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Gut Microbiota Metabolite Messengers in Brain Function and Pathology at a View of Cell Type-Based Receptor and Enzyme Reaction

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Abstract

The human gastrointestinal (GI) tract houses a diverse microbial community, known as the gut microbiome comprising bacteria, viruses, fungi, and protozoa. The gut microbiome plays a crucial role in maintaining the body's equilibrium and has recently been discovered to influence the functioning of the central nervous system (CNS). The communication between the nervous system and the GI tract occurs through a two-way network called the gut-brain axis. The nervous system and the GI tract can modulate each other through activated neuronal cells, the immune system, and metabolites produced by the gut microbiome. Extensive research both in preclinical and clinical realms, has highlighted the complex relationship between the gut and diseases associated with the CNS, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. This review aims to delineate receptor and target enzymes linked with gut microbiota metabolites and explore their specific roles within the brain, particularly their impact on CNS-related diseases.

Key Words: Gut-brain axis, Gut microbiome metabolites, Short-chain fatty acids, Secondary bile acids, Tryptophan metabolites, Neurodegenerative disease

INTRODUCTION

The human gastrointestinal tract is a thriving ecosystem, hosting a diverse and abundant community of enteric microbiota, predominantly composed of Bacillota and Bacteroidota, which collectively constitute up to 75% of the gut's microbial population (Lay *et al*., 2005). This symbiotic relationship between the gut microbiome (GM) and its host is remarkably intricate, culminating in the generation of an array of metabolites crucial for maintaining gut homeostasis (Li *et al*., 2022). Of utmost importance in this interplay are the specialized receptors and enzymes specifically targeted and engaged by these microbial metabolites, orchestrating a plethora of indispensable biological processes (Wang *et al*., 2021). Simultaneously, the gut flora can influence the central nervous system (CNS) and nerve cells, impacting nervous system function and the progression of related diseases (Tremlett *et al*., 2017). From multiple reports regarding the gut microbiome's role in modulating CNS functions, the concept of microbiota-gut-brain axis has emerged (Browning and Travagli, 2014). Recent research has focused on this axis, exploring its implications in understanding gut microbiome and its effects on neurological function and human health (Ding *et al*., 2019). The microbiota-gut-brain axis orchestrates diverse pathways such as the autonomic and enteric nervous system, the immune system, and the microbiota alongside its metabolites (Piccioni *et al*., 2022).

Microbial signaling molecules exert both direct and indirect influence on the brain (Morais *et al*., 2021). Within the gut, certain microbes produce molecules, such as amino acids and neurotransmitters (Eicher and Mohajeri, 2022). However, neurotransmitters generated by gut bacteria like serotonin, γ-aminobutyric acid, acetylcholine, and noradrenaline, cannot directly cross the blood-brain barrier (BBB) (Eicher and Mohajeri, 2022). Exceptionally, amino acids like tryptophan enter systemic circulation and cross the BBB (Pardridge, 1979) to function as neurotransmitter precursors directly influencing brain functions (Höglund *et al*., 2019). Also, some metabolites successfully traverse the BBB and bind directly to receptors and target proteins (Zou *et al*., 2021). The expression of these receptors varies among different cell types and functional ar-

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eas of the brain. These metabolites play roles in regulating CNS inflammation (Sampson *et al*., 2016), maintaining BBB integrity (Parker *et al*., 2020), fostering neuron development (Kim and Shim, 2023), and mitigating neurotoxicity caused by various stressors (Dempsey *et al*., 2019).

Various metabolites from gut microbiome such as secondary bile acids, amino acids, and short-chain fatty acids (SCFAs), modulate immune system pathways that influence behavior, memory, learning, locomotion, and neurodegenerative disorders.(Kipnis, 2016; Mittal *et al*., 2017). Studies primarily conducted in germ-free (GF) animals or those treated with broad-spectrum antibiotics unveil how specific microbiota can exert considerable influence on CNS physiology and neurochemistry (Vernocchi *et al*., 2016). GF mice, lacking associated microflora, show deficiencies in learning, recognition, and memory, alongside alterations in crucial neurotransmitters when compared to conventionally colonized mice (Foster *et al*., 2017). Crucially, bidirectional communication along the gut microbiota–brain axis is observed notably in neurodegenerative diseases (Foster *et al*., 2017) which include illnesses like Alzheimer's (AD), Parkinson's (PD), and amyotrophic lateral sclerosis (ALS) (Boddy *et al*., 2021; Park and Kim, 2021; Swer *et al*., 2023).

