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Elucidating the specific mechanisms of the gut-brain axis: the short-chain fatty acids-microglia pathway

Qingyu Cao[1,3†], Mengmeng Shen[3†], Ruoqiu Li[2], Yan Liu[4], Zhen Zeng[3], Jidong Zhou[3], Dejun Niu[3], Quancai Zhang[3], Rongrong Wang[2], Jingchun Yao[3*] and Guimin Zhang[1,3*]

Abstract

In recent years, the gut microbiota has been increasingly recognized for its influence on various central nervous system diseases mediated by microglia, yet the underlying mechanisms remain unclear. As key metabolites of the gut microbiota, short-chain fatty acids (SCFAs) have emerged as a focal point in understanding microglia-related interactions. In this review, we further refine the connection between the gut microbiota and microglia by introducing the concept of the "SCFAs-microglia" pathway. We summarize current knowledge on this pathway, recent discoveries regarding its role in neurological diseases, and potential pharmacological strategies targeting it. Finally, we outlined the current challenges and limitations in this field of research. We hope this review provides new insights into the role of the gut microbiota in neuroimmune regulation.

Keywords Gut microbiota, Short-Chain fatty acids, Microglia, Neurological diseases

Introduction

Following the completion of the Human Genome Project in 2003, researchers identified only 26,600 protein-coding genes—far fewer than originally anticipated. This unexpected finding shifted scientific focus toward another "hidden genome"—the human microbiome, whose genetic content exceeds that of its host by approximately 150-fold [1]. Among the various microbial communities in the human body, the gut microbiota represents the largest and most complex ecosystem, comprising approximately 100 trillion bacterial and archaeal cells [2]. The diversity and richness of this microbiome contribute significantly to human biochemical processes, genetic individuality, and disease susceptibility. This not only deepens our understanding of human genome complexity but also underscores the critical role of gut microbiota in maintaining physiological homeostasis.

Emerging evidence suggests that the gut microbiota influences the central nervous system (CNS), modulating brain function and playing a crucial role in neurodevelopment and behavior [34]. This realization has led to the conceptualization of the "microbiota-gut-brain (GMB) axis," a complex bidirectional communication network between the gut and the brain, mediated through immune pathways, endocrine signals, the vagus

†Qingyu Cao and Mengmeng Shen contributed equally to this work.

*Correspondence:
Jingchun Yao
yaojingchun@yeah.net
Guimin Zhang
lunanzhangguimin@yeah.net
[1]College of Pharmacy, Yanbian University, Yanji 133002, Jilin Province, China
[2]Key Laboratory of Marine Drugs, School of Medicine and Pharmacy, Ministry of Education, Ocean University of China, Qingdao 266003, China
[3]State Key Laboratory of Integration and Innovation of Classic Formula and Modern Chinese Medicine, Lunan Pharmaceutical Group Co. Ltd, Linyi 276005, China
[4]School of Pharmacy, Qingdao University, Qingdao 266071, China

nerve, and the enteric nervous system [5]. Increasingly, the GMB axis has gained attention in the study of psychiatric, neurodevelopmental, aging-related, and neurodegenerative disorders. Researchers have identified associations between gut microbiota and conditions such as anxiety, depression, autism spectrum disorder (ASD), schizophrenia, and Alzheimer's disease (AD) [6]. However, these are largely correlations, and the specific mechanisms by which the gut microbiota regulates brain function via the GMB axis remain a major scientific challenge.

Within this communication network, the immune system plays an indispensable role [78]. As key mediators of neuroimmune interactions, microglia are considered a critical component of microbiota-immune-brain crosstalk [9, 10, 11], and experimental evidence has validated this relationship [12]. However, the microbial components and mechanisms underlying the gut microbiota's influence on microglial function remain largely undefined.

In 2015, the landmark study by Erny et al. unveiled the essential role of gut microbiota in regulating microglial homeostasis, with a particular emphasis on the contribution of SCFAs—microbial metabolites derived from bacterial fermentation—in this process [13]. This study suggested that the "SCFAs-microglia" pathway may represent a key communication link within the GMB network. However, despite the increasing recognition of its importance, significant knowledge gaps remain regarding the molecular mechanisms underlying this pathway, such as: (1) the precise signaling pathways through which SCFAs regulate microglial function (e.g., HDAC inhibition, GPCR activation); (2) the modes of SCFAs action on microglia; and (3) the dual roles of SCFAs in the same disease context, which remain subjects of debate.

Accumulating evidence indicates that gut microbiota-derived SCFAs ameliorate microglial dysfunction, thereby influencing neurological diseases such as AD, Parkinson's disease (PD), and ASD [14]. However, the dynamic regulation of microglial phenotypes by SCFAs and their involvement in disease progression remain major challenges in neuroimmunology. Interestingly, recent studies have found that microglial inhibitors, such as PLX5622, significantly alter gut microbiota β-diversity and increase lactate levels without affecting SCFAs concentrations, suggesting a unidirectional SCFAs-microglia pathway in which microglia do not regulate SCFAs production [15].

This review systematically integrates recent advances in SCFAs-microglia research, focusing on the following key questions: (1) the pathways and mechanisms by which SCFAs regulate microglial function; (2) the pathological significance of the SCFAs-microglia axis in neurological diseases; and (3) the therapeutic potential and limitations of targeting this axis. By elucidating the molecular network of this pathway, we aim to fill existing knowledge gaps and provide new perspectives on the role of the gut microbiota in neuroimmunology.

Overview of short-chain fatty acids

SCFAs are fatty acids with fewer than six carbon atoms, among which acetate, propionate, and butyrate account for more than 95% of the total SCFAs composition. These SCFAs are the most extensively studied. They are primarily produced in the cecum and colon through microbial fermentation of indigestible carbohydrates (e.g., dietary fiber) via glycolysis.

Acetate biosynthesis is widespread across microbial communities, with key acetate-producing bacteria including *Lactobacillus spp*, *Bifidobacterium spp.*, *Akkermansia muciniphila*, *Bacteroides spp.*, *Prevotella spp.*, *Ruminococcus spp.*, and *Streptococcus spp.* Acetate is primarily synthesized through two pathways: glycolysis and the Wood-Ljungdahl pathway. Additionally, certain bacterial species, such as lactic acid bacteria and Wolinella succinogenes, produce acetate via lactate oxidation and propionate oxidation, respectively [16].

Compared to acetate, the concentrations of propionate and butyrate are relatively lower, which may be attributed to their species-specific production pathways. For instance, propionate is synthesized predominantly from indigestible fibers or amino acids via the succinate, acrylate, and propanediol pathways, with *Akkermansia muciniphila* being a major contributor. In contrast, butyrate is produced through glucose metabolism and three key enzymatic pathways: butyryl-CoA: acetate CoA-transferase, phosphate butyryltransferase, and butyrate kinase. Key butyrate-producing bacteria include *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Eubacterium hallii*, and *Ruminococcus bromii* [17, 18].

As mentioned above, most SCFAs begin their physiological journey in the cecum and colon [19]. Their concentrations exhibit a decreasing longitudinal gradient along the gut, following the order: cecum > proximal colon > distal colon [20]. During this process, colonic epithelial cells efficiently absorb SCFAs, with only 5–10% being excreted in feces [21]. The molar ratio of acetate, propionate, and butyrate in the gut typically ranges from 75:15:10 to 40:40:20, with an average of approximately 3:1:1 [22]. This ratio is also reflected in fecal SCFAs composition [23].

In certain conditions, protonated SCFAs diffuse across the intestinal epithelial cell membrane. However, the majority of SCFAs exist as anions and are transported into cells via monocarboxylate transporter 1 (MCT-1) and sodium-coupled monocarboxylate transporter 1 (SMCT-1) [24, 25]. As a primary energy source for colonic epithelial cells, most butyrate undergoes metabolic breakdown

within these cells [2627], which results in its lowest concentration among SCFAs in peripheral circulation. The remaining unmetabolized SCFAs cross the basolateral membrane and enter the portal circulation, where propionate is enzymatically metabolized in the liver, while acetate, present at the highest systemic concentration, is widely distributed throughout the body. Consequently, circulating propionate and butyrate concentrations typically range from 1 to 15 μM, whereas acetate concentrations are higher, ranging from 100 to 200 μM [28, 29, 30].

Notably, acetate, propionate, and butyrate have been shown to readily cross the blood-brain barrier (BBB) [3132]. Using gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS), their physiological concentrations in the brain have been determined. In humans, the cerebrospinal fluid (CSF) concentrations of acetate, propionate, and butyrate range from 0 to 171 mM, 0–6 mM, and 0–2.8 mM, respectively. The concentrations of these SCFAs in brain tissue have also been measured, ranging from 17 to 19 pmol/mg.

SCFAs exert a broad spectrum of physiological effects through activation of several G protein-coupled receptors (GPCRs) and other molecular targets, including the regulation of immune cell function, energy homeostasis, and hormone secretion [33]. Among these, free fatty acid receptor 2 (FFAR2, also known as GPR43) and free fatty acid receptor 3 (FFAR3, also known as GPR41) have been the most extensively studied [34, 35, 36]. Both FFAR2 and FFAR3 are widely expressed in colonic epithelium, immune cells, and cardiac tissues. However, FFAR2 is specifically enriched in adipocytes and skeletal muscle [37], whereas FFAR3 is highly expressed in the peripheral nervous system and BBB [3839]. It is worth noting that the expression of FFAR2/3 in microglia remains controversial [3740, 41], We speculate that the expression of FFAR2/3 in microglia may be regulated by certain yet unidentified factors, such as the stimulatory effects induced by sustained changes in SCFAs concentrations [42, 43].

Microglia overview

Microglia were first identified as resident immune cells of the CNS in 1919, accounting for about 10% of the cells in the brain [44]. Research suggests that microglia originate from myeloid hematopoietic progenitors in the embryonic yolk sac and, after migrating to the developing neural tube through primitive circulation, maintain homeostasis in the brain through a self-renewal process [45, 46, 47].

