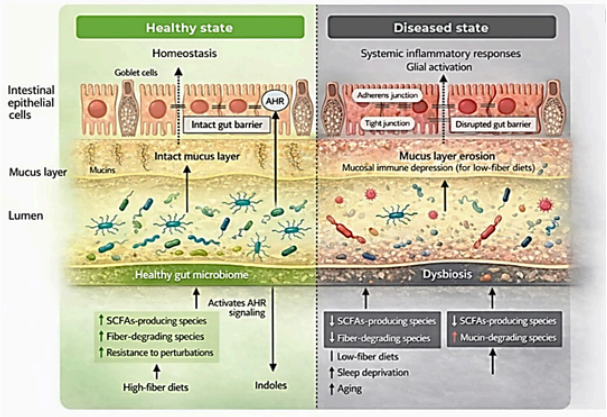
2.2.1. Cardiovascular impact

The same inflammatory environment that contributes to metabolic deterioration also affects the cardiovascular system. Sustained reduction in short-chain fatty acids (SCFAs) promotes endothelial dysfunction and vascular inflammatory activation, facilitating progressive deterioration and increasing cardiovascular risk.

Furthermore, SCFAs exert signaling functions that influence myocardial contractility, blood pressure regulation, and autonomic nervous system activity. Their reduction can alter these control mechanisms, amplifying their impact on cardiac and vascular function.

2.2.2. Impact on renal function

Short-chain fatty acids (SCFAs) play a central role in the gut-kidney axis, acting as mediators of renal protection. They help reduce inflammation, modulate blood pressure, strengthen the intestinal barrier, and limit the passage of uremic toxins into the systemic circulation. In this way, they attenuate low-grade chronic inflammation and promote the preservation of renal function.



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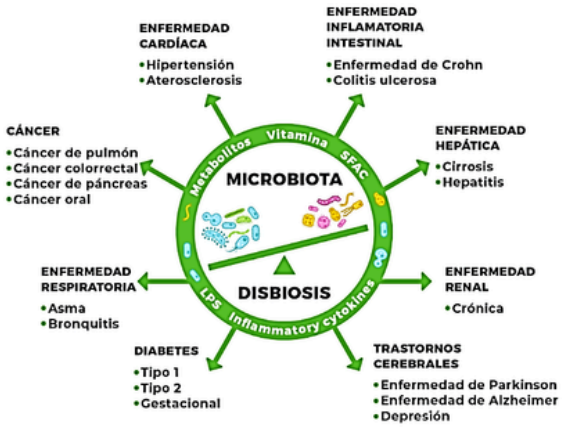

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In chronic kidney disease, the accumulation of urea alters the gut microbiota and promotes a dysbiotic profile with a decrease in short-chain fatty acid (SCFA)-producing bacteria. This alteration weakens the intestinal barrier and increases permeability, facilitating the passage of uremic toxins—such as indoxyl sulfate and TMAO—which promote systemic inflammation and accelerate kidney deterioration.

Prebiotics, such as inulin, selectively enrich the gut microbiota by increasing short-chain fatty acid (SCFA) producing bacteria. Through this mechanism, they promote the strengthening of the intestinal barrier and modulate systemic inflammation, reduce uremic toxins, and improve the glomerular filtration rate.

2.3. Role of SCFAs on the central nervous system

The gut, microbiota , and brain form a bidirectional communication system known as the gut-brain axis. Short-chain fatty acids (SCFAs) act as key mediators in this network, regulating the immune response, the integrity of biological barriers, and the function of the central nervous system .

Role of the AGCC:

- In the intestine, they reinforce the physiological structure of the mucosa by stimulating mucin production, strengthen epithelial tight junctions, and reduce the translocation of endotoxins such as LPS, whose arrival in the bloodstream can promote neuroinflammation .
- They exert a protective effect on the blood- brain barrier (BBB) by reinforcing its integrity, decreasing its permeability, and limiting the entry of pro-

inflammatory molecules into the central nervous system.

- They modulate the activity of microglia , the main innate immune cells of the central nervous system, responsible for essential functions such as neurogenesis , angiogenesis, synaptic transmission, myelin integrity, and the removal of apoptotic neurons and cellular debris. When these functions are altered, the progression of neurodegenerative processes is favored.
- Butyrate acts as an inhibitor of histone deacetylases (HDACs), an enzyme that regulates gene expression through epigenetic mechanisms . By inhibiting HDACs, it promotes a more open chromatin structure, encouraging the expression of genes with anti-inflammatory and neuroprotective functions . Through this mechanism, short-chain fatty acids (SCFAs) contribute to reducing chronic low-grade neuroinflammation and maintaining a more favorable brain environment for memory and learning.