In the context of brain pathology, microbiota metabolites exert their regulatory effects through various mechanisms, including modulation of the immune system and alteration of BBB integrity. Although there are numerous types of microbiota-derived metabolites, we focused on 3 types of metabolites, SCFAs, bile acids, and tryptophan metabolites, which are mainly considered crucial metabolites in a dynamic interplay between the gut microbiota and the central nervous system. While the precise mechanisms by which gut microbiome-derived metabolites impact the CNS remain largely obscure, numerous animal studies have underscored the microbiome's influence on vital neurological and behavioral processes. These metabolites might hold key positions in the critical phase of neurodegenerative disorders.

SCFAs FROM THE GUT MICROBIOME

SCFAs are short, organic monocarboxylic acids that generally comprise up to six carbon atoms (Cook and Sellin, 1998). Their primary source is anaerobic fermentation within the large intestine, starting from indigestible polysaccharides such as dietary fiber and resistant starch (Cummings and Macfarlane, 1991). SCFAs mainly consist of acetate (C2), propionate (C3), and butyrate (C4), in a proportion of roughly 60:20:20, respectively (Cummings *et al*., 1987), and their production in the gut ranges from 500 to 600 mmol per day (Bergman, 1990). Though fiber fermentation predominantly drives SCFA production, these compounds can also be synthesized from the metabolism of amino acids, although by a minority of the microbial population in the large intestine (Smith and Macfarlane, 1997). Upon absorption by the host, SCFAs serve as vital metabolic fuels, facilitating glucose and lipid synthesis to meet the host's energy requirements (Clausen and Mortensen, 1994; Hamer *et al*., 2008). Colonocytes absorb SCFAs and employ them in mitochondrial β-oxidation and the citric acid cycle, meeting their significant energy requirements (Hamer *et al*., 2008). Studies in humans suggest that butyrate alone fulfills approximately 70% of colonocyte energy needs (Roediger, 1980). Unmetabolized SCFAs enter portal circulation, with a fraction moving into the systemic circulation to provide energy to peripheral tissues (Bloemen *et al*., 2009). In humans, SCFAs contribute to about 10% of daily caloric intake (Bergman, 1990).

Acetate, a two-carbon SCFA, acts as a vital energy source for host cells, particularly in the brain and peripheral tissues (Bélanger *et al*., 2011). Apart from its role in energy metabolism, acetate demonstrates anti-inflammatory properties (Vinolo *et al*., 2011), reduces appetite (Frost *et al*., 2014), and fortifies gut integrity by enhancing tight junction protein expression, offering partial protection against colitis (Laffin *et al*., 2019). The primary route involves the decarboxylation of pyruvate to form acetyl-CoA, followed by the hydrolysis of acetyl-CoA into acetate through an acetyl-CoA hydrolase (Miller and Wolin, 1996). This process is primarily driven by enteric bacteria like *Prevotella* spp., *Ruminococcus* spp., *Bifidobacterium* spp., *Bacteroides* spp., *Clostridiodes* spp., *Streptococcus* spp., *A. muciniphila*, and *B. hydrogenotrophica*, contributing significantly to acetate production (Rey *et al*., 2010). Alternatively, acetogenic bacteria employ the *Wood-Ljungdahl* pathway to convert acetyl-CoA into acetate (Ragsdale and Pierce, 2008).