As a key component of the brain's immune system, microglia shape neuronal connections and activity, prune synapses to enhance synaptic plasticity, and support the survival of neurons and neural progenitor cells by secreting growth factors. More importantly, they are capable of responding to neural damage or pathological changes within the brain [4849].

Microglia possess highly branched cell morphology, demonstrating strong dynamic movement capabilities, which enable them to act as "sentinels" patrolling the brain (checking the entire brain every few hours) [50], and actively participate in maintaining the brain's microenvironment through rapid responses to pathogens and/or tissue damage [51]. Microglia express various receptors on their surface, which can sense pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), triggering selective responses to different stimuli. Various CNS diseases can activate different receptor patterns, leading to rapid activation and proliferation of microglia [52]. Upon activation, microglia undergo characteristic morphological and functional changes (e.g., an increase in cell body size and a reduction in the functions of other cells while enhancing phagocytic capacity) to execute specific immune tasks that lead to distinct functional outcomes [52, 53]. Traditionally, based on their morphology and functional capacity, activated microglia have been classified into two main types: pro-inflammatory and anti-inflammatory [54]. However, according to current research, the morphology, ultrastructure, and gene expression profiles of microglia depend on the inputs provided by the brain's microenvironment [55]. Therefore, nearly every brain disease induces specific microglial phenotypes within its pathological scope. Based on these findings, it has been suggested that the phenotypes adopted by microglia should be considered part of an evolving phenotype spectrum, depending on specific temporal, spatial, or pathological contexts. This may explain why neurodegenerative diseases, in which microglial dysfunction is a primary pathogenic factor, are difficult to cure. However, with the advent of novel single-cell technologies, such as single-cell RNA sequencing, researchers can explore the evolutionary processes and mechanisms of microglia in specific pathological contexts from both temporal and spatial perspectives. This will provide directions for exploring new therapeutic approaches.

Effects of short-chain fatty acids on microglia: pathways of communication

It has been established that SCFAs play a regulatory role in microglial homeostasis, yet the communication pathways between the two are still under exploration. In this section, we integrate recent advances in related research and identify relevant pathways(Fig. 1). However, it is important to note that some studies have found SCFAs receptors in the vagal afferent fibers that control the portal vein, and feeding mice with inulin increases the levels of butyrate and propionate in the portal vein [42]. This

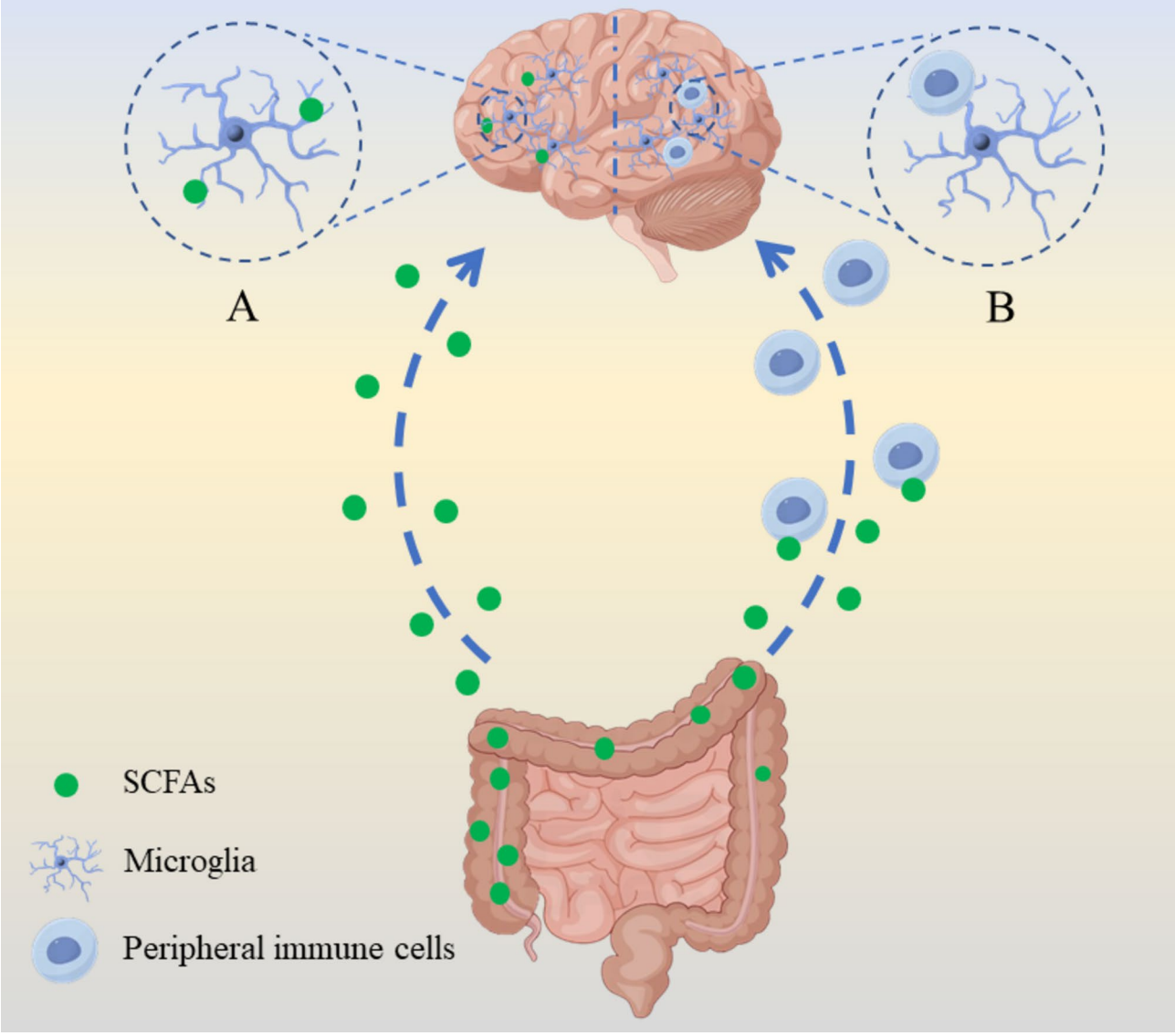

Fig. 1 Communication pathway between SCFAs and microglia. Gut-derived SCFAs influence the physiological or pathological activity of microglia in the central nervous system through two major mechanisms. (A) Direct pathway: SCFAs enter the brain parenchyma via systemic circulation and act directly on microglial cells. (B) Indirect pathway: SCFAs activate peripheral immune cells (e.g., neutrophils, monocytes) by binding to specific receptors, thereby inducing the release of cytokines and promoting immune cell migration into the brain, where they indirectly influence microglial function

suggests that SCFAs might potentially influence microglia through a neural pathway, but due to insufficient evidence, we have not included this in the main text.

Direct action

Reportedly, SCFAs can cross the BBB via monocarboxylate transporters (MCTs) highly expressed on brain microvascular endothelial cells (BMECs). After the injection of radioactive-labeled SCFAs, their localization in brain tissue was observed [31], confirming the potential for SCFAs to enter the brain. Recently, a study measured and localized SCFAs receptors in the mouse brain [43], using fluorescent in situ hybridization to confirm that SCFAs receptors (FFARs) were highly co-localized with microglia and serotoninergic neurons. The study found that over 60% of FFAR3 mRNA in the hippocampus was present in activated microglia, providing anatomical support for SCFAs interaction with microglia in the brain and their functional impact. In related in vitro experiments [56], acetate, propionate, and butyrate, either alone or mixed in ratios approximating physiological concentrations, were used to treat THP-1 cells. The results showed that SCFAs at physiological concentrations, either alone or in combination, could regulate the function of damaged microglia, reduce the expression of related inflammatory factors, and inhibit phagocytic activity in THP-1 cells. Notably, the inhibitory effect of SCFAs appeared to be only partially dependent

on FFAR2/3 receptors, as FFAR2/3 antagonists did not block the inhibitory effects of SCFAs mixtures on IL-1β secretion by THP-1 cells. More convincingly, gut-derived ^{13}C-acetate can reach the brain and be metabolized by microglia into TCA cycle intermediates, including citrate, α-ketoglutarate, fumarate, malate, and succinate, thereby restoring the mitochondrial dysfunction observed in germ-free mice [57]. In summary, SCFAs at physiological concentrations can directly enter the central nervous system and exert effects on microglia.

Peripheral immune cell interaction

Although direct interaction between SCFAs and microglia is well-supported by evidence, SCFAs seem to also regulate microglial function through other pathways. Studies have shown that FFAR2-deficient mice exhibit microglia similar to germ-free mice, even though FFAR2 is not expressed in any adult brain cells, including microglia and endothelial cells [58]. However, FFAR2/3 have been shown to have strong expression in peripheral immune cells, including eosinophils, neutrophils, and monocytes, in both humans and mice [59, 60]. Therefore, it is hypothesized that SCFAs may exert their effects on microglia by acting directly on peripheral myeloid or lymphoid cells, which then relay SCFAs signals to microglia [61]. Notably, both propionate and butyrate can promote the generation of Treg cells in the spleen [62], and the depletion of circulating Treg cells affects microglial activation and cytokine release [63].

