

Review on Exploring the Role of Short-Chain Fatty Acids in Neuroinflammation: Mechanisms and Therapeutic Perspectives

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ABSTRACT

Alzheimer's disease, Parkinson's disease, multiple sclerosis, and autism spectrum disorders are only a few of the neurodegenerative and neuropsychiatric conditions that are significantly influenced by neuroinflammation. The gut microbiota produces Short-Chain Fatty Acids (SCFAs), mainly acetate, propionate, and butyrate, by fermentation of dietary fibers. These are among the new modulators of neuroinflammation, have attracted significant scientific interest. This review critically examines the multifaceted mechanisms through which SCFAs influence neuroinflammatory processes. We explore how SCFAs modulate microglial activation and polarization, strengthen blood-brain barrier integrity, and regulate peripheral immune responses, often via G-protein-coupled receptor activation and histone deacetylase inhibition. While generally exhibiting neuroprotective and anti-inflammatory effects, SCFAs may also exert proinflammatory actions under specific pathological or concentration-dependent contexts, highlighting their dualistic role. Additionally, the efficacy of SCFAs is shaped by diet, gut microbiota composition, disease state, and interindividual variability. We discuss therapeutic strategies aimed at leveraging SCFA biology, including dietary interventions, prebiotics, probiotics, engineered microbial consortia, and novel delivery systems designed to enhance colonic and systemic SCFA availability. In order to maximize SCFA-based therapies, the review concludes by highlighting important research gaps, highlighting the necessity of extensive human clinical trials, the incorporation of multi-omics techniques, and the creation of precision medicine or tailored nutrition plans. Novel, microbiota-targeted treatments for neurodegenerative and neuroinflammatory diseases may be made possible by an understanding of the dynamic interactions between gut microbiota-derived SCFAs and neuroinflammation.

Keywords: Short-chain Fatty Acids, Neuroinflammation, Gut-brain Axis, Microbiota, Neurodegenerative Diseases.

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INTRODUCTION

Overview of Neuroinflammation

Neuroinflammation is now recognized to play a significant role in the onset and progression of many neurological and psychiatric disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, depression and autism spectrum disorders. Unlike the common inflammatory reaction that occurs in the peripheral tissue, the microglia and astrocyte cells which are resident brain immune cells as well as peripheral immune cells that infiltrate the brain, the Central



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Nervous System (CNS), under certain disease conditions show well-ordered crosstalk with neuroinflammation being characterized.¹ Neuroinflammation is primarily initiated by microglia - the brain's resident immune cells - which transition from a resting, surveillance state to an activated state upon insult (injury, infection) or insults (misfolded proteins, like β -amyloid or α -synuclein). This activation leads release of different proinflammatory mediators such pro-cytokines (e.g., TNF- α , IL-1 β , IL-6), chemokines, privative oxygen species and nitric oxide. Acute brain inflammation can be necessary for protection, acting to clear harmful agents and cellular debris, however, if neuroinflammation becomes chronic or uncontrolled, it can result in synapse dysfunction, neuronal loss and disease progression. Furthermore, neuroinflammation is inextricably linked to BBB disruption that permits peripheral immune cells to enter the CNS and amplify inflammation. Adds and refs - Parker ednuxus 12:53, 24 June 2005 (UTC) Neuroinflammation is primarily initiated by microglia - the brain's resident immune cells - which transition from a resting, surveillance state to an activated state upon insult (injury, infection) or insults (misfolded proteins, like β -amyloid or α -synuclein). This activation leads to the release of different proinflammatory mediators such as pro-cytokines (e.g., TNF- α , IL-1 β , IL-6), chemokines, privative oxygen species, and nitric oxide. Secondly, the outcome of neuroinflammation largely depends on the balance between pro-inflammatory and anti-inflammatory responses. This balance is influenced by the activity of microglia (particularly the M2-like phenotype), astrocytes, and adaptive immune cells, all of which must reach a dynamic equilibrium.²

Gut Microbiota and the Production of Short Chain Fatty Acids (SCFAs)

The human GI tract is inhabited by a complex and metabolically active microbial consortium called the gut microbiota. This complex ecosystem of bacteria, archaea, viruses, and fungi plays a major role in health by facilitating digestion, synthesising vital vitamins, modulating immune responses and shaping numerous aspects of metabolism. One of the major bioactive metabolites generated by these microbes are Short-Chain Fatty Acids (SCFAs), the most abundant and functionally significant of which include acetate (C2), propionate (C3) and butyrate (C4).³ SCFAs are primarily produced through the anaerobic fermentation of non-digestible dietary fibers, resistant starch and certain oligosaccharides by commensal gut bacteria, most notably from phyla Firmicutes and Bacteroidetes. The particular proportion of SCFAs generated is determined by the microbial populations in the system, as well as the concentration of fermentable substrates where, in general, acetate is the most abundant and propionate and butyrate are less so lacking. Following synthesis, SCFAs are rapidly taken up by colonocytes via monocarboxylate transporters. They may exert their effect locally in the gut or enter the systemic circulation, which might affect an array of other

distant organs, including brain.⁴ In the colon, butyrate is a major energy substrate for proliferation of intestinal epithelial cells and has substantial effects on the preservation of mucosal integrity and regulation of inflammation. In contrast, acetate and propionate are absorbed into the blood and delivered to the liver through the portal vein, servicing critical metabolic processes such as gluconeogenesis and lipid metabolism.⁵ A fraction of such SCFAs escapes hepatic metabolism and reaches the systemic circulation, from which they can access the Blood-Brain Barrier (BBB) by passive diffusion as well as specific transport systems. Besides their metabolic functions, SCFAs function as signaling molecules via the G protein-coupled receptors GPR41 (FFAR3) and GPR43 (FFAR2) as well as Histone Deacetylases (HDACs), altering gene expression. These processes allow SCFAs to control immune response regulation, induce the differentiation of tolerogenic Tregs, inhibit the inflammatory cytokines, and to help maintain the integrity of the BBB. Because of the multitude of (potentially beneficial) effects, there is increasing scientific interest about the SCFAs as mediators to influence neuroinflammation and inhibit neurological diseases by gut microbiota products.⁶