Propionate is a three-carbon SCFA which regulates gut hormone release such as peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), leading to reduced weight gain (Psichas *et al*., 2015). It influences brain regions related to food intake regulation, alters preferences towards high-energy foods (De Vadder *et al*., 2014; Byrne *et al*., 2016), diminishes gut inflammation (Akhtar *et al*., 2022), and fortifies tight junctions, and enhances mucin production maintaining gut barrier function (Ma *et al*., 2012). Propionogenic bacterial pool is composed of *Lactobacillus plantarum*, *Bacteroides thetaiotaomicron*, *Ruminococcus obeum*, *Coprococcus catus*, *Bacteroides vulgatus*, *Akkermansia muciniphila*, and *Veillonella parvula* (El Hage *et al*., 2019).

Butyrate, a four-carbon SCFA, exhibits robust anti-inflammatory effects (Inan *et al*., 2000; Klampfer *et al*., 2003; Schwab *et al*., 2007). It also modulates gut permeability (Peng *et al*., 2009), and influence gene expression through epigenetic pathways. Furthermore, it regulates energy metabolism by boosting ketone body production, notably beta-hydroxybutyrate to provide an alternative energy source for the brain, possibly via increased FGF21 (Li *et al*., 2012). The majority of Firmicutes is known for butyrate production (Singhal *et al*., 2021). Among these, at the genus level, *Ruminococcus*, *Clostridiodes*, *Eubacterium*, and *Coprococcus* stand out as common butyrate producers. Within the *Clostridiodes* genus, *Clostridiodes butyricum* (*C. butyricum*) is particularly prevalent (Fu *et al*., 2019). Other notable genera include *Faecalibacterium* and *Butyrivibrio* (Benevides *et al*., 2017).

Beyond their role in energy provision, SCFAs influence various aspects of health, impacting insulin sensitivity, regulating appetite, and potentially preventing diet-induced insulin resistance and obesity (Shimizu *et al*., 2019). While only a small portion of SCFAs derived from the colon enters systemic circulation (Bloemen *et al*., 2009), they exert diverse effects on organs and systems. Well-documented effects include modulating the immune system, particularly butyrate's role in inducing regulatory T cell differentiation and controlling inflammation (Furusawa *et al*., 2013). Moreover, SCFAs affect gut conditions such as inflammatory bowel disease (Zhang *et*

al., 2022), regulate brown adipose tissue activation (Hu *et al*., 2016), and influence liver mitochondrial function (Mollica *et al*., 2017). Recent discussions have revolved around the microbiota's role and the effects of SCFAs on the CNS.

SCFAs and target proteins

The engagement of SCFAs with G protein-coupled receptors (GPCRs) represents a critical axis in their regulatory functions. GPCR43 (GPR43, FFAR2) and GPR41 (FFAR3) exhibit varied responses to short-chain fatty acids (C2–C6), displaying differing affinities determined by the length of the carbon chain. Among these, GPR43 shows heightened sensitivity to acetate and propionate, while GPR41 displays a preference for propionate, butyrate, and pentanoate (Brown *et al*., 2003; Le Poul *et al*., 2003; Nilsson *et al*., 2003). These receptors are expressed not only in the gastrointestinal tract but also in various immune cells, adipocytes, the brain, and other tissues (Brown *et al*., 2003; Le Poul *et al*., 2003). Their activation triggers intracellular signaling cascades, primarily involving G-proteins and downstream effectors such as cAMP (Park *et al*., 2022), ERK1/2 (Kim *et al*., 2013), and intracellular calcium flux (Maruta and Yamashita, 2020; Park *et al*., 2022).