Supporting evidence for this indirect effect comes from studies showing that propionate pre-treatment reduced microglial activation and related inflammatory factor expression in the brains of mice with perioperative cognitive dysfunction, thereby improving cognitive impairment caused by neuroinflammation. This effect was mainly mediated through the reduction of peripheral Th17 cell infiltration into the CNS and the decreased IL-17 A levels produced by Th17 cells [64]. The presence of central Th17 cells promotes microglial activation, producing IL-17 A that leads to severe neuronal dysfunction. It is noteworthy that IL-17 A exacerbates neuronal loss in the presence of microglia, while inhibiting IL-17 A receptors on microglia attenuates these effects [65]. In another study, researchers knocked out the SCFAs receptor FFAR2 in mouse myeloid cells and induced intestinal inflammation using dextran sulfate sodium(DSS). The results showed that the knockout of FFAR2 in immune myeloid cells led to downregulation of microglial inflammatory genes in DSS mice, indicating that SCFAs can influence microglial inflammatory responses via peripheral immune cells, at least partially [66]. Moreover, after SCFAs were added to the drinking water of male mice with stroke, researchers observed that SCFAs induced the migration of peripheral lymphocytes from the intestinal immune compartment to the brain, thereby promoting microglial activation. However, when peripheral lymphocytes were depleted, SCFAs lost their effects on microglia, clearly demonstrating that circulating lymphocytes mediate the activation of brain microglia by SCFAs [67]. These highly mobile circulating cells provide the cellular link for SCFAs' effects on microglia [68]. However, these data suggest varying effects of SCFAs on microglial activation, and future studies should carefully consider this point.

Mechanisms of SCFAs-microglia pathway action

Histone modifications

In eukaryotes, genomic DNA forms the fundamental unit of chromatin—the nucleosome—by winding around histones. Histones act as molecular "spools" that achieve DNA compaction and functional regulation [69]. Chromatin exhibits dynamic structure throughout the cell cycle: in interphase, chromatin is loosely distributed in the nucleus to support gene transcription, whereas during mitosis, it condenses into chromosomes to ensure accurate genetic material distribution. The core regulatory mechanism behind this structural plasticity is post-translational modifications (PTMs) of histones, primarily managed by two types of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). Typically, HATs promote gene transcription by relaxing chromatin structure, while HDACs inhibit gene transcription by tightening chromatin [70]. HDACs play a critical role in CNS diseases and are classified into Class I (HDAC1-3, 8), Class II (HDAC4-7, 9, 10), Class III (Sirtuins 1–7), and Class IV (HDAC11) [71]. In the hippocampus, HDAC1, HDAC2, and HDAC8 enhance neuroinflammation associated with cognitive impairments [72], while HDAC3 reduces dendritic spine density and the levels of proteins related to synaptic plasticity [73].

Early research found that prolonged treatment with acetate salts could reduce mRNA levels of HDAC2, HDAC5, HDAC7, and HDAC8 [74], suggesting that SCFAs can regulate HDAC expression. In in vitro experiments, direct application of acetate salt to microglia reversed LPS-induced low acetylation of H3K9 in the promoter regions of COX-1, COX-2, and NF-κB p65 genes, thereby reducing the expression of microglia-related inflammatory factors [7576]. Sodium butyrate treatment induced hyperacetylation at the H3K9 and H3K18 sites in LPS-stimulated BV-2 microglia [77], exhibiting similar effects in the cortex, striatum, and hippocampus of a cerebral ischemic stroke model mouse [78]. In a recent study, the researchers found that acetate, propionate, and butyrate, when administered alone or in combination, reduced HDAC activity and NF-κB nuclear translocation in microglia, decreasing cytokine production. These effects appeared to be additive.

Although single-cell RNA sequencing detected SCFAs transporters MCT1 and MCT4, inhibiting monocarboxylate transporters on microglia did not interfere with the anti-inflammatory effects of SCFAs, suggesting that SCFAs' regulation of microglia may involve a post-diffusion epigenetic mechanism [42]. In conclusion, SCFAs can induce the inhibitory effect on HDACs, with butyrate being the most potent inhibitor of Class I and II HDACs [79]. It is noteworthy that SCFAs likely affect mechanisms such as neuroinflammation and energy metabolism through epigenetic mechanisms(Fig. 2).

Neuroinflammation

Neuroinflammation refers to the inflammatory response within the CNS triggered by various pathological insults, including infection, trauma, ischemia, and toxins. The hallmark of this process is the production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-18, tumor necrosis factor (TNF), chemokines such as CCL1, CCL5, and CXCL1, small molecule messengers including PGE2, NO, and ROS in the CNS [80]. Microglial activation is a key factor in inducing neuroinflammation.

Research has shown that sodium butyrate induces reversible extension of microglial processes under both normal and inflammatory conditions, accompanied by significant changes in the markers of reactive microglia, including pro-inflammatory and anti-inflammatory markers. These changes are primarily involved in the AKT-RhoGTPase signaling pathway [81]. In another similar study, butyrate supplementation improved the inflammatory response in LPS-induced BV-2 microglia; however, this effect was blocked by pre-treatment with MCT1 inhibitors and HDAC3 agonists but was mimicked by TLR4 and p-P65 antagonists, suggesting that butyrate alleviates microglial inflammation through the interaction between TLR4/NF-κB and MCT1/HDAC3 signaling pathways [82]. In a recent study [83], Moriyama and colleagues examined the effects of acetate on LPS-stimulated primary rat microglia and BV-2 microglia. They found that acetate dose-dependently reduced

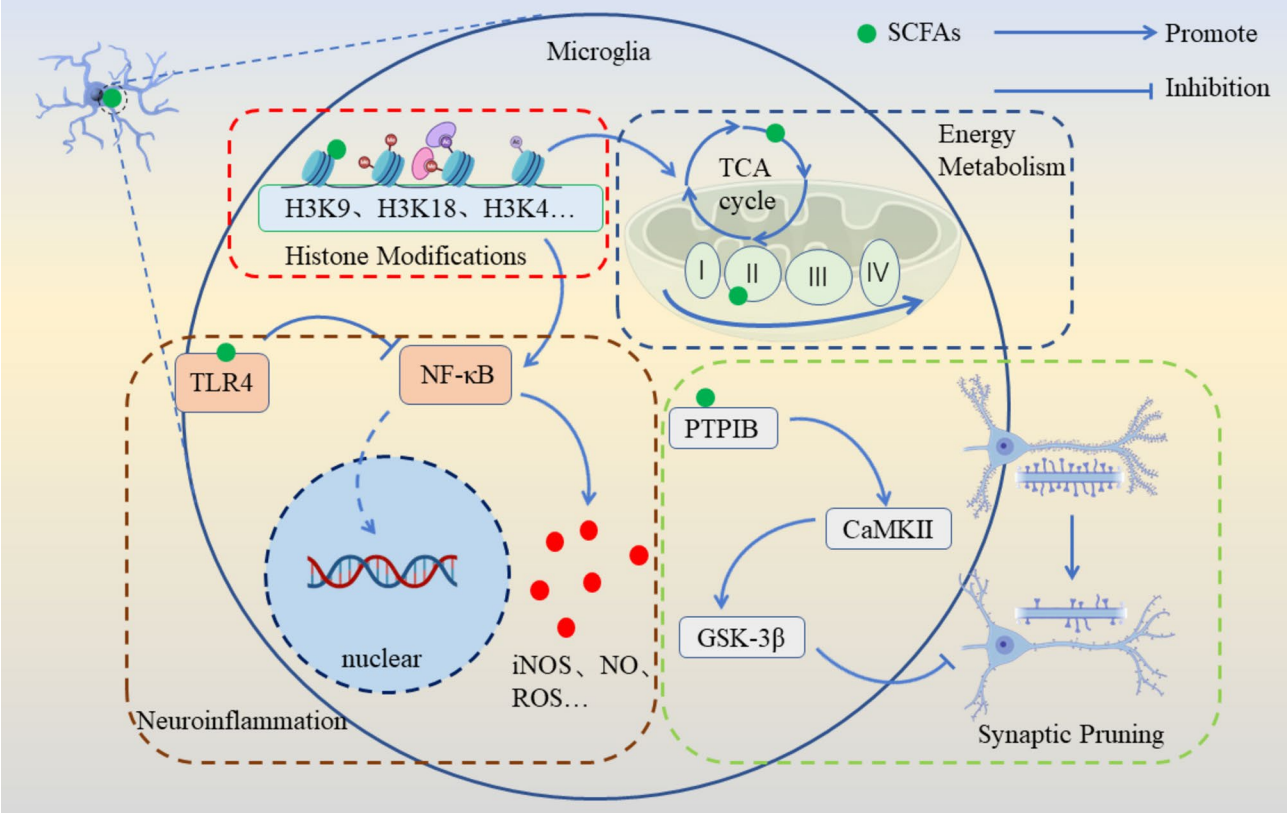

Fig. 2 Proposed mechanisms by which SCFAs modulate microglial function. SCFAs regulate microglial activity through epigenetic modification, signaling pathway modulation, and metabolic reprogramming, thereby influencing energy metabolism, neuroinflammation, and synaptic regulation. In terms of histone modification, SCFAs inhibit histone deacetylation at key lysine residues such as H3K9, H3K18, and H3K4, thereby affecting metabolic and inflammatory gene expression in microglia. For neuroinflammation, SCFAs suppress the activation of TLR4/NF-κB signaling and the nuclear translocation of NF-κB, resulting in reduced production of pro-inflammatory mediators including ROS, NO, and iNOS. Regarding energy metabolism, SCFAs help restore mitochondrial complex II function, stimulate short-chain acyl-CoA and acetyl-CoA production, and enhance TCA cycle flux to maintain microglial energy balance and immunological competence. In the context of synaptic regulation, SCFAs modulate the PTP1B/CaMKII/GSK-3β pathway to attenuate excessive microglial-mediated synaptic remodeling, thereby contributing to synaptic integrity and cognitive homeostasis

LPS-induced iNOS, NO, and ROS production in primary microglia, with significant effects seen at concentrations above 10 mM, without affecting cell viability. However, this inhibitory effect on NO and ROS production was not observed in BV-2 microglia, which the authors attributed to differences between primary and BV-2 microglia. In in vivo studies, researchers used a high-salt diet to induce microglial activation in mice, leading to increased expression of related inflammatory factors in the cortex. After supplementation with SCFAs, microglial activation in the cortex decreased, inflammatory factor levels dropped, and the brain's apoptosis and cognitive dysfunction caused by the high-salt diet were improved [84].