Anaerobic Fermentation of SCFAs

Anaerobic fermentation refers to the process by which gut microbiota, primarily bacteria, break down non-digestible carbohydrates (such as dietary fibers, resistant starches, and certain oligosaccharides) in the absence of oxygen. This fermentation occurs mainly in the colon, where the microbial community, including bacteria from the Firmicutes and Bacteroidetes phyla, ferment these substrates into Short-Chain Fatty Acids (SCFAs), such as acetate, propionate, and butyrate. These SCFAs are produced through different metabolic pathways, such as the acetyl-CoA pathway for acetate, the succinate and acrylate pathways for propionate, and the butyryl-CoA: acetate CoA-transferase pathway for butyrate.

This fermentation process plays a critical role in maintaining gut health, modulating immune function, and influencing systemic inflammation, including neuroinflammation. The produced SCFAs are absorbed by colonocytes and may enter the systemic circulation, where they exert a range of biological effects, including their ability to influence the brain through the gut-brain axis.

Scope and Objectives of the Review

As appreciation of the gut-brain axis (a bidirectional communication pathway between the GIT and CNS) grows, the potential role of SCFAs and their ability to impact neuroinflammation offers a fascinating frontier in both the fields of neuroscience and microbiome research. Although preclinical and clinical studies have contributed significantly the mechanism(s) by which SCFA regulate neuroinflammatory pathways is less clear and often conflicting dependent on disease context and experimental models employed.⁷

This review provides a critical overview of the current evidence on the role of SCFAs in neuroinflammation. Specifically, this review summarizes the production and systemic distribution of Short-Chain Fatty Acids (SCFAs), emphasizing the dietary, microbial, and host factors that influence their availability and biological function within the gut-brain axis. It explores the mechanistic pathways through which SCFAs modulate microglial activation, reinforce blood-brain barrier integrity, regulate peripheral immune responses, and affect gene expression via epigenetic mechanisms in the central nervous system. The review examines the dual roles of SCFAs-highlighting both their protective and potentially harmful effects across different neurological disease contexts-and discusses emerging therapeutic strategies, including dietary interventions, probiotics, and synthetic SCFAs formulations, while acknowledging challenges in clinical translation. By identifying key knowledge gaps and proposing future research directions, this work aims to clarify whether modulating SCFAs levels through diet, microbiome engineering, or pharmacological approaches can be a viable strategy to prevent or treat neuroinflammatory and neurodegenerative diseases, ultimately integrating mechanistic insights with translational perspectives to advance the field of microbiota-brain interactions.

Major SCFAs and Their Microbial Origins

SCFAs are a series of saturated aliphatic organic acids with fewer than six carbon atoms, that include acetate (C2), propionate (C3) and butyrate (C4) as the easiest and most prevalent and physiologically active SCFAs in human beings. They are mainly produced in the colon by the anaerobic fermentation of dietary fibers, resistant starches, and certain oligosaccharides by the intestinal microbiota. The actual SCFAs composition within the gut lumen is dependent on the diet substrate content and metabolic capacities of resident bacterial communities.⁸ Acetate is primarily produced by most enteric bacteria as a common end-product of carbohydrate fermentation, including members of the genera *Bifidobacterium*, *Lactobacillus*, and many *Bacteroides* species. Propionate is mainly generated by bacteria utilizing the succinate and acrylate pathways, such as *Bacteroides*, *Veillonella*, and *Dialister*. Butyrate production is largely attributed to specific members of the Firmicutes phylum, particularly *Faecalibacterium prausnitzii*, *Roseburia* spp., and *Eubacterium rectale*. These bacteria metabolize dietary fibers via the butyryl-CoA:acetate CoA-transferase pathway, leading to the synthesis of butyrate.⁹

In addition to the major SCFAs, smaller amounts of other short-chain fatty acids such as valerate (C5), caproate (C6), and branched-chain fatty acids like isobutyrate and isovalerate are also produced, primarily through the fermentation of amino acids from dietary proteins. Although these SCFAs are present at lower concentrations, they may still exert important local or systemic biological effects, many of which are not yet fully understood. The amounts and ratios of SCFAs are strongly impacted by the gut

microbiota population composition/diversity. Numerous factors - age, genetics, antibiotic usage, health conditions, and perhaps most of all diet - help determine the composition of microbial communities. Especially the quantity and quality of dietary fiber have a marked effect on SCFAs production. High-fiber, plant-based diets support the growth of butyrate-producing bacteria but low-fiber or high-protein diets can result in decreased overall SCFAs production.¹⁰