GPR41's mRNA expression profile indicates its predominant presence in various tissues such as adipose tissue, pancreas, spleen, lymph nodes, bone marrow, and peripheral blood mononuclear cells (Silva *et al*., 2020), notably including monocytes (Silva *et al*., 2020) and sympathetic ganglia (Kimura *et al*., 2011). However, its detection in the pituitary gland and neuron in Genotype-Tissue Expression (GTEx) project data is notably faint (Lonsdale *et al*., 2013). GPR43 is predominantly present in cells within the distal ileum, colon, lung and adipose tissue, showcasing its highest expression among immune cells like monocytes and neutrophils (Le Poul *et al*., 2003; Ren *et al*., 2023). This distribution aligns closely with leukocyte markers, particularly notable in macrophages and the germ line of leukocytes, indicating a strong presence in immune cells (Brown *et al*., 2003). The widespread yet relatively moderate expression of GPR43 could be linked to its association with infiltrating neutrophils and macrophages, suggesting a regulatory role within these immune cells. Interestingly, studies suggest that GPR43 expression levels can be influenced during inflammatory responses. When exposed to immune challenges such as lipopolysaccharide (LPS), tumor necrosis factor (TNF), or treatment with granulocyte-macrophage colony-stimulating factor (GM-CSF), human monocytes exhibited increased GPR43 transcript levels (Senga *et al*., 2003; Ang *et al*., 2015). In the central nervous system (CNS), GPR43 expression remains comparatively repressed compared to other FFARs. Its detection is limited to glial cells and neurons within the caudate nucleus, although GPR43 can also be identified in cortical neurons and the pituitary gland (Silva *et al*., 2020). Moreover, GPR109A (HCAR2) serves as another key receptor for SCFAs, primarily butyrate (Blad *et al*., 2012). It exhibits tissue-specific expression, especially in colonic epithelial cells and immune cells (Blad *et al*., 2012; Ganapathy *et al*., 2013). Upon activation, GPR109A can modulate inflammatory responses by regulating immune cell differentiation and cytokine production (Singh *et al*., 2014).

The effects of SCFAs on different cell types are multifaceted. For instance, in enteroendocrine cells, SCFA-mediated activation of GPR41 and GPR43 stimulates the secretion of GLP-1 and PYY (Freeland *et al*., 2010). GLP-1 acts as an incretin hormone, regulating insulin secretion, while PYY influences gut motility and satiety (De Silva and Bloom, 2012). In pancreatic β-cells, SCFAs primarily activate GPR41, leading to increased insulin secretion (Veprik *et al*., 2016). In an *in vivo* study using rats, butyrate demonstrated a neuroprotective effect by mitigating neuronal apoptosis through the GPR41/Gβγ/PI3K/AKT pathway (Zhou *et al*., 2021). These mechanisms highlight the intricate role of SCFAs in regulating glucose homeostasis, pancreatic function, neuroprotection and potentially offering insights into therapeutic interventions for metabolic disorders. Additionally, it's important to note that the signaling outcomes initiated by GPCRs such as GPR43 and GPR41 can be significantly modulated by the presence of specific metabolites, leading to biased signaling. This phenomenon indicates that different SCFAs can selectively activate certain signaling pathways over others within the same receptor, altering the physiological response based on the metabolic context. This mechanism of biased signaling underscores the importance of the metabolic environment in determining the specific outcomes of GPCR activation by SCFAs, highlighting a complex interplay between metabolism, receptor signaling, and physiological regulation.

Beyond GPCR-mediated signaling, SCFAs' impact on histone deacetylase (HDAC) activity is pivotal in epigenetic regulation (Waldecker *et al*., 2008). HDAC facilitates the removal of acetyl groups on histone complex, prompting the negatively charged DNA to interact with positively charged histones (Smith and Denu, 2009). This interaction causes condensation of chromatin structure, which creates less accessible environment for gene expression therefore suppressing gene transcription (Kuo and Allis, 1998). HDACs are widely expressed in nearly all tissues investigated, including the brain (de Ruijter *et al*., 2003). SCFAs inhibit HDACs particularly class I and II to promote histone acetylation (Waldecker *et al*., 2008). This epigenetic modification affects gene expression profiles across various cell populations, influencing immune responses (Liu *et al*., 2023), metabolic pathways (Donohoe *et al*., 2012), and neuronal functions (Szentirmai *et al*., 2019). The intricate interplay between SCFAs and their receptors, along with their regulation of HDAC activity, extends its influence beyond the gut (Duan *et al*., 2023; Moțățăianu *et al*., 2023).