Energy metabolism

SCFAs have been shown to exert beneficial metabolic effects on energy and glucose homeostasis, as they can serve as energy substrates in the TCA cycle [85]. Microglia, as high-energy-demanding immune sentinels, rely heavily on SCFAs to maintain a dynamic balance between mitochondrial ATP supply and metabolic intermediates, which is critical for their function.

Acetate has been shown to drive microglial maturation and improve their metabolic state, which underpins its role in modulating microglial phagocytosis and alleviating cognitive impairments in neurodegenerative diseases. By supplementing acetate levels in germ-free mice, researchers found that damage to Complex II (CII) of the mitochondrial electron transport chain and the resulting mitochondrial defects were reversed. This effect was primarily attributed to acetate's regulation of epigenetic marks associated with proteins like H3K4me3 and H3K9ac [57]. Later, in a 5×FAD mouse model of Alzheimer's disease (AD), acetate was found to inhibit phagocytosis by inducing the expression of microglia-related cytokines, thereby exacerbating Aβ burden in 5×FAD animals [86]. In primary Aβ-phagocytosing microglia from 5×FAD mice, acetate treatment also led to metabolic changes in microglia, including increased mitochondrial activity, ROS production, oxidative phosphorylation, and membrane potential. Another study related to acetate showed that acetate improved TCA cycle flux by stimulating short-chain CoA metabolism and increasing acetyl-CoA levels, thereby reducing microglial reactivity [87].

Furthermore, a recent study explored the role of butyrate in the depletion of the mitochondrial co-chaperone (FXN), a mitochondrial protein that regulates the activity of the mitochondrial electron transport chain (ETC) and aconitase. FXN depletion disrupts mitochondrial oxidative capacity, leading to increased reactive oxygen species (ROS) production [88, 89]. The results indicated that the lack of FXN led to a significant loss of microglial homeostatic responses, with increased glycolytic metabolism and a stronger inflammatory response. However, butyrate reversed these immune-metabolic changes by stimulating the itaconate-Nrf2-GSH pathway through GPR109A, exhibiting significant neuroprotective effects [90]. These studies suggest that SCFAs regulate mitochondrial metabolism (such as TCA cycle and electron transport chain) to balance microglial energy supply and immune function.

Synaptic pruning and synaptic plasticity repair

Microglia play an essential role in synaptic pruning, a process of synapse removal critical for healthy brain development. This is primarily mediated by the recognition of complement proteins (Cmp) on synapses via microglial complement receptors [91]. However, under pathological conditions, excessive phagocytosis by microglia can induce memory impairments. Studies have shown that microglia can regulate synaptic elimination via the C3/complement receptor 3 (CR3) pathway, leading to postoperative cognitive impairment [92]. Recently, SCFAs have emerged as novel targets for intervening in synaptic pathology by regulating microglial phagocytic activity and synaptic pruning balance.

Earlier research indicated that SCFAs could specifically regulate genes associated with microglial activity and phagocytic function during the post-stroke recovery phase [67]. Therefore, SCFAs might indirectly mediate their effects on post-stroke recovery and neuronal plasticity through microglial activation. To verify this, researchers treated primary microglia from the hippocampus and brain tissues of mice with SCFAs during postoperative cognitive dysfunction. The results showed that SCFAs treatment increased histone H3 acetylation in microglia, inhibiting neuroinflammation and modulating the complement C1q pathway, significantly reversing synaptic elimination in cognitive deficit rats [93]. Additionally, SCFAs deficiency led to increased phagocytosis of synapses by microglia, damaging synaptic ultrastructure in the hippocampus, characterized by widened synaptic gaps, thinning of postsynaptic densities, and reduced synaptic protein expression. This effect was primarily linked to the inactivation of SCFAs receptors (FFAR2/3) and the PTPIB-pCaMKII-pGSK-3β pathway [94]. Notably, in chronic ischemic brain injury, activated microglia were found to colocalize with postsynaptic markers like PSD95, suggesting that in the hippocampus, microglia were phagocytosing postsynaptic rather than presynaptic terminals. This process was significantly alleviated by SCFAs, indicating that phagocytosis of postsynaptic terminals may be a key mechanism through which SCFAs combat synaptic loss [95]. Moreover, a single intraperitoneal injection of propionate (175 mg/kg) into adolescent male rats activated hippocampal microglia and altered the ultrastructure of axon-dendritic synapses

in the CA1 region [96], further confirming that SCFAs influence microglial-mediated regulation of brain functions, especially synaptic pruning and plasticity.

SCFAs-microglia pathways and related neurological diseases

In the previous sections, we have highlighted how SCFAs regulate microglial epigenetic modifications, immune-metabolic reprogramming, and synaptic pruning functions, dynamically modulating neuroinflammation and synaptic homeostasis. However, the effects of SCFAs on microglia are highly dependent on the disease type, pathological stage, and microenvironment characteristics. This section focuses on the SCFAs-microglia pathway in neurodegenerative diseases, neurodevelopmental disorders, and psychiatric diseases, with a particular emphasis on the underlying molecular mechanisms (Table 1).

Alzheimer's disease (AD)

The GMB is a major regulator of inflammation in the body and plays a crucial role in the development and progression of diseases involving peripheral and central inflammation. Although several studies have proposed general hypotheses on how GMB regulates AD-related pathology, few specific, targetable pathways have been identified [97]. To identify such pathways, one study developed a computational algorithm that links microbial metabolites with AD risk genes and phenotypes, providing evidence for SCFAs targeting AD-associated microglial-mediated gut-microbiome-brain interactions at genetic, functional, and phenotypic levels. This study also indicated that SCFAs target the APP gene and AD-related pathways, including "Aβ", "immune system" and "glial cell proliferation", correlating with various AD-associated phenotypes such as "abnormal synaptic transmission", "Aβ deposition" and "glial cell proliferation" [98].

Researchers administered acetate orally for 4 weeks to male APP/PS1 mice and observed significant cognitive improvement. Additionally, acetate increased the levels of GPR41 in BV-2 microglia stimulated with Aβ, while inhibiting the phosphorylation of NF-κB, p65, ERK, and JNK, and reducing COX-2 and IL-1β levels. These findings suggest that acetate exerts anti-neuroinflammatory effects in AD model mice by upregulating GPR41 and inhibiting the ERK/JNK/NF-κB pathway [99]. In another experiment, butyrate treatment also reduced Aβ-induced CD11b and COX-2 levels in BV-2 microglia, and inhibited the phosphorylation of NF-κB p65 [100]. In vivo experiments showed that butyrate treatment suppressed excessive activation of microglia in 5×FAD mice, reduced pro-inflammatory cytokines and Aβ levels, and enhanced synaptic plasticity and expression of synaptic proteins (e.g., PSD-95, SYP, NR2B) [101].

However, when SCFAs receptors GPR41 and GPR43 were knocked out, no significant changes in the microglial phenotype were observed in both wild-type and 5×FAD mice, but cognitive decline was accelerated. Moreover, adult hippocampal neurogenesis was impaired in both 5×FAD and wild-type mice, whereas SCFAs intake reversed this phenomenon and altered the microglial transcriptome, significantly upregulating genes involved in defensive responses (e.g., B2m, Fgl2, H2-K1) and antigen processing and presentation pathways, suggesting that microglia play an effective role as antigen-presenting cells during AD. The study emphasized that peripheral immune pathways mediated by SCFAs-microglia interactions could be a potential target for AD [102].

Interestingly, not all effects of SCFAs-microglia pathways in AD are beneficial. A related study created a germ-free AD mouse model to explore and identify microbial metabolites mediating the gut-brain axis in AD. Surprisingly, the germ-free AD mice exhibited a significantly reduced Aβ plaque load. However, supplementation with SCFAs in both germ-free and conventional SPF (specific pathogen-free) AD mice increased Aβ plaque levels, accompanied by notable changes in microglial transcriptomic profiles and behavioral patterns, including upregulation of APOE and reduced phagocytic ability of microglia toward Aβ plaques [103]. This result suggests that SCFAs could promote Aβ plaque deposition, with microglia mediating this effect. Consistent with this, another study found that propionate treatment reduced the phagocytic ability of Aβ-induced IMG microglia [104]. However, propionate also decreased the expression of APOE and related immune genes. Furthermore, this study observed that propionate altered the microglial metabolism, maintaining a homeostatic phenotype rather than shifting from M1 to M2 phenotype.

In summary, SCFAs-microglia pathways in AD mainly influence neuroinflammation, synaptic damage and plasticity repair, and Aβ protein deposition. The dual effects on Aβ may depend on SCFAs concentration and proportion, the pathological stage of AD, and the experimental model used.