Absorption, Transport, and Bioavailability

After colon production, SCFAs play crucial local effects and a part of them are absorbed into the systemic circulation. SCFAs can be absorbed by the intestinal epithelium through two main ways: passive diffusion in the non-ionized form and active transport through Monocarboxylate Transporters (MCTs), especially for MCT1 and MCT4. Sodium-Coupled Monocarboxylate Transporter 1 (SMCT1) is also involved in SCFAs transport in colonocytes. One of these short-chain fatty acids, butyrate, is in fact the most important energy source of colonocytes, which it provides with up to 70% of their energy. This local use supports the integrity of the epithelial barrier, and stimulates expression of tight junction proteins, exerting an anti-inflammatory action by inhibiting NF- κ B signaling pathways. Less metabolized by colonocytes, propionate and acetate cross the epithelium into the portal circulation and then are carried to the liver. In the liver, propionate is primarily cleared and metabolized as a gluconeogenesis substrate, whereas acetate is accessible to lipogenesis. A large fraction of its constituents escapes hepatic first-pass metabolism and enter directly into the systemic circulation, thus increasing peripheral SCFAs pools. Butyrate is mostly utilized in the intestine but may also enter the liver and, to a limited extent, the systemic circulation.¹¹ SCFAs are normally present in plasma of healthy human beings around 20-100 μ M for acetate, 1-13 μ M for propionate and 1-12 μ M for butyrate, and acetate is always the most abundant. The bioavailability and tissue distribution of SCFAs are regulated by different physiological aspects: intestinal transit time, barrier function, and hepatic metabolic capacity. Of note, the ratios and overall levels of blood SCFAs can be altered in pathological conditions, including metabolic syndrome, inflammatory bowel disease, and neurodegenerative diseases, and can potentially modulate biological functions (Table 1).¹²

Crossing the Blood-Brain Barrier

For SCFAs to have a direct effect on neuroinflammation and CNS function, they need to enter the brain. The Blood-Brain Barrier (BBB), a highly regulated structure consisting of endothelial cells, tight junctions, astrocytes, and pericytes, regulates substance entry from the bloodstream into the CNS. While the BBB is very efficient in excluding compounds, studies indicate that small CNS penetration of SCFAs is possible by passive diffusion and carrier-mediated transport.¹³ Particularly, Monocarboxylate

Table 1: Overview of Major Short Chain Fatty Acids (SCFAs): Microbial Origins, Pathways, Distribution, and Functions Relevant to Neuroinflammation.

SCFA	Carbons	Main Producing Microbes	Fermentation Pathways / Substrates	Relative Abundance in Colon	Local Effects in Colon	Systemic Distribution & BBB Crossing	Key Biological Roles & Mechanisms in Neuroinflammation	References
Acetate (C2)	2	Broad range: <i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Bacteroides</i> , many <i>Firmicutes</i>	Acetyl-CoA pathway; fermentation of dietary fibers & resistant starch	~60% (most abundant)	Lowers colonic pH; inhibits pathogens; moderate energy source	Highest systemic levels; significant hepatic bypass; crosses BBB via MCTs	Activates GPCRs (e.g., GPR43); systemic immune modulation; precursor for cholesterol & lipid synthesis.	17
Propionate (C3)	3	<i>Bacteroides</i> , <i>Veillonella</i> , <i>Dialister</i> , <i>Selenomonas</i>	Succinate & acrylate pathways; dietary fibers, lactate	~25%	Moderate effect on colonocyte metabolism	Moderate systemic levels; mainly taken up by liver; limited BBB crossing	GPCR activation; promotes regulatory T cells; reduces proinflammatory cytokines; substrate for gluconeogenesis.	18
Butyrate (C4)	4	<i>Faecalibacterium prausnitzii</i> , <i>Roseburia</i> spp., <i>Eubacterium rectale</i> , <i>Clostridium</i> spp.	Butyryl-CoA:acetate CoA-transferase pathway; mainly dietary fibers & acetate	~15%	Major energy source for colonocytes; maintains barrier integrity	Mostly consumed locally; small systemic amounts; minimal BBB crossing	Strong HDAC inhibitor; anti-inflammatory microglial modulation; strengthens BBB; supports neuronal health.	19
Valerate (C5)	5	Certain <i>Clostridium</i> spp., protein-fermenting bacteria	Amino acid fermentation	Trace	Potential epithelial effects	Low systemic presence; understudied BBB dynamics	Limited data; may influence local immune balance and barrier function.	20
Caproate (C6)	6	Certain <i>Clostridium</i> spp.	Amino acid fermentation	Trace	Limited known effects	Low systemic levels; minimal data	Limited evidence; potential local effects on gut environment.	21
Branched-chain SCFAs (e.g., isobutyrate, isovalerate)	4-5	Protein-fermenting bacteria (from valine, leucine, isoleucine)	Amino acid fermentation	Trace	May affect motility & microbial ecology	Low systemic presence	May modulate epithelial health & local inflammation.	22

This table provides a detailed overview of the major SCFAs-acetate, propionate, and butyrate-including their microbial origins, metabolic pathways, relative abundance in the colon, and systemic distribution. The table also highlights the key biological roles of these SCFAs, particularly their relevance to neuroinflammation. By understanding the production pathways and functional mechanisms of SCFAs, we can better appreciate their potential as therapeutic agents for neuroinflammatory conditions and their complex roles in both protecting and exacerbating neuroinflammation under different circumstances.

Transporters (MCTs), particularly MCT1, are found on both the luminal and abluminal sides of brain capillary endothelial cells and facilitate the influx of SCFAs into brain tissue. Of these, acetate and propionate seem to be able to cross the BBB more efficiently compared with butyrate, probably based on their smaller size and larger blood levels. Once in the brain, SCFAs might interact with local cells such as neurons, microglia, and astrocytes. They are known to influence microglial activation and promote anti-inflammatory phenotypes in addition to controlling neuronal gene expression through inhibition of

Histone Deacetylases (HDACs). Furthermore, SCFAs could modulate neuroinflammatory signalling through the activation of G-Protein-Coupled Receptors (GPCRs) occurring in both CNS and immune peripheral cells.¹⁴ Beyond direct CNS penetration, SCFAs also influence neuroinflammation through peripheral mechanisms. By modulating systemic immune responses-such as increasing regulatory T cell populations and reducing proinflammatory cytokine production-SCFAs can alter the overall inflammatory milieu that communicates with the CNS via humoral and neural pathways (e.g., the vagus nerve).

