Advances in the Mechanisms of Short-Chain Fatty Acids in Neurodegenerative Diseases: A Postprint

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Abstract

Neurodegenerative diseases represent a group of disorders arising from progressive loss of neuronal function or structure in the central nervous system. Although the physical or mental symptoms of neurodegenerative diseases can be alleviated through combination therapy, there are currently no strategies that directly slow down or prevent these diseases. Recent research on the gut microbiota-gut-brain axis has revealed that gut microbiota and their metabolites play important roles in the pathogenesis of neurological diseases. As the primary metabolites of gut microbiota, short-chain fatty acids serve as key mediators in gut-brain communication and exert neuroprotective effects against neurodegenerative diseases, yet their specific mechanisms remain unclear. This article primarily reviews the mechanisms of action of short-chain fatty acids in neurodegenerative diseases, aiming to provide references for therapeutic interventions.

Full Text

Research Progress on the Mechanisms of Short-Chain Fatty Acids in Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases comprise a group of disorders characterized by progressive and irreversible loss of neuronal function or structure in the central nervous system. While combined therapies can alleviate physical or mental symptoms, no strategies currently exist to directly slow or prevent disease progression. Recent research on the gut microbiota-intestine-brain axis has revealed that intestinal microbiota and their metabolites play crucial roles in the pathogenesis of neurological disorders. Short-chain fatty acids (SCFAs), as the primary metabolites of gut microbiota, serve as key mediators of gut-brain communication and exert neuroprotective effects in neurodegenerative diseases, though their specific mechanisms remain unclear. This review summarizes the mechanisms through which SCFAs act on neurodegenerative diseases, providing a reference for therapeutic development.

Keywords: neurodegenerative diseases; short-chain fatty acids; oxidative stress; mitochondrial function; neuroinflammation; microglia

Neurodegenerative diseases such as Alzheimer' s disease (AD), Parkinson' s disease (PD), Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) are characterized by progressive and irreversible neuronal loss in specific brain regions, ultimately leading to motor and/or cognitive dysfunction. Over one billion people are reportedly affected by neurodegenerative diseases, with approximately seven million deaths annually worldwide, making these disorders the second leading cause of global mortality. Previous studies have identified protein aggregation, neuronal oxidative stress, mitochondrial dysfunction, neuroinflammation, and gut microbiota dysbiosis as key pathological mechanisms. Accumulating clinical evidence demonstrates extensive intersection between gut microbiota and these common mechanisms of neurodegeneration. Dietary changes and other factors that disrupt gut microbiota homeostasis can promote disease progression. Although the underlying mechanisms remain largely unknown, the hypothesis that SCFAs influence neurodegenerative diseases through the gut-brain axis has garnered increasing attention.

1 Neurodegenerative Diseases and SCFAs

Short-chain fatty acids (SCFAs), also known as volatile fatty acids, are saturated fatty acids containing six or fewer carbon atoms. They represent the primary metabolites produced by bacterial fermentation of dietary fiber and resistant starch in the colon, mainly including acetate, propionate, butyrate, valerate, and caproate (typically existing as anions). Acetate, propionate, and butyrate are the most abundant SCFAs, accounting for approximately 95% of total human SCFAs in a ratio of 60:20:20. The specific types of SCFAs produced by gut microbiota depend largely on microbial composition; for instance, Firmicutes

primarily generate butyrate, while Bifidobacterium species mainly synthesize lactate and acetate.

SCFAs serve as crucial regulators of human homeostasis with important biological functions, including energy provision, anti-inflammatory effects, immune modulation, and maintenance of intestinal integrity. Consequently, SCFAs are implicated in various diseases such as inflammatory bowel disease, type 1 and type 2 diabetes, metabolic syndrome, obesity, colon cancer, and neurodegenerative disorders. In multiple neurodegenerative diseases, significant alterations occur in SCFA profiles and associated gut microbiota concentrations. Studies have demonstrated that PD patients exhibit markedly reduced populations of SCFA-producing bacteria in the colon, with decreased concentrations of total fecal SCFAs and individual acetate, propionate, and butyrate levels. Similar findings have been reported in AD, where mouse models show lower propionate and butyrate levels in both brain and fecal samples compared to wild-type controls. Additionally, MS patients display significant reductions in acetate, propionate, and butyrate in feces and blood. These observations establish a relationship between SCFAs and the pathological processes of neurodegenerative diseases, highlighting the therapeutic relevance of elucidating SCFA mechanisms.