Parkinson's disease (PD)

Clinical studies have shown that the ratio of fecal SCFAs in PD patients differs from that of healthy controls, with a significant increase in the relative concentration of butyrate, suggesting a role for SCFAs in Parkinson's disease [105]. Researchers found that compared to normal PD model mice, germ-free PD model mice or those with antibiotic-cleared gut microbiota exhibited lower levels of microglial activation, α-synuclein inclusions, and motor deficits. However, supplementation with SCFAs restored all the major disease features in the germ-free PD model, indicating that the gut microbiota is essential in PD animal models, and that gut microbiota-derived

Table 1 Targets of SCFAs-microglia pathway

Drug	Disease Models	Target	Effects	References
Acetate	LPS-stimulated BV-2 microglia	p-P38, p-MAPK, p-JNK↓ H3K9 acetylation↑	IL-1β、IL-6、TNF-α、COX-2↓ PLCβ、COX-1↑	[76、77]、
Acetate	LPS stimulation of primary rat microglia	————	iNOS、NO、ROS↓、GSH↑	[84]
Propionate	Microglia from germ-free mouse brain	H3K9ac↑、HDAC1↓	IL-1β、INF-γ、MCP-1↓	[144]、
Propionate	Aβ stimulates IMG microglia	HDACs↓	ApoE、CD36、Msr1、NO↓、Ip1↑Aβ phagocytosis↓	[105]
Butyrate	Aβ stimulates BV-2 microglia	ERK/JNK/NF-κB↓、GPR41↑	CD11b、COX-2、IL-1β↓	[100]、
Butyrate	LPS stimulates BV-2 microglia	H3K9ac、H3K18 acetylation↑、IL-10/STAT3、AKT-RhoGTP、GPR109A/Nrf2/HO-1↑, p-P38、p-ERK1/2、JNK、MAPKs、NF-κB —	PGs、COX-2、IL-10、CD206↑ NOS2、TNF-α、IL-1β、ROS、iNOS↓	[78、79、82、115、141]
Butyrate	Aβ-induced BV-2 microglia	NF-κB p65↓	CD11b、COX-2↓	[101]
Butyrate	Brain microglia of MPTP-induced PD mouse model and BV-2 microglia stimulated by MPP^+	RAS- NF-κB↓	COX-2、iNOS↓	[145]
Butyrate	5×FAD mouse brain microglia	NF-κB↓	PSD-95、SYP、NR2B↑、IL-1β、IL-6、TNF-α↓	[102]
Butyrate	Microglia in the substantia nigra pars compacta of MPTP-induced PD mouse model	NF-κB p65、p-P38、p-JNK↓	IL-1β、IL-6、TNF-α、iNOS↓	[109]
Butyrate	Oxygen-glucose deprived rat primary microglia	————	CD200↑、CD86、IL-1β↓	[111]
Butyrate	Oxygen-glucose deprivation and re-oxygenation stimulate BV-2 microglia	TLR4/MyD88/NF-κB↓	TNF-α、IL-6↓、TGF-β、IL-10↑	[112]

Table 1 (continued)

Drug	Disease Models	Target	Effects	References
Butyrate	High-fat diet-induced primary hypothalamic microglia in mice	AKT/Cdc42、HO-1、AgRp/NPY↑、NOX4、caspase-3、Bax↓	Hypothalamic microglial processes extend and appetite decreases、ROS↓	[130]
Butyrate	Microglia in the cerebellum of Friedreich's ataxia model mice	itaconate-Nrf2-GSH↑	Glycolytic flux↓	[91]
SCFAs	Primary microglia in the hippocampus and spinal cord of a mouse model of neuropathic pain	————	Iba1、CD11b、CD68、IL-1β、TNF-α↑、CD206、IL-4—	[146]
SCFAs	Microglia in the hippocampus of a dietary fiber-deficient mouse model	pCaMK II/pGSK-3β/pTau、GPR41、GPR43↑	GAP43、SV2C↑	[147]
SCFAs	Microglia in the brain of mice with chronic cerebral ischemia model	Stxla↑	Ndufb2、Atp5mc1↑	[96]
SCFAs	Japanese encephalitis virus-infected N9 microglia	miR-200a-3p/ZBTB20/Ikβα↑	MCP-1、TNF-α↓	[142]

metabolites, such as SCFAs, likely mediate their effects on microglia [106].

A recent in vitro study confirmed the anti-inflammatory effects of butyrate in PD. In BV-2 cells treated with MPP^+, sodium butyrate (5 μM) activated the KATP channels by increasing the expression of the inward rectifier potassium channel 6.1 (Kir6.1), which decreased nitrate and pro-inflammatory cytokine production, thereby suppressing microglial activation [107]. In an in vivo study, researchers assessed the effects of three SCFAs (acetate, propionate, and butyrate) on motor impairment, dopaminergic neuron degeneration, and associated neuroinflammation mechanisms in MPTP-induced PD model mice. After 6 weeks of oral gavage of high doses (2 g/kg) or low doses (0.2 g/kg) of sodium acetate, propionate, or butyrate, butyrate showed the most significant effects in reducing microglial activation in the substantia nigra pars compacta (SNPC), lowering α-synuclein levels, increasing tyrosine hydroxylase (TH) levels, and improving PD-induced motor deficits. In addition, butyrate inhibited the activation of NF-κB and MAPK signaling pathways in the SNPC region [108].

However, another study showed completely opposite results. After treatment with sodium butyrate (165 mg/kg/day) in PD model mice, butyrate significantly stimulated microglial activation, enhancing neuroinflammation, reducing dopamine and serotonin levels, and downregulating tyrosine hydroxylase expression, which exacerbated motor deficits in the PD model [109]. The authors attributed this discrepancy to differences in the dose and duration of butyrate administration between the two studies. This suggests that low doses and short-term administration of SCFAs may promote PD pathology,

whereas high doses and long-term administration may improve PD pathology.

In conclusion, the SCFAs-microglia pathway in PD primarily affects neuroinflammation and α-synuclein through the activation of KATP channels. Among the three SCFAs, butyrate appears to have the most significant therapeutic effects on PD pathology. However, careful consideration of the SCFAs dosage and administration duration is necessary.

Cerebral ischemic diseases

Cerebral ischemic diseases (such as stroke and brain injury after cardiac arrest) are among the leading causes of disability globally. The pathological core of these diseases lies in the ischemia/reperfusion-induced cascade of damage, in which the excessive activation and metabolic imbalance of microglia play crucial roles. In recent years, groundbreaking research on the gut-brain axis has revealed the multidimensional protective effects of SCFAs in regulating cerebral ischemic injury, but the specific molecular mechanisms involving the SCFAs-microglia pathway require further in-depth investigation.

In one study, primary murine microglial cells were subjected to an in vitro oxygen-glucose deprivation (OGD) protocol and treated with sodium butyrate (0.1 mM, 1 mM, 10 mM). The results showed that sodium butyrate treatment inhibited microglial proliferation induced by OGD, reduced the expression of pro-inflammatory genes such as CD86 and IL-1β, and increased the expression of anti-inflammatory M2 markers, such as arginase and CD200. This indicates that sodium butyrate shifted the polarization of microglia from the detrimental M1 phenotype to the beneficial M2 phenotype after OGD, highlighting the protective role of SCFAs in cerebral ischemia [110]. In another study, sodium butyrate treatment significantly reduced the levels of MyD88, phosphorylated NF-κB p65, and TLR4 proteins in the brains of model mice and OGD/reperfusion-exposed BV2 cells, promoting the transition of microglial cells from the M1 to the M2 phenotype. This suggests that sodium butyrate can effectively protect the brain from global ischemic insult by lowering neuroinflammation [111]. In a chronic cerebral hypoperfusion model established by bilateral common carotid artery occlusion [95], SCFAs supplementation significantly altered the protein levels of Ndufb2 and Atp5mc1, increased the activities of mitochondrial electron transport chain complexes I and V, improved the metabolic status of microglia, and induced a shift in microglial phenotype from M1 to M2. This suppressed microglial-mediated synaptic loss and maintained normal processes of synaptic vesicle fusion and release, thereby improving synaptic plasticity. Among these, Stx1a protein is considered a key target of SCFAs influencing synaptic transmission. In conclusion, the SCFAs-microglia pathway in cerebral ischemic diseases primarily exerts its protective effects by improving the metabolic state and inducing the polarization of microglia from the M1 to the M2 phenotype, which subsequently plays roles in anti-neuroinflammation and enhancing synaptic plasticity.

Neuropsychiatric disorders (Anxiety, Depression, Autism)

The SCFAs-microglia pathway plays a crucial role not only in brain function development but also in the pathology of stress-related diseases and neurodevelopmental disorders. For example, individuals with ASD often show elevated levels of toxin-producing gut bacteria and their produced SCFAs [112, 113]. In rodents, microglial sensitization and the migration of monocytes to the brain are considered one of the reasons for repeated anxiety after prolonged stress. Similarly, peripheral and central inflammation in humans are associated with psychological symptoms.

In vitro studies have shown that sodium butyrate improves depressive-like behavior caused by microglial activation by inhibiting epigenetic regulatory mechanisms, rather than the NF-κB signaling pathway [114]. In in vivo studies, SCFAs supplementation suppressed microglial activation and neuroinflammation, rescued the reduction of hippocampal neurogenesis in model mice, and reduced blood-brain barrier permeability, thereby improving depressive-like behavior in mice exposed to chronic stress and high fructose intake [115]. Furthermore, cerebrovascular dysfunction and hypoperfusion have been identified as the basis of vascular depression. A recent study used a bilateral common carotid artery occlusion (BCCAO) rat model to simulate vascular depression. The study found that SCFAs supplementation reduced the number of microglia in the hippocampus of BCCAO rats, inhibited microglial activation through the NF-κB signaling pathway, and promoted the conversion of tryptophan (Trp) to serotonin (5-HT) rather than kynurenic acid (Kyn), improving depressive-like behavior. Controversially, the study also found that one of the SCFAs receptors, GPR41, was expressed in microglia [116].

Regarding anxiety, recent studies indirectly explored whether the SCFAs-microglia pathway was involved in CNS diseases induced by acute sleep deprivation. The results showed that after inducing ASD, the gut microbiome in mice was disrupted, with decreased levels of propionate in feces and a significant increase in microglial activation markers such as IBA1 and the chemokine ICAM1 in the cerebral cortex, along with anxiety-like behaviors in the mice [117]. This suggested a potential protective role of propionate in anxiety. However, a single low-dose intraperitoneal injection of propionate (175 mg/kg) contradicted this result, leading to a rapid

and relatively persistent decline in social motivation in adolescent mice, while non-social motivation and emotional domains were unaffected. Morphological analysis of the mice's brains showed an increased number of activated microglia, a significant reduction in presynaptic contour area, and moderate demyelination in some axons. Moreover, early studies have described autism-like behaviors in mice after chronic injection of high-dose propionate (500 mg/kg) [118]. We believe the dual effects of propionate in neuropsychiatric disorders may be due to differences in concentration.

In summary, the SCFAs-microglia pathway exerts bidirectional effects in neuropsychiatric disorders by regulating neuroinflammation, epigenetics, and metabolic reprogramming: butyrate improves depressive-like behavior by inhibiting microglial activation, while propionate may show conflicting effects depending on the dosage and timing of intervention.