Moreover, SCFAs have been shown to support BBB integrity by enhancing tight junction protein expression and reducing permeability under inflammatory conditions, thereby limiting the infiltration of peripheral immune cells that can exacerbate neuroinflammation.¹⁵ Collectively, the ability of SCFAs to cross the BBB, modulate peripheral and central immune responses, and influence BBB function positions them as key mediators in the gut-brain axis. Understanding the complex pharmacokinetics and distribution of SCFAs is critical to elucidating their roles in neuroinflammation and exploring their potential as therapeutic targets in neurological disorders.¹⁶⁻¹⁸

Mechanistic Insights into SCFAs and Neuroinflammation

Modulation of Microglial Activation and Polarization

Microglia, the resident immune cells in the Central Nervous System (CNS), are crucial in maintaining neuroinflammatory response. Normally, they contribute to maintaining brain homeostasis by clearance of cellular debris and supporting neuronal health.¹⁹⁻²² Yet in the context of disease or injury, microglia exist in different forms, ranging from resting, surveilling types to active ones, generally considered as proinflammatory (M1-like) or anti-inflammatory and tissue repair or (M2-like). The relative domination of these activation states plays a pivotal role in the initiation and resolution of the neurodegenerative diseases.²³

Like SCFAs, acetate mediates the microglial activation. In particular, butyrate and propionate may inhibit the exaggerated expression of proinflammatory mediators, such as TNF- α , IL-1 β , and nitric oxide, from activated microglia. Preclinical evidence suggests that the phenotype shift toward M2-like anti-inflammatory phenotypes involving the production of cytokines such as Interleukin (IL)-10 and Transforming Growth Factor (TGF)- β and phenotypically associated with tissue remodeling and neuroprotection is a SCFAs dependent process.²⁴ Mechanistically, these actions seem to be associated with the ability of SCFAs of inhibiting the Nuclear Factor kappa B (NF- κ B) pathway, a main intracellular signalling pathway implementing the gene expression profile of microglia towards the proinflammatory profile. SCFAs supplementation has been shown in animal models of neurodegeneration to decrease microglial reactivity and ameliorate disease-related neuroinflammation, implying a protective response. Nevertheless, in certain contexts, increased SCFAs levels can also activate microglia, and therefore the role of dosage, context, and composition of microbiota should be considered.²⁵

Effects on Blood-Brain Barrier Integrity

The Blood-Brain Barrier (BBB) is a selective barrier that protects the CNS from pathogens and regulates molecular exchange. Disruption of BBB integrity is a hallmark of many neurodegenerative diseases and facilitates the infiltration of

peripheral immune cells, amplifying neuroinflammation. SCFAs, particularly butyrate and propionate, have been shown to strengthen BBB integrity. Experimental evidence from germ-free mice, which typically display increased BBB permeability, demonstrated that recolonization with SCFA-producing bacteria or direct SCFAs supplementation reduced permeability and upregulated tight junction proteins such as claudin-5 and occludin.²⁶ The molecular mechanisms include SCFA-mediated activation of signaling pathways that enhance tight junction assembly and suppression of endothelial inflammatory responses. Additionally, SCFAs modulate the production of neurovascular protective factors by astrocytes and pericytes, further supporting BBB stability. These findings position SCFAs as key mediators connecting gut microbiota health to BBB function and CNS immune protection.²⁷

Regulation of Peripheral Immune Responses

SCFAs' influence extends beyond the CNS to the peripheral immune system, which indirectly impacts neuroinflammation. Acetate, propionate, and butyrate promote the differentiation and expansion of regulatory T cells (Tregs), which secrete anti-inflammatory cytokines like IL-10, dampening systemic inflammation. In addition, SCFAs reduce the production of proinflammatory cytokines (e.g., IL-6, IL-12) by dendritic cells and macrophages, and they decrease neutrophil chemotaxis and adhesion, limiting inflammatory cell recruitment. By shaping systemic immune tone, SCFAs can influence neuroinflammation indirectly through reduced peripheral cytokine spillover and decreased trafficking of inflammatory cells into the CNS. These systemic effects are particularly relevant in disorders where peripheral immune activation is implicated, such as multiple sclerosis and systemic lupus erythematosus, where gut-derived SCFAs may help mitigate CNS inflammation.²⁸

Epigenetic Modulation and Gene Expression

One of the most intriguing properties of SCFAs, especially butyrate and propionate, is their function as inhibitors of Histone Deacetylases (HDACs). HDAC inhibition increases histone acetylation, leading to a more relaxed chromatin state and altered transcription of genes involved in inflammation, neuroprotection, and synaptic plasticity. In microglia and astrocytes, HDAC inhibition by SCFAs suppresses proinflammatory gene expression (e.g., TNF- α , iNOS) while enhancing the transcription of neuroprotective and anti-inflammatory genes (e.g., IL-10, Brain-Derived Neurotrophic Factor [BDNF]). In neurons, this epigenetic modulation may support synaptic plasticity and cognitive resilience. Furthermore, SCFAs can influence microRNAs that regulate gene networks involved in inflammation and neuronal function, adding another layer of gene expression control. These epigenetic effects highlight how microbial metabolites can directly alter the transcriptional landscape of the CNS.²⁹