2.1 SCFAs and Protein Aggregation

Although each neurodegenerative disease presents distinct clinical manifestations and selective neuronal loss, they share a common feature of abnormal protein deposition, including misfolded proteins and intracellular inclusions. In AD, extracellular amyloid-β (Aβ) deposition and intracellular hyperphosphorylated tau aggregates form neurofibrillary tangles; in PD, widespread α-synuclein (α-Syn) deposition creates intracellular inclusions (Lewy bodies); and in ALS, misfolded TDP-43 and superoxide dismutase 1 (SOD1) proteins abnormally accumulate. These deposits induce neuronal dysfunction and death, with some aggregates exhibiting direct neurotoxicity that drives neurodegeneration.

Research indicates that SCFAs can modulate protein misfolding and accumulation, exerting beneficial effects in neurodegenerative diseases. Ho et al. found that valerate prevents Aβ aggregation. Treating monomeric Aβ peptides with various SCFAs revealed that valerate directly inhibits formation of A$ 1 − 40 and A 1−42 dimers and trimers at different concentrations (butyrate and propionate shows imilar but weaker ef 40 and A 1−42 into fibrils. In AD mouse models, oral butyrate administration reduces brain A $ levels and improves cognitive memory performance. Moira et al. demonstrated that brain Aβ deposition correlates positively with blood lipopolysaccharide (LPS), acetate, valerate, and pro-inflammatory cytokine levels, but negatively with butyrate and IL-10 levels. Cheng et al. showed that sodium butyrate promotes α-syn degradation in PD models through Atg5-dependent and PI3K/Akt/mTOR-related autophagy pathways. Hou et al. found that sodium butyrate and high-dose sodium acetate reduce α-syn accumulation in the substantia nigra pars compacta of MPTP-induced PD mouse models, alleviating motor dysfunction. Collectively, these findings demonstrate that SCFAs are

closely associated with abnormal protein aggregation in neurodegenerative diseases, and that supplementation or modulation of SCFAs can ameliorate proteinopathies and confer neuroprotection.

2.2 SCFAs and Oxidative Stress

Oxidative stress arises from oxygen metabolism reactions and occurs when oxygen-derived free radicals exceed endogenous antioxidant clearance capacity. Excessive free radicals damage cellular lipids, proteins, and DNA, impairing normal function. Brain tissue is particularly vulnerable to oxidative damage due to its high content of unsaturated fatty acids and lipids combined with relatively weak antioxidant capacity. Previous studies have demonstrated region-specific free radical damage in neurodegenerative diseases such as AD, where oxidative stress plays a central role in pathophysiology, making antioxidant therapy a viable treatment strategy.

2.2.1 SCFAs as Activators of the Keap1-Nrf2 Defense Pathway to Regulate Cellular Redox Homeostasis Nuclear factor erythroid 2-related factor 2 (Nrf2) is the master regulator of cellular antioxidant defense, controlling over 200 genes. Under physiological conditions, Nrf2 primarily binds to its inhibitor Kelch-like ECH-associated protein 1 (Keap1) and undergoes rapid degradation via the ubiquitin-proteasome pathway, maintaining low transcriptional activity. However, during oxidative stress or in the presence of electrophilic xenobiotics, Keap1 activity decreases, allowing Nrf2 to accumulate in the nucleus. Nrf2 then forms heterodimers with small Maf proteins that bind to antioxidant response elements (ARE), upregulating antioxidant enzyme transcription to combat oxidative stress. Butyrate activates Nrf2 by inhibiting histone deacetylases (HDACs) and induces epigenetic modifications of the Nrf2 promoter associated with cooperative antioxidant effects. Dumitrescu et al. established a reciprocal relationship between oxidative stress and Aβ production/aggregation in AD, where oxidative stress enhances Aβ deposition and Aβ triggers oxidative reactions. Szczechowiak et al. demonstrated that SCFAs activate Nrf2 to prevent Aβ accumulation. In another study on butyrate reducing β-site amyloid precursor protein cleaving enzyme 1 (BACE1) expression and Aβ accumulation, cells were shown to uptake butyrate via sodium-coupled monocarboxylate transporter-1 (SMCT1). Following Sp1 acetylation, the p21/Nrf2 pathway is activated, inhibiting NADPH oxidase 2 (NOX2) and upregulating SOD1 to prevent excessive free radical production and alleviate oxidative stress. Hoyles et al. used an in vitro blood-brain barrier (BBB) model with hCMEC/D3 cells to show that propionate activates Nrf2, regulates cellular redox homeostasis, reduces reactive oxygen species (ROS) release, and protects the BBB from oxidative stress damage. These studies collectively demonstrate that SCFAs exert beneficial effects in neurodegenerative diseases through Nrf2 signaling.