2.3.1. Impact on neurodegenerative diseases

The endotoxin LPS, a component of the cell wall of Gram-negative bacteria, promotes the aggregation of the β- amyloid peptide (Aβ), derived from the amyloid precursor protein , which is capable of crossing both the intestinal barrier and the blood-brain barrier (BBB). Intestinal dysbiosis and increased intestinal permeability facilitate the passage of LPS into the systemic circulation, activating the peripheral immune system, enhancing neuroinflammation , and promoting the deposition of amyloid proteins in the central nervous system, thus contributing to the pathogenesis of Alzheimer's disease.

More than 50 microbial metabolites have been positively associated with accelerated cognitive decline and earlier age of onset. Among these metabolites is trimethylamine -N-oxide (TMAO), derived from the microbial metabolism of dietary animal fats. TMAO has been shown to be present in the human central nervous system, further supporting evidence that microbial metabolites migrate to the brain. The systemic and neurological impact of these metabolites is largely dependent on the integrity of the intestinal barrier. Under physiological conditions of eubiosis , a functional intestinal barrier limits their passage into the systemic circulation. Conversely, altered intestinal permeability facilitates the translocation of metabolites such as TMAO, allowing them to reach the central nervous system and contributing to the pathogenesis of Alzheimer's disease.

In Parkinson's disease, gut dysbiosis also plays a central role. The increase in Gram-negative bacteria, the greater release of LPS, and intestinal permeability promote chronic inflammation and oxidative stress, conditions that encourage the misfolding and aggregation of α- synuclein in the enteric nervous system. This pathological protein can spread to the brain via the vagus nerve and progressively disseminate, particularly affecting dopaminergic neurons in the substantia nigra. This process is associated with persistent microglial activation, disruption of the blood-brain barrier (BBB), and progression of both motor symptoms (bradykinesia , rigidity, tremor) and non-motor manifestations, including gastrointestinal disorders and cognitive decline.

Both Alzheimer's and Parkinson's diseases have been shown to reduce butyrate-producing bacteria and lower concentrations of short-chain fatty acids (SCFAs), associated with increased microglial activation, disruption of the blood-brain barrier (BBB), and progression of synaptic damage. Since SCFAs modulate gene expression and limit inflammatory activation, their decrease not only reflects dysbiosis but also the loss of a fundamental regulator of brain stability and a critical point in the evolution of neurodegenerative diseases. Furthermore, reduced levels of SCFAs have been linked to mood disorders, particularly depression, where low-grade systemic inflammation and BBB dysfunction play a significant role.

2.4. Role of SCFAs on the immune system

In immunological diseases, intestinal dysbiosis promotes the establishment of a persistent inflammatory state that compromises systemic homeostasis. The decrease in short-chain fatty acids (SCFAs) weakens the regulatory mechanisms of the immune response and alters the integrity of the intestinal barrier, promoting a sustained pro-inflammatory profile .

Increased intestinal permeability facilitates the translocation of bacterial components, especially LPS, into the bloodstream. These are recognized by innate immune receptors, activating intracellular signaling cascades that induce the transcription and release of pro-inflammatory cytokines . This sustained activation increases oxidative stress and perpetuates a state of chronic low-grade inflammation that can affect distant organs.

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Role of the AGCC:

- They contribute to maintaining the intestinal barrier. They promote mucin production and strengthen the mucus layer that covers the epithelium, reinforcing the structural integrity of the mucosa. By preserving this physical and functional barrier, they decrease intestinal permeability and limit immune activation secondary to microbial translocation.
- They modulate the intestinal and systemic immune response. SCFAs help maintain a balance between activation and control of inflammation. They promote an effective response to stimuli without it becoming excessive or persistent, preventing the damage associated with chronic inflammation.
- They promote an anti-inflammatory profile by stimulating the production of cytokines with an anti-inflammatory effect and reducing the expression of pro-inflammatory cytokines . They exert a systemic immunomodulatory effect .Its regulatory action on the inflammatory profile extends beyond the intestine, influencing the immune response in different tissues.
- They regulate gene expression through epigenetic mechanisms . Butyrate, and to a lesser extent other SCFAs, act as HDAC inhibitors, modulating chromatin structure and promoting the expression of genes with anti-inflammatory, antiproliferative , and pro-apoptotic functions . This mechanism helps limit chronic inflammation and is associated with potential anticarcinogenic and antitumor effects.