SCFAs-Mediated Signaling Pathways (e.g., GPR41, GPR43, HDAC Inhibition)

SCFAs exert many of their biological effects by acting as ligands for G-protein-coupled receptors (GPCRs), primarily GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A, which are expressed on immune cells, neurons, and glial cells. Activation of these receptors can modulate intracellular signaling cascades that influence inflammation, cell proliferation, and barrier function. For example, GPR43 activation promotes anti-inflammatory signaling in immune cells, while GPR41 signaling has been linked to neuroendocrine regulation and sympathetic nervous system activity. GPR109A, activated by butyrate, exerts anti-inflammatory effects by inhibiting NF- κ B signaling.³⁰ Complementing these receptor-mediated actions, SCFAs' inhibition of HDACs represents a receptor-independent mechanism, broadening their influence on gene transcription and chromatin remodeling. Together, these pathways underscore SCFAs' ability to integrate microbial metabolism with host immune regulation and CNS health (Table 2).³¹

Protective vs. Harmful Roles of SCFAs in the Central Nervous System

Dual Roles of SCFAs in the Central Nervous System

Short-Chain Fatty Acids (SCFAs) play dual roles in the body, particularly in the context of neuroinflammation. While SCFAs, such as butyrate, propionate, and acetate, generally exhibit neuroprotective and anti-inflammatory effects, their impact can vary depending on factors like concentration, microbiota composition, and the underlying disease state. At physiologically relevant concentrations, SCFAs help maintain brain health by modulating immune responses, promoting anti-inflammatory microglial activity, and strengthening the Blood-Brain Barrier (BBB). However, at elevated concentrations or in specific pathological conditions, SCFAs can exhibit proinflammatory effects, exacerbating neuroinflammation and potentially contributing to disease progression.

This dual nature of SCFAs-beneficial at lower concentrations but potentially harmful at higher levels-highlights the complexity of their role in neuroinflammation and underscores the need for a nuanced understanding of how these metabolites interact with the immune system and the CNS.

Neuroprotective Effects and Anti-Inflammatory Potential

Emerging evidence suggests that Short-Chain Fatty Acids (SCFAs), particularly butyrate and propionate, exert neuroprotective and anti-inflammatory effects in the CNS. Butyrate, a potent inhibitor of HDACs, can reduce the expression of proinflammatory genes by negatively regulating their expression, along with up regulating neuroprotective factor including Brain Derived Neurotrophic

Factor (BDNF). This epigenetic control leads to a fostered neuronal health, an improved synaptic plasticity, and maintenance of cognitive capabilities. In models of neurodegenerative diseases, butyrate has been reported to decrease β -amyloid-induced inflammation and memory impairment in Alzheimer's disease models, as well as protect dopaminergic neurons and reduce the activation of microglia in models of Parkinson's disease. Furthermore, propionate supports an anti-inflammatory environment that is established by an increased frequency of regulatory T cells and a reduced systemic cytokine profile, indirectly affecting CNS inflammation. SCFAs also contribute to maintaining the integrity of the BBB by promoting the expression of tight junction proteins and suppressing oxidative stress, both of which prevent the infiltration of peripheral immune cells (a mechanism central to neuro-inflammation) to the brain.³⁷ Collectively, these properties suggest that SCFAs can function as endogenous modulators of neuroinflammation, supporting CNS resilience against neurodegenerative and neuroinflammatory insults (Figure 1).

Factors Influencing SCFA Efficacy: Microbiota Composition, Diet, and Disease State

It represents the dual roles of SCFAs-acetate, propionate, and butyrate-in modulating neuroinflammation. As shown in the figure, SCFAs generally exhibit neuroprotective effects by regulating microglial activation, promoting anti-inflammatory phenotypes, and strengthening the blood-brain barrier. However, under certain conditions, such as elevated SCFA levels or specific disease contexts, SCFAs can exhibit proinflammatory effects that exacerbate neuroinflammation. This figure is central to understanding the context-dependent nature of SCFA actions, which are influenced by factors such as concentration, microbiota composition, and disease state. The interplay between these protective and harmful roles is a key aspect of SCFA-based therapeutic strategies for neuroinflammation and neurodegenerative diseases.

Conditions and contexts leading to proinflammatory actions

Despite the generally protective profile, emerging data reveal that SCFAs can, under certain conditions, contribute to CNS inflammation and even exacerbate pathology. The dual nature of SCFAs-contextually dependent on concentration, microbial balance, and disease state-reflects the complexity of the gut-brain axis. At supraphysiological concentrations or during specific pathological states, SCFAs may promote proinflammatory responses. For example, some studies report that high doses of acetate increase microglial reactivity and inflammatory cytokine production. Similarly, butyrate, while anti-inflammatory in many settings, can act as a metabolic stressor in neurons when mitochondrial function is compromised, potentially contributing to oxidative stress and neuronal injury.³⁸

Table 2: Mechanisms by which Short Chain Fatty Acids (SCFAs) Modulate Neuroinflammation.