2.2.2 SCFAs Directly Mediate Oxidative Stress Nurrahma et al. investigated probiotic supplementation (Lactobacillus salivarius) and its metabolites in

6-hydroxydopamine (6-OHDA)-induced PD rats, finding neuroprotective effects on dopaminergic neurons partly through increased antioxidant enzyme activity of glutathione peroxidase (GPx) and SOD and reduced ROS production, with SCFAs identified as the key active metabolites. In an in vitro model of hydrogen peroxide-induced oxidative damage in mouse mononuclear macrophages, sodium propionate intervention upregulated expression of antioxidant enzymes including heme oxygenase-1 (HO-1) and manganese superoxide dismutase (Mn-SOD), thereby attenuating oxidative stress. Aguilar et al. demonstrated that butyrate reduces oxidative stress during atherosclerosis progression by decreasing NADPH oxidase activity, reducing ROS production and endothelial cell damage. Since cerebrovascular endothelial oxidative stress represents a primary cause of brain tissue damage in various neurodegenerative diseases, SCFAs likely exert therapeutic effects by mediating oxidative stress enzymes.

2.3 SCFAs and Mitochondrial Dysfunction

Mitochondria are double-membrane organelles in eukaryotic cytoplasm that serve as critical hubs for numerous metabolic pathways. The mitochondrial respiratory chain within the inner membrane, comprising complexes I, II, III, IV, and V, generates most cellular ATP through oxidative phosphorylation. The central nervous system has exceptionally high energy demands and thus depends heavily on mitochondrial function, with substantial evidence implicating mitochondrial dysfunction in the pathogenesis of multiple neurodegenerative diseases.

Mitochondrial dysfunction affects mitochondrial biogenesis, dynamics, and mitophagy, leading to impaired electron transport chain function, increased ROS generation, calcium dysregulation, and ultimately neuronal apoptosis, pyroptosis, or necrosis. This causes neurological damage and directly correlates with various neurodegenerative diseases, making mitochondrial function and homeostasis potential therapeutic targets.

2.3.1 SCFAs Influence Mitophagy to Affect Neurodegenerative Disease Progression Mitophagy is the process by which aged or damaged mitochondria are engulfed by autophagic machinery and cleared by lysosomes. Reduced mitophagy leads to accumulation of dysfunctional mitochondria, decreased ATP production, and increased ROS, directly or indirectly causing neurodegenerative diseases. Tang et al. demonstrated that propionate induces degradation of defective mitochondria through mitophagy, inhibiting release of pro-apoptotic factors and blocking apoptotic cascade activation. Shannon et al. showed that butyrate enhances mitochondrial function under physiological stress and/or mitochondrial dysfunction in autism spectrum disorder cell models, potentially by upregulating mitophagy-related genes (PINK1, LC3, PTEN) to promote mitochondrial clearance and regulate mitochondrial function.

2.3.2 SCFAs Influence Mitochondrial Biogenesis to Improve Mitochondrial Dysfunction Shannon et al. also found that sodium butyrate upregulates peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), a master regulator of mitochondrial biogenesis that controls transcription of nuclear respiratory factor 1/2 (NRF1/2), mitochondrial transcription factor A (TFAM), and nuclear-encoded mitochondrial genes, thereby promoting mitochondrial biogenesis and improving energy metabolism deficits. Wang et al. demonstrated that sodium butyrate treatment in AD mouse models increases PGC-1α expression in astrocytes, enhancing mitochondrial biogenesis to maintain normal astrocytic mitochondrial function and improve energy exchange between astrocytes and neurons, ultimately ameliorating cognitive impairment. Liu et al. found that SCFA supplementation increases mitochondrial biogenesis in the brains of diabetic mice with cognitive dysfunction following intermittent fasting intervention. Duscha et al. observed that propionic acid supplementation for 14 days in MS patients significantly and persistently increased regulatory T (Treg) cells while reducing T helper 1 (Th1) and T helper 17 (Th17) cells, with restoration of normal mitochondrial respiratory function and morphology in Treg cells. MS is a chronic autoimmune disease targeting white matter, characterized by myelin destruction around CNS axons, increased pro-inflammatory autoreactive T cells (Th17 and Th1), and reduced Treg cell numbers and function. Since improving Treg cell function correlates with clinical symptom alleviation in MS, propionate' s ability to normalize Treg cell mitochondrial function is crucial for therapeutic efficacy. In summary, SCFAs can influence neurodegenerative diseases directly or indirectly by positively impacting mitochondrial function.

2.4 SCFAs and Neuroinflammation

Neuroinflammation is an inflammatory response in the central nervous system and an essential component of innate immunity that plays critical roles in pathogen clearance and maintenance of neural tissue homeostasis. Microglia are the primary innate immune cells in the CNS, functioning as macrophages that contribute to neuronal development, synaptic pruning, and brain homeostasis. Microglia express various pattern recognition receptors that recognize pathogen-associated molecular patterns, leading to M1 polarization and release of pro-inflammatory mediators. These mediators can directly induce neuronal death and activate other brain cells to release cytokines, promoting peripheral immune cell recruitment to the CNS and triggering inflammatory cascades that damage healthy neurons and drive neurodegeneration. Therefore, modulating microglia-mediated neuroinflammation represents a viable therapeutic strategy.