In immunological pathologies, SCFAs play a crucial role as modulators of the inflammatory response. Their ability to balance cytokine production, preserve the integrity of the intestinal barrier, and

limit increased permeability—thus reducing microbial translocation and sustained immune activation—makes them key elements for maintaining immune homeostasis .

When their production decreases, the epithelial barrier weakens, intestinal permeability increases, and inflammatory activation is perpetuated. This scenario favors the progression of inflammatory bowel and respiratory diseases (asthma), as well as the creation of a microenvironment conducive to cellular alterations associated with tumor development. Thus, SCFAs are established as key regulatory metabolites of immunological processes linked to chronic inflammation.

3. Strategies to increase the production of AGCC

3.1 Prebiotics

Prebiotics are selectively fermentable fibers that modulate the composition and activity of the gut microbiota, promoting a more favorable microbial environment and increasing the production of SCFAs.

Difference between fiber and prebiotic fiber

Fiber is defined as carbohydrate polymers containing ≥ 10 monomeric units that resist digestion by endogenous enzymes in the small intestine. Fiber can be divided into soluble and insoluble fiber.

Although all prebiotics are fiber, not all fiber is prebiotic.

For a fiber to be considered prebiotic, it must meet the following characteristics:

-Resisting gastric acidity and enzymatic hydrolysis (it is not affected by enzymes present in saliva, as well as pancreatic and intestinal enzymes) and absorption in the upper gastrointestinal tract.

-Selectively stimulate the growth and/or activity of beneficial intestinal bacteria that contribute to health and well-being.

-It must be fermented by the intestinal microbiota .

Inulin is one of the most studied and recognized prebiotic soluble fibers. It is characterized by its bifidogenic effect , as it selectively stimulates the growth of Bifidobacteria , and its colonic fermentation leads to the production of short-chain fatty acids (SCFAs) .

3.1.1. Health Benefits of INULIN

-Enriches the intestinal microbiota :

Inulin reaches the colon intact and is fermented primarily by species of the genera Bifidobacterium and Lactobacillus , increasing their abundance. Furthermore, Bifidobacteria and Lactobacilli compete for nutrients and adhesion sites on the mucosa, limiting the space available for pathogens and thus reducing their proliferation. In this way, inulin contributes to a balanced and protective intestinal ecosystem.

-Produces SCFAs: acetate, butyrate and propionate :

The fermentation of inulin by intestinal bacteria produces short-chain fatty acids (SCFAs) as its main metabolites, which are the primary mediators of inulin's beneficial effects. These metabolites improve the intestinal barrier by strengthening tight junctions and reducing intestinal permeability. SCFAs lower intestinal pH, creating a less favorable environment for pathogenic microorganisms. SCFAs also stimulate intestinal motility and have an anti-inflammatory effect by regulating the expression of pro-inflammatory cytokines . Systemically, they act on the metabolic balance of glucose and lipids.

-Improves intestinal transit, reduces constipation and improves stool consistency.

Short-chain fatty acids (SCFAs) stimulate intestinal motility. Inulin fermentation increases bacterial biomass, which increases stool volume. Furthermore, inulin retains water, promoting softer stools that are easier to pass. Overall, this improves gastrointestinal transit and bowel regularity.

-Improves the absorption of nutrients, especially key minerals for bone health.

The short-chain fatty acids (SCFAs) produced during inulin fermentation lower the pH of the intestinal lumen , increasing the solubility of minerals such as calcium, magnesium, and iron , thus facilitating their absorption. Inulin supplementation has been shown to increase intestinal absorption of calcium and magnesium, key nutrients for bone health , especially relevant in postmenopausal women and other populations with higher requirements. Clinical studies have demonstrated increased calcium absorption when inulin supplements were used.

-Improves anthropometric parameters

Because inulin is not digestible, it delays gastric emptying, increasing the secretion of satiety hormones and improving anthropometric parameters.

Studies have shown that high doses administered over a prolonged period lead to an increase in Bifidobacteria , which is associated with improvements in these values, especially body weight and body mass index.

Short-chain fatty acids (SCFAs) play a crucial role in energy metabolism; through their participation in various pathways, they help regulate appetite.

-It increases glucose metabolism, reducing insulin

levels.

Inulin slows down the absorption of glucose in the intestine, helping to regulate the rise in blood glucose levels after meals, thus promoting glycemic homeostasis. Bifidogenic effect has been associated with increased insulin sensitivity and improved blood insulin levels. Propionate , butyrate, and especially acetate activate receptors on pancreatic beta cells, regulating insulin secretion and improving glucose homeostasis.