Obesity

The hypothalamus is a key brain region that regulates energy homeostasis, controlling food intake, energy storage, and energy expenditure by integrating signals related to body fluids, nerves, and nutrition. The arcuate nucleus (ARC), located near the third ventricle in the middle basal hypothalamus, is a critical cluster for regulating and integrating appetite signals [119]. However, a high-fat and high-carbohydrate diet stimulates the production of late-stage glycation products in neurons that regulate appetite, such as neuropeptide Y (NPY), agouti-related peptide (AgRP), and pro-opiomelanocortin (POMC) in the ARC. This activation leads to microglial reactivity in the hypothalamus, releasing various pro-inflammatory mediators, including cytokines, chemokines, and ROS [120, 121], causing dysfunction of anorexic neurons [122]. Over time, this can lead to obesity and related syndromes. Thus, modulating microglial function and activity through gut microbiome-derived metabolites, such as SCFAs, has become an important pathway for influencing hypothalamic appetite-related neural networks and treating obesity.

Previous clinical and rodent studies have shown that dietary fiber can increase the satiety hormone peptide YY (PYY) from colonic L-cells, thereby suppressing appetite [123, 124]. It has been reported that SCFAs, as metabolites of fiber fermentation, can stimulate human intestinal endocrine cells to produce PYY [94]. These studies suggest that SCFAs supplementation can increase satiety, leading to reduced appetite and energy intake. In related studies [125], high-fat diet (HFD)-fed mice showed significantly reduced butyrate levels in the gut, serum, and brain. However, butyrate supplementation reduced the activation and number of microglia in the hypothalamus and increased dendritic spine density. Furthermore, transcriptomic analysis revealed that microglia are the main target of butyrate treatment, highlighting the importance of the SCFAs-microglia pathway in obesity treatment. Additionally, it has been reported that acetic acid, one of the SCFAs, can cross the blood-brain barrier and preferentially accumulate in the hypothalamus, altering the expression of POMC and AgRP genes [31, 87, 126], while also inhibiting leptin resistance caused by microglial TLR4 activation and subsequent IKKβ/NF-κB signaling [127], though this is still controversial [128].

Further research showed that oral supplementation with sodium butyrate significantly reduced microglial proliferation, inflammatory cytokine expression, endoplasmic reticulum stress, neuronal apoptosis, and NPY expression in the hypothalamus of HFD-induced obese mice. In vitro studies indicated that sodium butyrate inhibited the expression of IL-1β in high-glucose-induced microglia and exerted antioxidant effects by balancing the expression of HO-1 and NOX4. Notably, sodium butyrate treatment upregulated AKT phosphorylation and CDC42 expression under both normal and high-glucose conditions, promoting the extension of microglial filopodia, suggesting that sodium butyrate induces the transition of microglia from an activated to a resting state [129].

In summary, the SCFAs-microglia pathway can improve the homeostatic balance between AgRP and POMC neurons in the hypothalamus by inhibiting neuroinflammation and oxidative stress, thereby enhancing central control of feeding behavior and energy expenditure.

Alcohol use disorder

The pathophysiology of alcohol use disorder (AUD) is believed to involve not only the functional remodeling of the central reward system but also the interactions between gut microbiota and the brain [130]. Chronic alcohol exposure leads to gut microbiota dysbiosis, with reduced SCFAs production, which in turn amplifies addictive behaviors through both neuroinflammation and epigenetic regulation mechanisms. Microglia, as central immune sentinels, play a significant role in sensing and responding to alcohol consumption. Their excessive activation and the release of inflammatory factors are critical contributors to alcohol-related behaviors and brain damage [131, 132, 133]. Moreover, the imbalance in the M1/M2 phenotypes of microglia leads to abnormal synaptic pruning, further stabilizing addiction-related neural circuits. However, the specific role of the SCFAs-microglia pathway and its underlying molecular mechanisms in alcohol use disorder still require further investigation.

A recent study examined the effects of SCFAs on alcohol preference in UCHB rats. The results showed that SCFAs mixtures inhibited voluntary ethanol intake by

85–90%, with butyrate exhibiting the strongest effect. Furthermore, SCFAs reduced the activation of microglia induced by alcohol. This emphasizes the therapeutic potential of SCFAs in reducing alcohol-seeking behaviors associated with addiction [134]. To explore the molecular mechanisms of SCFAs' protective effects on microglia in response to alcohol, researchers used antibiotics to eliminate the gut microbiota in mice. The results indicated that, compared to the untreated group, high-dose alcohol intake increased microglial activation and proliferation in the hippocampus of antibiotic-treated mice, as well as the mRNA levels of key cytokines (MCP-1, TNF-α, IL-1β, IL-6, and IL-10). However, sodium butyrate supplementation blocked these changes, suggesting that gut microbiota metabolites, especially sodium butyrate, can influence drinking behaviors by modulating neuroinflammation [135]. Further studies found that sodium butyrate interacts with GPR109A [136, 137], upregulating PPAR-γ and downregulating TLR4/NF-κB pathway activity, thereby modulating microglial polarization (M1/M2) imbalance in the hippocampus and cortex. Specifically, the elevated state of iNOS + TNF-α + M1 was downregulated, while Arg-1^{+}IL-10^{+}M2 was upregulated, leading to decreased levels of related pro-inflammatory cytokines in both the brain and peripheral blood circulation [138].

In summary, the SCFAs-microglia pathway inhibits neuroinflammation by balancing microglial M1/M2 polarization in the hippocampus, improving abnormal behaviors associated with alcohol use disorder.

Bacterial and viral inflammatory encephalopathy

Neuroinflammation plays a key role in the pathophysiology of inflammatory encephalopathies. Therefore, targeting the SCFAs-microglia pathway has significant therapeutic potential. In a study using Wistar rats with cecal ligation and puncture (CLP) to induce a sepsis model, [^{11}C]PBR28 positron emission tomography scans showed increased [^{11}C]PBR28 uptake in the brain, along with elevated glial cell counts and cytokine levels. This indicated that sepsis increased TSPO expression and stimulated microglial activation and proliferation in the brain, while the sepsis rats also exhibited gut microbiota dysbiosis and decreased levels of acetate, propionate, and butyrate [139]. Supplementation with sodium butyrate reduced oxidative stress and inflammation levels in the hippocampus of sepsis rats through the GPR109A/Nrf2/HO-1 signaling pathway and provided significant survival benefits [140]. Recently, a study explored the SCFAs mechanism based on microRNAs in Japanese encephalitis virus infection. Researchers pretreated N9 microglial cells with an SCFAs mixture before viral infection and used bioinformatics tools to analyze differentially expressed microRNAs and conduct weighted gene co-expression network analysis to identify relevant targets. The results showed that SCFAs treatment promoted the expression of the ZBTB20 transcription factor by inhibiting histone deacetylase activity, upregulating miR-200a-3p expression to regulate the NF-κB pathway, and alleviating the cytokine storm induced by infected host microglial cells [141]. This finding was further validated through in vivo experiments [142]. In conclusion, the SCFAs-microglia pathway exerts anti-neuroinflammatory effects and reduces oxidative stress through epigenetic mechanisms, thereby improving neurodegeneration caused by bacterial and viral encephalopathies.

Therapeutic approaches

The interaction between gut microbiota-derived SCFAs and microglia presents a unique therapeutic target for diseases such as neurodegenerative disorders, neuropsychiatric conditions, neuroinflammatory diseases, and metabolic disorders. However, the methods for precisely modulating this pathway to achieve therapeutic effects remain an urgent scientific issue. This section systematically reviews and provides recent pharmacological methods, aiming to offer insights for future precision and personalized medical treatments.

Prebiotics

The International Scientific Association for Probiotics and Prebiotics defines prebiotics as "a substrate that is selectively utilized by host microorganisms and confers health benefits" [143]. One of the primary categories of prebiotics is dietary fiber, which is typically defined as "carbohydrates with a degree of polymerization greater than 2 that cannot be hydrolyzed or absorbed in the small intestine" [144]. These include inulin, fructooligosaccharides, galactooligosaccharides, resistant starch, and other soluble dietary fibers.

Inulin, a soluble dietary fiber, has been shown to increase the abundance of bacteria that produce butyrate. In studies where inulin or butyrate alone was administered to aged mice, the baseline inflammation and immune response of brain microglia were reduced, suggesting that high-solubility fiber may primarily alleviate microglial overactivity induced by immune aging through butyrate production [145]. More recently, in a study where inulin was administered to both young (3–4 months old) and aged (23–24 months old) mice for 8 weeks, inulin supplementation increased SCFAs levels in the cecum of aged mice, inhibited microglial activation in the brain, and restored most microglial gene expression and TNF-α secretion to levels similar to those seen in young mice [146]. More importantly, dietary inulin reduced the expression of senescence markers (Ccl4 and lgals3) in microglia of aged mice, indicating that dietary inulin can improve the immune aging status of microglia, lower the elevated baseline inflammation

levels associated with aging, and thus prevent the onset of various age-related diseases. Additionally, a recent studyinvestigated the effects of different fiber types (soluble, insoluble, high fiber, and low fiber) on microglia in the hippocampus of mice. The results showed that the expression of SCFAs receptors in the hippocampus was driven by the amount of fiber in the diet, meaning that the effectiveness of exogenous SCFAs administration on microglia was influenced by the concentration of the treatment [43]. In another study, the effects of a fiber diet on microglial function in α-synuclein overexpressing (ASO) mice were examined. The study found that prebiotic supplementation improved the gut microbiota dysbiosis in ASO mice, reduced microglial activation, promoted the expansion of disease-associated macrophage subpopulations with protective effects, reduced α-synuclein aggregation in the substantia nigra, and alleviated motor deficits in the mice [147]. Notably, the beneficial effects of prebiotics were abolished by the use of CSFIR inhibitors, but no change in SCFAs levels was observed in the brain tissue of prebiotic-fed mice. This suggests that, at least in this experiment, SCFAs did not transmit signals through known receptor pathways or epigenetic mechanisms but instead influenced microglial response and gene expression through peripheral immunity.