SCFAs can suppress inflammation by inhibiting microglial overactivation, restoring microglial function, and inducing phenotypic transformation. Hou et al. evaluated the effects of three major SCFAs (sodium acetate, sodium propionate, and sodium butyrate) in MPTP-induced PD mouse models, finding that sodium butyrate attenuated microglial overactivation in the substantia nigra pars com-

pacta, thereby suppressing neuroinflammation and exerting neuroprotective effects. Matt et al. demonstrated that butyrate reduces pro-inflammatory cytokine release (IL-1β and TNF) from microglia in LPS-induced neuroinflammation models in aged mice. Erny et al. showed that mixed SCFAs (acetate, propionate, and butyrate) can restore defective microglia to normal dendritic length, segment number, and cell volume, influencing immune regulation and CNS function. Sadler et al. found that mixed SCFA supplementation converts pro-inflammatory M1 microglia to anti-inflammatory M2 phenotype, improving post-stroke cortical reorganization, synaptic plasticity, and motor deficits. Liu et al. demonstrated that acetate reduces neuroinflammation in AD mouse models by inhibiting microglial M1 polarization, thereby significantly alleviating cognitive impairment.

However, the biological effects of SCFAs on microglia appear highly context-dependent. Alessio et al. reported that SCFA supplementation in mice significantly alters microglial transcriptome profiles, upregulating genes related to inflammatory function and apolipoprotein E (ApoE). ApoE co-aggregation with Aβ fibrils promotes plaque seeding and core stability, further increasing Aβ plaque burden. Dokalis et al. found that acetate modulates microglial phagocytic function during neurodegeneration, affecting disease progression. In germ-free mouse models, microglia remain largely immature with increased mitochondrial ROS production and respiratory chain dysfunction, which acetate supplementation can reverse. However, in AD germ-free mice, while acetate reduces mitochondrial ROS, it also decreases microglial phagocytosis of Aβ plaques, leading to increased plaque deposition. The detailed mechanisms underlying SCFA regulation of microglial transcriptomes and functions remain unclear, and the reasons for differential SCFA effects under various disease conditions require further investigation for personalized therapeutic development.

3 Summary and Outlook

Currently, no clinical strategies exist to directly slow or prevent neurodegenerative diseases. However, growing evidence from gut-brain axis research demonstrates that SCFAs, as gut microbiota metabolites, play important roles in neurodegenerative diseases. SCFAs exert beneficial effects through multiple pathways, including modulation of abnormal protein deposition, reduction of oxidative stress, alleviation of mitochondrial dysfunction, and regulation of microglia-mediated neuroinflammation. Therefore, modifying dietary habits to increase fiber intake, supplementing with SCFA-producing probiotics, and administering exogenous SCFAs may represent safe and effective novel targets for neurodegenerative disease prevention and treatment.

Nevertheless, controversies remain regarding SCFA roles in disease pathogenesis. For example, oral sodium butyrate (200 mg/kg for 3 weeks) alleviates PD symptoms in mouse models, whereas lower doses (165 mg/kg for 1 week) exacerbate inflammation and worsen MPTP-induced PD symptoms. In AD patients, brain amyloid deposition correlates positively with acetate and valerate levels

but negatively with butyrate. These discrepancies illustrate that SCFAs can be a double-edged sword in neurodegenerative disease management. Determining optimal doses, ratios, and SCFA types for personalized treatment strategies requires further exploration. Additionally, most current research involves animal models, with limited clinical studies. Future investigations should focus on dietary interventions and probiotic supplementation to evaluate how altered SCFA levels affect neurodegenerative diseases, providing a reliable foundation for clinical translation.

Literature Search Strategy: English databases (PubMed, Medline, Web of Science, SCI-hub) were searched using keywords: "short-chain fatty acids," "SCFAs," "neurodegenerative diseases," "oxidative stress," "mitochondrial function," "neuroinflammation," "microglia," "mitochondrial autophagy," "mitochondrial biogenesis." Chinese databases (CNKI, Wanfang, VIP, SinoMed) were searched using corresponding Chinese terms. Search period: database inception to July 20, 2022. Inclusion criteria: published literature. Exclusion criteria: insufficient data, duplicate publications, unavailable full text, or poor-quality studies. A total of 53 articles were included.

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Note: Figure translations are in progress. See original paper for figures.