-Positive impact on the lipid profile.

Inulin can interfere with the absorption of dietary fat and cholesterol, helping to lower blood levels of low-density lipoprotein (LDL).

At different doses, inulin can reduce total cholesterol, LDL, and triglyceride levels in the blood, since short-chain fatty acids (SCFAs) can regulate lipogenesis through various mechanisms.

Furthermore, it can increase serum levels of high-density lipoprotein (HDL) when administered over a prolonged period.

-Beneficial effects on inflammation and immune function

Studies show that inulin significantly increases different species of Bifidobacteria , notably B. longum , B. teenageis , and B. angulatum . Bifidobacteria have well-documented effects on modulating inflammation and reducing inflammatory markers, both in the gut and systemically.

pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β.

-Increased levels of anti-inflammatory cytokines such as IL-10.

-Reduction of C-reactive protein (CRP), a systemic inflammatory marker.

Inulin, by lowering the pH of the colon and improving the biomass of the microbiota, hinders and prevents the development of pathogenic species, significantly reducing the number of populations of species belonging to the genus Clostridium , which leads to a reduction in inflammation and improved overall digestive health and nutrient absorption.

-Favorable effects on chronic kidney disease

In chronic kidney disease, the accumulation of urea alters the intestinal microbiota and increases the permeability of the epithelial barrier, favoring the entry of uremic toxins such as indoxyl sulfate , p- cresol and TMAO, compounds that promote endotoxemia and systemic inflammation.

Modifying the gut microbiota using prebiotics such as inulin is proposed as a complementary therapeutic strategy to reduce the production of uremic toxins of intestinal origin and inflammation.

Clinical studies have shown that inulin supplementation can:

- To favorably modify the composition of the intestinal microbiota.
- To reduce serum uric acid levels and increase its fecal degradation in patients with renal insufficiency.
- indole production in patients undergoing peritoneal dialysis.
- Decrease serum levels of indoxyl sulfate .
- Improve the glomerular filtration rate.
- Reduce levels of high-sensitivity C-reactive protein.

3.2. Probiotics

Probiotics are live microorganisms recognized as normal inhabitants of the human gut that, when ingested, modulate the microbiota and promote the fermentation of non-digestible substrates, contributing to increased short-chain fatty acid (SCFA) production. While SCFAs represent one of the main mechanisms by which the microbiota exerts its effects, probiotics also provide independent benefits, including direct modulation of the immune system, competition with pathogens, production of bioactive metabolites , and regulation of intestinal barrier function.

Probiotics must be administered in adequate amounts: at least one billion colony-forming units (CFU) are recommended daily, and they must be accurately identified at the genus/species/subspecies level, as their effects are strain-dependent. When correctly identified strains are used at appropriate concentrations, their consumption is considered safe.

CONCLUSION:

Short-chain fatty acids (SCFAs) can no longer be understood as mere byproducts of bacterial fermentation. They are true biological metabolites that facilitate communication between the microbiota and the organism, regulating metabolic, immunological, and structural processes that support systemic health.

When their production is preserved, they contribute to energy balance, the integrity of biological barriers, and the control of inflammation, maintaining a stable and functional environment. But when dysbiosis reduces their availability, a delicate regulatory system breaks down: the integrity of the intestinal barrier decreases, permeability increases, the passage of microbial

components into the bloodstream (LPS) is facilitated, chronic low-grade inflammation emerges, metabolism is altered, immunological mechanisms are weakened, and degenerative processes are favored.

Thus, a progressive loss of structural and functional integrity originates in the gut, where increased permeability acts as a tipping point between local microbiota alteration and its systemic consequences. Understanding the role of SCFAs allows us to integrate metabolic, immunological, and degenerative alterations within a single pathophysiological framework, revealing that multiple chronic diseases share a common origin in the loss of homeostasis mediated by dysbiosis and the decrease in its regulatory metabolites.

In short, the gut is not just a digestive organ, but a systemic regulatory center. Short-chain fatty acids (SCFAs), far from being mere metabolites, are key players in the delicate balance between health and disease.

Understanding the role of SCFAs allows us to integrate multiple metabolic, immunological, and degenerative alterations within a single pathophysiological framework. However, modulation of the microbiota through prebiotics and probiotics transcends SCFA production, involving independent immunological, structural, and molecular mechanisms that broaden its biological impact. Thus, preserving microbial homeostasis implies maintaining both SCFA production and the microbiota 's multiple independent regulatory functions, the disruption of which contributes to the development of chronic diseases.

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