In conclusion, dietary prebiotics can modulate microglial function by increasing circulating SCFAs levels, thereby reducing the elevated baseline inflammation levels associated with aging.

Fecal Microbiota Transplantation (FMT) and specific microbial colonization

Colonization of specific microbial strains in rodents has proven to be an effective method for studying the interaction between microbiota and physiological processes. A typical FMT procedure in non-sterile rodents involves treating the recipient with an antibiotic mixture (usually administered via drinking water) and subsequently orally administering fecal material from a donor for one or more days. Studies have shown that FMT from aged donor mice leads to impaired spatial learning and memory in young adult recipient mice, which correlates with changes in protein expression in the hippocampus related to synaptic plasticity and neurotransmission. Moreover, bacteria associated with SCFAs production (*Lachnospiraceae*, *Faecalibaculum*, *and Ruminococcaceae*) were significantly reduced. Notably, microglia in the hippocampus exhibited aging-like phenotypes, and label-free quantitative proteomics revealed significant changes in proteins such as Ras/RapGTPase-activating protein SynGAP in microglia. These changes in microglial proteins are related to critical CNS functions and disorders, including filopodia formation, synaptogenesis, learning impairments, behavioral abnormalities, and neuronal plasticity, ultimately contributing to neurodegenerative diseases [148]. These findings suggest that gut microbiota associated with disease can cause neurodamage via the SCFAs-microglia pathway, leading to abnormal behavior [149]. However, transplanting a healthy gut microbiota from a normal donor may help mitigate these effects.

In a related study, Sun et al. performed FMT from healthy mice to PD model mice and observed that this treatment significantly reduced microglial activation in the substantia nigra of PD mice and increased dopamine (DA) and serotonin 5-HT levels in the striatum. This effect was associated with the inhibition of the TLR4/TBK1/NF-κB signaling pathway by the FMT, although the exact molecular mechanisms still require further exploration [150]. In a clinical study on Clostridium difficile infection, a quantitative analysis of SCFAs and short-chain carboxylic acids (SCCA) in the serum before and after FMT treatment showed that successful FMT was associated with improved mental and physical health, along with significant changes in several circulating SCCAs, including increased butyrate, 2-methylbutyrate, valerate, and isovalerate, and a decrease in 2-hydroxybutyrate [151]. In animal experiments, treatment with a mixture of SCCAs (rather than a single SCCA type, as no anti-inflammatory effects were observed with individual SCCAs) significantly reduced inflammation, including reduced cytokine release, decreased nitric oxide (NO) release, and reduced lipid droplet accumulation in primary rat microglia, suggesting that caution is required when interpreting results between humans and rodents.

Regarding specific microbial colonization, *Clostridium butyricum* has been shown to promote butyrate levels and inhibit microglial activation in APP/PS1 mice [100]. Similarly, *Roseburia hominis* (R. hominis) inhibits microglial activation in germ-free (GF) mice and reduces neuroinflammation, mediated by propionate or butyrate through the inhibition of HDAC1 and promotion of Ac-H3K9 expression [152]. Pre-treatment with *Akkermansia muciniphila* increases acetate and butyrate levels, inhibiting extensive activation of microglia in the hippocampus of sleep-deprived mice and preventing synaptic loss in neurons, thus improving cognitive impairment [153]. *Blautia producta* produces butyrate, which primarily inhibits microglial activation in PD model mice by modulating the RAS-NF-κB and COX-2/iNOS pathways [154].

Natural products

Natural products, owing to their multitarget regulatory properties and high biocompatibility, have become ideal pharmacological tools for targeting the SCFAs-microglia pathway. Preclinical studies have accumulated evidence indicating that the dysregulation of pain mediators (such as pro-inflammatory cytokines) released by

pathologically activated microglia plays a crucial role in the development and maintenance of temporomandibular joint (TMJ) inflammation and trigeminal neuralgia [155, 156]. In related studies, resveratrol administered intraperitoneally in a dose-dependent manner restored blood-brain barrier (BBB) permeability and reduced TNF-α release in the trigeminal nucleus caudalis, thereby inhibiting TMJ inflammatory pain. This effect was attributed to the improvement of gut microbiota composition by resveratrol, which increased the regulatory effect of SCFAs on microglial activation in the trigeminal nerve. Additionally, FMT from resveratrol-treated mice significantly alleviated TMJ inflammatory pain. In a spinal cord injury (SCI) mouse model, resveratrol also restored the microbiota pattern, reversed gut dysbiosis, increased butyrate levels, and inhibited microglial activation, thereby promoting functional recovery from SCI [157]. Further research indicated that the action of resveratrol is primarily due to increased SCFAs levels and the expression of their receptors (GPR109A, GPR43), which in turn suppress oxidative stress and inflammation through the SCFAs-microglia pathway, thus repairing neural damage and improving cognitive impairments [158].

In addition to resveratrol, berberine has been widely studied for its association with the SCFAs-microglia pathway. Berberine regulates the gut microbiota to promote elevated levels of butyrate in circulation. The use of butyrate synthesis inhibitors, such as heptanoyl-CoA, indicated that butyrate mainly inhibits the production of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) in microglia in the brains of model mice, thereby improving stroke outcomes [159]. Current studies on berberine focus on its role in alleviating irritable bowel syndrome [160]. Berberine has been shown to significantly improve the gut microbiota structure in experimental mice, increasing acetate and propionate concentrations in feces and restoring the morphological changes of microglia in the spinal cord and hippocampus caused by microbial dysbiosis. This improvement also alleviated visceral hypersensitivity in model mice, as multiple animal studies have shown that microglia in the spinal cord and hippocampus play a key role in visceral hypersensitivity [161]. A recent study confirmed that berberine treatment significantly reduced chronic stress-induced visceral hypersensitivity and the activation of dorsal spinal microglia, while altering the microbiota composition and SCFAs profile. Correlation analysis showed that berberine treatment enriched SCFAs-producing genera, and these genera were positively correlated with microglial morphological parameters [162].

Other natural products include Scutellarin, which improves the Aβ pathology, neuroinflammation, and cognitive deficits in APP/PS1 mice. This effect is mediated by Scutellarin inhibiting the SCFAs downstream Camp-PKA-CREB-HDAC3 pathway in microglia [163]. Ginsenoside Rh4 improves gut microbiota composition, increases SCFAs levels, and significantly inhibits microglial activation and the overexpression of pro-inflammatory cytokines through the LPS/NLRP3/caspase-1/IL-1β signaling pathway, thereby alleviating neuronal apoptosis and synaptic structural damage in the hippocampus [164]. Notably, LPS expression in the colon of model mice and macrophage infiltration into the brain were significantly increased, and Rh4 intervention reversed this phenomenon. This suggests that Rh4 may not directly act on microglia but may regulate microglial function through the SCFAs-microglia peripheral immune pathway. However, this point has not been validated in the study. Additionally, oolong tea polyphenols can inhibit systemic inflammation by regulating the gut microbiota composition, promote SCFAs production, and increase BDNF levels in microglia, as well as the expression of PSD-95 and synaptophysin SYN, thereby improving cognitive impairments caused by circadian rhythm disturbances in model mice. Unlike other drugs, oolong tea polyphenols can enhance the brain's GABA/glutamate balance and improve the conversion rate by inhibiting high levels of glutamate [165].

Chemical drugs

Compared to natural products, synthetic chemical drugs offer advantages such as high specificity, controllable dosages, and well-established safety profiles. Therefore, finding new targets for existing chemical drugs represents a promising direction for treating various diseases. Reports indicate that atorvastatin significantly improved the sensory-motor behavioral deficits in mice with permanent middle cerebral artery occlusion and, by increasing butyrate levels, promoted gut barrier function and inhibited pro-inflammatory polarization of microglia in the ischemic cortex [166]. Rifaximin (150 mg/kg) also elevated butyrate levels in the brain, enhanced the release of anti-inflammatory cytokines from microglia, weakened abnormal phagocytosis by microglia, and prevented abnormal neurogenesis caused by chronic unpredictable mild stress. This result suggests that butyrate might be a key mediator in rifaximin's regulation of microglia [167]. Recently, studies have explored whether dimethyl itaconate administered intraperitoneally could improve the gut-brain axis and prevent cognitive deficits in high-fat diet (HFD)-fed mice. Results showed that dimethyl itaconate improved HFD-induced microbiome alterations, including an increase in propionate- and butyrate-producing bacteria and higher serum levels of propionate and butyrate. This further inhibited microglial activation and neuroinflammation, reduced synaptic ultrastructural damage, and prevented the loss of related proteins (BDNF, SYN, and PSD95), effectively

mitigating HFD-induced cognitive decline [168]. Furthermore, considering the previously discussed unidirectional nature of the "SCFAs–microglia" pathway and the dual (beneficial and detrimental) roles of SCFAs, the development of microglia-specific modulators targeting SCFAs receptors may represent a promising therapeutic strategy. GLPG0974, a potent and selective FFAR2 antagonist, has demonstrated favorable safety and significant, sustained inhibition of neutrophil activation in a recently completed randomized, double-blind, placebo-controlled, single-center clinical trial [169]. Additionally, synthetic FFAR2/3 agonists have been shown to suppress the expression of inflammatory mediators such as IL-1α, IL-1β, and ICAM-1 in human monocytes [170]. However, to our knowledge, no current studies have reported the development of delivery systems designed to target microglia with FFAR2/3 agonists or antagonists for the treatment of neurological diseases. Future studies may focus on the development of microglia-targeted delivery systems in the brain to enable precise modulation of microglial function and thereby maximize the beneficial effects of SCFAs.