Mechanistic Level / Target	Key Effects of SCFAs	Examples / Pathways / Receptors	Major SCFAs involved	References
Microglial activation & polarization (3.1)	Reduce proinflammatory cytokine production; promote anti-inflammatory (M2-like) phenotypes	Inhibition of NF- κ B signaling; enhanced IL-10 and TGF- β expression	Butyrate, propionate	32
Blood-brain barrier integrity (3.2)	Strengthen tight junctions; reduce permeability	Upregulation of claudin-5, occludin; modulation via endothelial MCT transport and GPCR signaling	Butyrate, propionate	33
Peripheral immune regulation (3.3)	Increase regulatory T cells; suppress dendritic cell and macrophage activation; reduce neutrophil chemotaxis	GPCR43 activation on immune cells; lower IL-6, IL-12, TNF- α	Acetate, propionate, butyrate	34
Epigenetic modulation & gene expression (3.4)	Inhibit HDACs; increase histone acetylation; modulate microRNA expression	Enhanced expression of neuroprotective genes (e.g., BDNF, IL-10); reduced iNOS, TNF- α	Primarily butyrate; also propionate	35
GPCR signaling & receptor-mediated effects (3.5)	Modulate inflammation, neuroendocrine signaling, and barrier function	Activation of GPR41 (FFAR3), GPR43 (FFAR2), GPR109A; anti-inflammatory and metabolic effects	Acetate, propionate, butyrate	36

It summarizes the key mechanisms through which SCFAs-acetate, propionate, and butyrate-exert their effects on neuroinflammation. The table outlines the cellular targets and signaling pathways involved, such as the modulation of microglial activation, the regulation of the blood-brain barrier integrity, and the impact on epigenetic modulation through Histone Deacetylase (HDAC) inhibition. Additionally, the table highlights the involvement of G-Protein-Coupled Receptors (GPCRs), which are activated by SCFAs and contribute to immune modulation. By understanding these mechanisms, we can appreciate how SCFAs, through their diverse molecular actions, regulate inflammation and neuronal function in both protective and potentially harmful ways. This table is crucial for linking the biological actions of SCFAs to their potential therapeutic applications in neurodegenerative diseases and neuroinflammation.

In animal models of autism spectrum disorders, elevated levels of propionic acid have been associated with behavioral abnormalities and neuroinflammatory responses, suggesting a context-dependent pathogenic role. The mechanisms underlying these effects include overactivation of GPCR-mediated signaling, excessive HDAC inhibition leading to dysregulated gene expression, and metabolic overload within CNS cells. These findings highlight that SCFAs are not universally beneficial: their effects depend critically on concentration, exposure duration, and the underlying state of CNS and systemic health (Figure 1).³⁹

The balance between protective and harmful effects of SCFAs is shaped by multiple interrelated factors, chiefly gut microbiota composition, dietary patterns, and the presence of disease.

Microbiota composition is central: the abundance of SCFAs-producing bacteria (e.g., *Faecalibacterium prausnitzii*, *Roseburia* spp., *Bacteroides* spp.) determines the type and quantity of SCFAs produced. Dysbiosis-imbalance favoring pathogenic or proteolytic bacteria-may shift fermentation from beneficial fibers to amino acids, increasing branched-chain and potentially harmful SCFAs, reducing butyrate production, and promoting inflammation.⁴⁰

Dietary factors profoundly influence SCFAs output. Diets rich in diverse plant fibers and resistant starches increase beneficial SCFA levels, whereas low-fiber, high-fat or high-protein diets can reduce total SCFAs production or favor the generation of less beneficial metabolites. Moreover, specific fiber types selectively support butyrate or propionate producers, shaping SCFAs profiles and downstream CNS effects.⁴¹

Disease context also modifies SCFAs action. In neurodegenerative diseases, BBB integrity, microglial priming, and mitochondrial health can influence whether SCFAs exert protective or harmful effects. For instance, in advanced Alzheimer's disease, microglia may become hyperresponsive, making them susceptible to further activation even by SCFAs. Similarly, metabolic conditions like diabetes can alter SCFAs absorption, systemic levels, and CNS bioavailability.⁴²

Together, these factors underline the importance of a systems-level perspective: SCFA efficacy emerges not only from their chemical nature but from dynamic interactions among diet, microbiota, host metabolism, and disease status.