Environmental factors

It is well established that sustained environmental stress, including both psychological and physiological stressors, represents a major risk factor for neuropsychiatric disorders [171]. The microbiota–gut–brain axis plays a critical role in mediating this association [172, 173]. In a model of repeated social psychological stress for three weeks, mice exhibited gut microbiota dysbiosis, decreased SCFAs production, increased intestinal permeability, and anxiety- and depression-like behaviors. Notably, exogenous SCFAs supplementation reversed these stress-induced alterations [174]. These findings suggest that environmental stress may contribute to brain dysfunction by disrupting the "SCFAs–microglia" signaling pathway and amplifying its pathological influence on the central nervous system. This also highlights a novel therapeutic perspective—targeting environmental factors to activate or restore the SCFAs–microglia axis may serve as a potential intervention strategy. Enriched environments, characterized by enhanced sensory stimulation, social interaction, and physical activity, have been shown to significantly reduce stress levels in experimental animals. Studies have shown that there are significant differences in the gut microbiota composition between mice raised in enriched environments and those in standard conditions. Mice in enriched environments exhibit significantly higher SCFAs levels. The removal of the microbiota from enriched environment mice using antibiotics significantly lowered SCFAs levels and strongly reduced microglial branching and filamentous length in the visual cortex, hindering visual dominance plasticity, dendritic spine dynamics, and microglial rearrangement in adult mice. Supplementing SCFAs in standard environment mice mimicked the effects of enriched environments, promoting visual dominance plasticity and microglial remodeling. These findings suggest that environment-dependent changes in the gut microbiome can regulate brain circuitry function and plasticity, likely through SCFAs-driven microglial remodeling, which activates cortical plasticity mechanisms [175]. In contrast to the aforementioned beneficial effects, chronic environmental stress may impair brain function by suppressing SCFAs production and consequently weakening their regulatory influence on microglial activity. For example, Chronic lead exposure resulted in a dose-dependent reduction in serum butyrate levels in mice, leading to learning and memory deficits and anxiety-like behaviors. Butyrate was found to inhibit the STAT3 signaling pathway, reduce neuroinflammation in the hippocampus and microglia, promote the binding of histone H3K9ac to the BDNF promoter region, thereby promoting neurogenesis and long-term memory consolidation, and improving learning and memory deficits in the mice [176].

Clinical translational challenges and limitations

Despite the substantial evidence from preclinical studies supporting the beneficial effects of SCFAs on microglial function, clinical data regarding SCFAs–microglia interactions in humans remain limited. Here, we summarize several key challenges and limitations that may hinder the clinical translation of the SCFAs–microglia axis, aiming to provide useful reference points for future research.

1) SCFAs metabolism and delivery: Under current therapeutic strategies, whether by stimulating endogenous SCFAs production or through direct oral supplementation, a major challenge lies in the rapid absorption and metabolism of SCFAs in the gut, resulting in extremely low systemic levels. Moreover, SCFAs must cross the blood–brain barrier to effectively target microglia within the brain, yet efficient and stable delivery systems are currently lacking. Notably, mice possess a relatively large cecum that facilitates hindgut fermentation [177], a structure largely absent in humans, which may contribute to differential SCFAs-related effects between species. Additionally, most animal studies employ high-dose oral gavage or intraperitoneal injection, which does not accurately reflect the pharmacokinetics or physiological concentrations achieved via human oral intake.

2) Microglial heterogeneity and monitoring: Human microglia exhibit dynamic phenotypic changes in disease conditions, highly dependent on the local microenvironment. Current techniques offer limited ability to monitor microglial heterogeneity in vivo in humans, which may result in SCFAs-based interventions being ineffective due to variability in disease stages or individual differences.

3) Species differences between animal models and human pathology: Animal models cannot fully replicate the complexity of microglial phenotypes in human diseases and are subject to species-specific differences in immune-metabolic responses [178]. For instance, human and murine monocytes exhibit distinct signaling and cytokine profiles in response to FFAR2/3 agonists [170]. Furthermore, preclinical findings often fail to predict the real-world efficacy of SCFAs in the human context, which involves high gut microbiota diversity and chronic neuroinflammatory backgrounds, thereby increasing the risk of translational failure. Collectively, these limitations constitute a critical bottleneck in the progression from mechanistic insights to clinical application.

Summary and discussion

In this review, we have summarized the current knowledge on the "SCFAs-microglia" pathway, including the mechanisms of interaction between SCFAs and microglia, the neurodegenerative diseases involved, and pharmacological approaches targeting this pathway. Despite substantial evidence highlighting the potential of SCFAs in neuroimmune modulation, significant challenges remain in this field of research.

1)SCFAs Concentrations: Most studies to date have used SCFAs concentrations much higher than those typically found in human serum [56], making it difficult to determine the actual physiological role of SCFAs in the human body. Furthermore, the results from related experiments have shown some inconsistencies, indicating a need for a standardized approach to measure the biological effects of SCFAs at various concentrations.

2)SCFAs Administration Routes: Most studies use oral administration (such as SCFAs added to drinking water) to supplement SCFAs. This method may cause abnormally high concentrations of SCFAs in the upper gastrointestinal tract. However, physiological SCFAs are primarily produced by intestinal microbes through fermentation in the colon [179]. Oral administration does not accurately mimic the physiological pattern of SCFAs production in the body, which may influence the mechanism and effects of SCFAs.

3)Disease States: The impact of the "SCFAs-microglia" pathway may also depend on specific disease conditions, as well as individual factors such as genetic traits and age [103]. The ratio and administration method of SCFAs may significantly influence their effects, which could be a key reason for the existing controversies in the field.

4) Mechanisms of SCFAs Action on Microglia: Before considering the "SCFAs–microglia" pathway as a potential therapeutic target, an important question must be addressed: how can SCFAs more effectively regulate the physiological functions of microglia? In other words, under current conditions, is it necessary for SCFAs to reach the brain parenchyma in order to exert their neuroimmune effects more efficiently? As discussed in this review, the effects of SCFAs on microglia can be categorized into direct and indirect pathways. Different routes of action lead to differences in SCFAs localization and signal transduction within the body. For instance, in the indirect pathway, SCFAs may act through FFAR2/3 on neutrophils and monocytes, thereby enhancing microglial activation. In contrast, most direct effects of SCFAs are mediated through inhibition of HDACs, exerting anti-inflammatory effects to suppress excessive immune responses in microglia.

Given the current lack of effective and specific delivery strategies for targeting SCFAs to microglia in the brain, indirect regulation of microglial activity may represent a more feasible intervention. Encouragingly, researchers have begun to explore this direction and have already made progress. For example, special diets containing acylated starch can prevent SCFAs absorption in the upper gastrointestinal tract, allowing efficient delivery to the colon, significantly increasing cecal SCFAs concentrations and alleviating anxiety-like behavior in mice [180, 181]. Furthermore, some clinical studies have demonstrated that SCFAs chemically conjugated to inulin via ester bonds can be selectively released in the colon [182, 183]. Additional mechanistic studies showed that colon-targeted SCFAs administration significantly reduced cortisol responses to psychosocial stress in healthy males [184]. Although administration of butyrate alone only significantly affected subjective fear memory without impacting physiological stress responses [185], these findings suggest that colon-targeted SCFAs delivery may be a better and more practical approach for future clinical translation.

5) Measurement and Interpretation of Fecal SCFAs Levels: Currently, due to its non-invasive nature, ease of access, and compatibility with high-throughput and standardized analysis, fecal SCFAs measurement is widely used to evaluate gut microbial metabolic activity. However, fecal SCFAs reflect only the unabsorbed fraction and cannot directly represent the total production, bioavailability, or physiological activity of SCFAs in distant tissues such as the brain [25]. Moreover, fecal SCFAs concentrations are influenced by multiple confounding factors, including dietary fiber intake, microbial cross-feeding, epithelial absorption capacity, and colonocyte metabolism. For example, elevated fecal SCFAs levels may suggest increased microbial production but could also result from impaired absorption or accelerated intestinal transit. Conversely, decreased fecal SCFAs levels may not necessarily indicate reduced production but rather efficient absorption by the host. Therefore, relying solely on fecal SCFAs levels to assess gastrointestinal energy dynamics, nutrient absorption, and microbial

output is insufficient. Future research should consider integrating fecal data with SCFAs measurements in blood circulation and target tissues to more accurately evaluate their physiological significance.

Overall, recent research suggests that SCFAs have region-specific and complex effects on the central nervous system. While we have identified potential impacts of SCFAs on brain behavior markers, studies on the specific brain regions involved and their mechanisms remain scarce. Future research should shift from simple correlation analyses to more in-depth, prospective longitudinal studies, aiming to deepen our understanding of the "SCFAs-microglia" pathway. This research should focus on the spatiotemporal effects of SCFAs at physiologically relevant concentrations and explore how SCFAs influence microglial function through epigenetics, metabolic reprogramming, and neuroimmune communication. We also look forward to large-scale clinical trials to further validate the clinical application prospects of the "SCFAs-microglia" pathway as a potential therapeutic target.

Limitations

It is important to acknowledge that many of the studies cited in this review did not clearly distinguish between resident microglia and infiltrating peripheral macrophages, which may limit the specificity of our understanding regarding the SCFAs–microglia axis. For instance, in animal models of neuroinflammation, peripheral macrophages may extensively infiltrate the brain parenchyma through a compromised BBB, and their immune responses may be mistakenly attributed to activated microglia. This could lead to an overestimation of the role of microglia in certain pathological contexts.

Author contributions

Conceptualization: QC; Investigation: QC, MS and RL; Writing– Original Draft: QC; Review & Editing: YL, ZZ, JZ and DN; Supervision: QZ and RW; Funding Acquisition: JY and GZ.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to participate

Not applicable.

Consent to publish

All the authors agreed to submit the manuscript to "Journal of Neuroinflammation".

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare that there is no conflict of interest with any financial organization, corporation, or individual that can inappropriately influence this work.

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