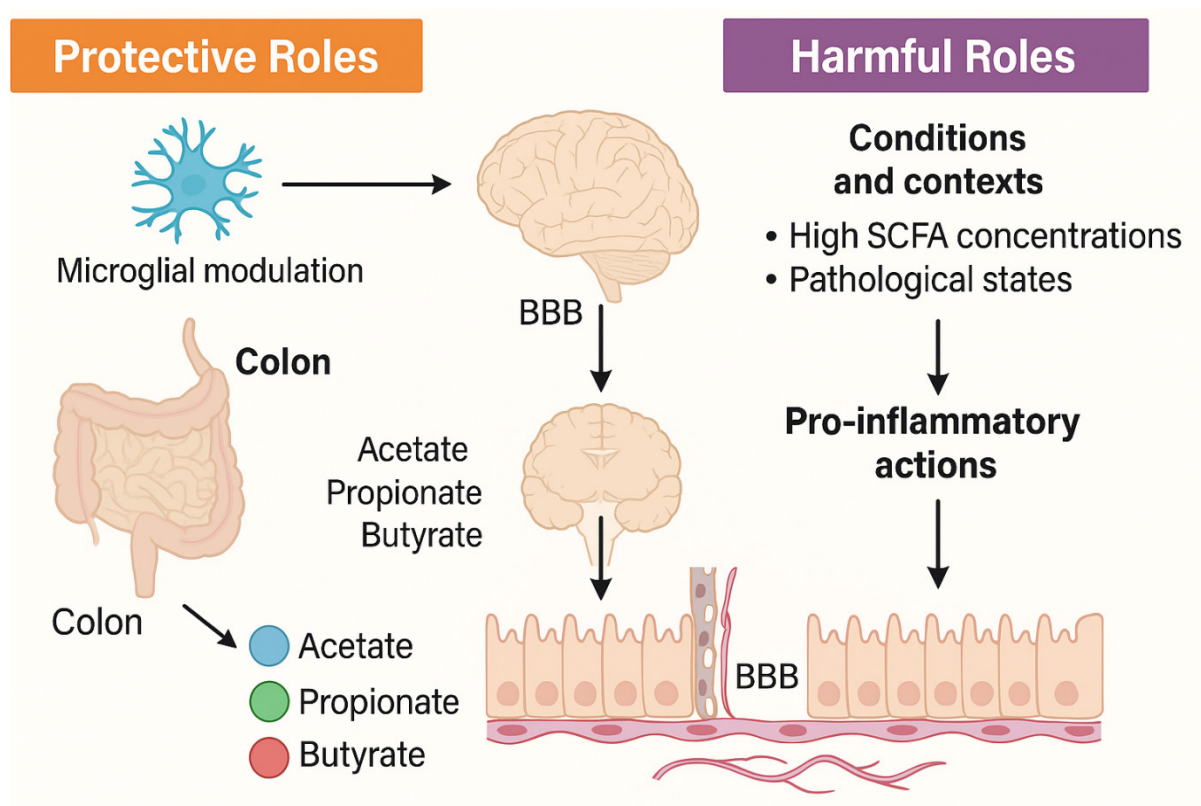


Figure 1: Dual roles of Short-Chain Fatty Acids (SCFAs) in the Central Nervous System (CNS).

Therapeutic Perspectives and Clinical Translation

Challenges

While the potential of Short-Chain Fatty Acids (SCFAs) in modulating neuroinflammation has been demonstrated in preclinical studies, translating these findings into clinical practice faces several challenges. Key obstacles include the interindividual variability in responses to SCFAs, which is influenced by factors such as microbiota composition, genetics, diet, and disease status. Additionally, determining the optimal dosing regimens and long-term safety profiles of SCFA-based interventions remains a significant hurdle. Despite promising results in animal models, the human microbiome is more complex, and the effects of SCFAs

may vary across different populations. Furthermore, clinical trials are needed to establish efficacy and safety, as the majority of current data are based on *in vitro* studies or animal models.⁴³ In addition to these biological challenges, there are methodological barriers to effectively harness SCFAs as therapeutic agents. For instance, SCFA absorption, bioavailability, and targeted delivery to the Central Nervous System (CNS) remain areas of concern, as most SCFAs are rapidly absorbed and metabolized in the gut, limiting their systemic availability. Personalized nutrition, guided by microbiome profiling and metabolic phenotyping, may be crucial to overcoming some of these challenges.⁴⁴

Therapeutic Methods for SCFA-Based Interventions

Despite these challenges, several therapeutic methods are being explored to leverage SCFA biology for treating neuroinflammatory and neurodegenerative diseases. These approaches aim to enhance the production, delivery, and effectiveness of SCFAs in the body.⁴⁵

Dietary Interventions and Prebiotics

One of the most widely studied strategies to increase SCFA production is through dietary fiber enrichment via prebiotics. Prebiotics, such as inulin, Fructooligosaccharides (FOS), Galactooligosaccharides (GOS), and resistant starch, selectively promote the growth of beneficial gut bacteria that ferment these fibers into SCFAs, particularly butyrate and propionate. Several studies have shown that fiber-rich diets can increase the abundance of SCFA-producing bacteria, improve biomarkers of neuroinflammation, and potentially benefit cognitive function. However, the type of fiber, its chemical structure, and the individual's microbiota composition critically influence SCFA production and therapeutic outcomes. Personalized nutrition approaches may enhance the effectiveness of these interventions by tailoring fiber intake to the specific microbiota profile of the individual.⁴⁶

Probiotics and Engineered Microbial Consortia

Probiotics offer another route to enhance SCFA production. Certain probiotic strains, such as *Lactobacillus plantarum*, *Bifidobacterium longum*, and *Clostridium butyricum*, can ferment dietary fibers and increase colonic SCFA levels. In addition to traditional probiotics, engineered microbial consortia are being developed to produce targeted SCFA profiles. These microbial consortia are designed to deliver more predictable and potent anti-inflammatory effects by increasing the levels of specific SCFAs like butyrate. However, the colonization efficiency of probiotics and microbial consortia, as well as their long-term stability in the host microbiota, remain critical factors for their success in clinical settings.⁴⁷

Synthetic and Formulated SCFA Delivery Systems

Direct administration of SCFAs is an attractive strategy but is limited by rapid absorption and poor palatability. To address these limitations, novel drug delivery systems, such as enteric-coated capsules, SCFA prodrugs, and polymeric nanoparticles, are under investigation. These systems aim to increase stability and target SCFA release to the colon, where they can have the most significant effects. For example, sodium butyrate encapsulated in microcapsules has been shown to raise colonic butyrate levels and reduce inflammation in animal models of colitis. Tributyrin, a triglyceride form of butyrate, offers improved bioavailability and sustained release properties, making it a promising candidate for clinical use. These delivery systems aim to provide more controlled dosing and avoid the variability inherent to microbiota-dependent SCFA production.⁴⁸⁻⁵⁰

Combination Therapies

Combining SCFA-based interventions with other therapies, such as prebiotics with probiotics or SCFA delivery systems, may enhance therapeutic efficacy. These approaches could also be tailored based on disease stage, biomarker profiles, and genetic factors. The use of multi-omics approaches (e.g., metagenomics, metabolomics) to identify responders and optimize treatment strategies could improve the success of SCFA-based therapies.⁵¹

Future Directions and Research Gaps

Future Directions

To advance the translational potential of SCFA-based interventions in neuroinflammatory and neurodegenerative disorders, the following research directions merit priority attention:

Human Clinical Trials of SCFAs and Metabolite Interventions

For example, a recently registered trial (NCT07183488) is investigating the acute physiological and metabolic effects of ingesting the SCFAs propionate and butyrate in healthy individuals. While this study is in a metabolic (rather than strictly neuroinflammatory) context, it provides a useful model for assessing SCFA kinetics, bioavailability and safety in humans. Future trials should extend this approach to patient populations with neuroinflammatory conditions (e.g., multiple sclerosis, Alzheimer's disease, traumatic brain injury) to assess SCFA effects on Central Nervous System (CNS) inflammation, microglial phenotypes, blood-brain barrier integrity and clinical outcomes.⁵²

Mechanistic Studies on SCFA Receptor Signalling and Neuro-Immune Pathways

A recent review highlights the mechanistic roles of SCFAs via GPCRs (e.g., GPR41, GPR43, GPR109a) and Histone Deacetylase (HDAC) inhibition in immune and neurological disorders. These mechanistic pathways remain under-studied in the context of human neuroinflammation. Future work should target these axes using advanced *in vivo* imaging, cell-specific interventions (e.g., receptor knock-outs or inhibitors) and biomarker-driven patient stratification.⁵³⁻⁵⁶

Intervention Studies in Specific Neuro-Inflammatory Models

Recent animal work demonstrates that SCFA supplementation after traumatic brain injury improved white-matter connectivity, reduced microglial inflammatory gene expression and protected behavioural outcomes (Northwestern University poster). Translating such findings into human neurotrauma or demyelinating disease cohorts (with appropriate dosing, route of administration and outcome metrics) would fill a key translational gap.^{57,58}

Personalised Nutrition/Microbiome-Based Approaches

Given the high inter-individual variability in microbiome composition, SCFA production and host response, future studies should incorporate microbiome profiling, SCFA metabolomics, and dietary interventions (e.g., prebiotics, resistant starch) to tailor interventions. For example, a recent rodent study showed that a high soluble-fiber diet increased acetate, reduced hippocampal pro-inflammatory cytokines and increased BDNF. This supports the notion of diet-microbiome-SCFA-brain mechanistic axis, which can be tested in well-controlled human cohorts.⁶⁰⁻⁶²

Dose-Response, Safety and Long-Term Outcomes

Many of the current studies focus on short-term effects in healthy participants or animal models. Gaps remain regarding optimal dosing regimens, long-term safety of SCFA supplementation (especially in disease contexts), organ-specific distribution (e.g., CNS uptake), and clinically meaningful outcomes (cognition, neuroimaging biomarkers, immune profiles). Future clinical trials should include these endpoints and consider adaptive designs to find the “therapeutic window” of SCFAs.⁶³

Integration of Multi-Omics and Biomarker-Driven Strategies

To move beyond proof-of-concept, future work should integrate metagenomics, metabolomics, proteomics and neuroimaging to identify biomarkers of response to SCFA interventions, identify subgroups with highest likelihood of benefit, and understand mechanistic pathways of effect (or non-response). For instance, expanding on the modelling work of SCFA-driven vagal signalling in gut-brain axis communication may illuminate novel biomarkers.⁶⁴

CONCLUSION

Short-Chain Fatty Acids (SCFAs) represent a compelling link between gut microbiota activity and Central Nervous System (CNS) health. Through a network of mechanisms-including modulation of microglial activation, reinforcement of blood-brain barrier integrity, regulation of peripheral immunity, and epigenetic effects-SCFAs hold significant potential to mitigate neuroinflammation and support neuroprotection.

Therapeutic strategies, from dietary fiber enrichment and prebiotics to probiotics and advanced SCFAs delivery systems, are being explored to harness these benefits. Yet, the field must address key research gaps: validating efficacy in human clinical trials, unraveling interactions with other microbial metabolites, and developing personalized approaches that account for individual variability.

Advancing our understanding of SCFAs’ dual roles-protective and potentially harmful-within specific disease contexts will

be crucial. Ultimately, integrating microbiome science with nutritional, pharmacological, and systems medicine approaches could pave the way for novel, targeted interventions to combat neuroinflammation and neurodegenerative diseases.

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ABBREVIATIONS

SCFAs: Short Chain Fatty Acids; **CNS:** Central Nervous System; **BBB:** Blood-Brain Barrier; **HDAC:** Histone Deacetylase; **BDNF:** Brain-Derived Neurotrophic Factor; **GPCR:** G-Protein-Coupled Receptor; **GPR41:** G-Protein-Coupled Receptor 41 (FFAR3); **GPR43:** G-Protein-Coupled Receptor 43 (FFAR2); **TNF- α :** Tumor Necrosis Factor-alpha; **IL:** Interleukin

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTIONS

Conceptualization: N.B., P.N., K.S.P.; **Methodology:** K.S.P., K. S., N.B.; **Data curation:** Y.D., S. N.; **Formal analysis:** N.B., S.M.; **Writing - Original draft:** N.B., K.S.P., N.P.; **Supervision:** N.B., K.J.; **Writing - review and editing:** N.B., K.J.

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Not applicable.

SUMMARY

This review explores the emerging role of Short-Chain Fatty Acids (SCFAs)-key metabolites produced by gut microbiota-in regulating neuroinflammation. It discusses the molecular mechanisms through which SCFAs influence the gut-brain axis, modulate immune cell activity, and maintain neuronal health. The paper highlights recent evidence linking altered SCFA levels to neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases. Furthermore, it emphasizes the therapeutic potential of targeting SCFA pathways to develop novel strategies for managing neuroinflammatory conditions.

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