SCFAs as functional molecules in the brain

SCFAs, apart from exerting local effects within the colon and peripheral tissues, are thought to play a pivotal role in the communication between the microbiota and the brain. Endothelial cells that are rich in monocarboxylate transporters (MCTs) suggest a potential pathway for SCFAs to cross the BBB (Uchida *et al*., 2011). In both human and rodent brain endothelium, MCT1 is a proton-dependent cotransporter/exchanger that allows the entry of SCFAs into the brain parenchyma (Gerhart *et al*., 1997; Leino *et al*., 1999). Studies in rats involving the injection of 14C-labeled SCFAs into the carotid artery have demonstrated the brain's uptake of SCFAs (Oldendorf, 1973). Reported concentrations in the human brain average 17.0 pmol/mg of tissue for butyrate and 18.8 pmol/mg of tissue for propionate (Bachmann *et al*., 1979). In mice supplemented with live *Clostridiodes butyricum*, butyrate levels in the brain were found to range from 0.4 to 0.7 μmol/g, approximately ten times higher than concentrations in peripheral blood (Li *et al*., 2018). SCFAs also have been implicated in modulating neurotransmitter and neurotrophic

factor levels, impacting brain neurochemistry. Acetate, for instance, has demonstrated the ability to alter neurotransmitter levels—glutamate, glutamine, and GABA—in the hypothalamus, alongside increasing the expression of anorexigenic neuropeptides (Frost *et al*., 2014). Propionate induced a rise in GABA levels within the brain, indicating a potential inhibition of GABA breakdown (Morland *et al*., 2018). Physiological levels of SCFAs promote human neural progenitor cell growth and mitosis, suggesting their role in regulating early neural system development (Yang *et al*., 2020).

Alterations in the composition of gut microbiota, especially a reduction in SCFA-producing bacteria, are linked to a variety of neuropathological conditions, such as Alzheimer's disease (Zhang *et al*., 2017a), Parkinson's disease (Wallen *et al*., 2020), multiple sclerosis (Saresella *et al*., 2020), stroke (Stanley *et al*., 2018) and vascular dementia (Liu *et al*., 2015). This association is evident from observations that neuropathological conditions often exhibit decreased levels of SCFAs, especially butyrate, in plasma or fecal samples, suggesting a potential biomarker for neurological disorders (Aho *et al*., 2021; Chen *et al*., 2022; Gao *et al*., 2023; Mayo-Martínez *et al*., 2024). The administration of butyrate or bacteria capable of producing butyrate has frequently been associated with improved neurological outcomes (Park and Sohrabji, 2016; Liu *et al*., 2017; Li *et al*., 2018), underlining the therapeutic potential of modulating SCFA levels in the treatment and management of brain pathologies.

Furthermore, the bidirectional communication between the gut and brain is highlighted by the fact that changes in the gut's microbial environment can both precipitate and result from neurological damage, as observed in cases like traumatic brain injury (Opeyemi *et al*., 2021). This interconnection is mediated through complex neuroendocrine and neuroimmune pathways, integrated with the autonomic and enteric nervous systems, thereby establishing a causal relationship between gut microbiota and brain function (Ahmed *et al*., 2022). The gut-brain axis is further influenced by SCFAs through their interaction with specific receptors on the intestinal epithelium, which regulate the secretion of hormones and neurotransmitters (Gershon and Margolis, 2021; Ahmed *et al*., 2022). These substances can communicate with the brain either directly through the bloodstream or indirectly through activation of the vagus nerve, impacting a wide range of neurological processes.

The integrity of the BBB holds immense significance for maintaining central nervous system homeostasis. Comprising microvascular endothelial cells equipped with tight junctions (TJs), it includes transmembrane proteins like claudin and occludin, alongside cytoplasmic proteins such as zonula occludens (ZO) (Ibrahim *et al*., 2022) (Fig. 1A). The transmembrane proteins occludins and claudins engage in interactions between adjacent endothelial cells, establishing a robust physical barrier that impedes paracellular diffusion (Fanning *et al*., 1999). The anchoring process involves members of the ZO family, specifically ZO-1 and ZO-2, which bind these transmembrane proteins together, reinforcing the barrier integrity (Umeda *et al*., 2006). SCFAs not only cross the BBB but also seem to play an important role in maintaining its integrity (Fock and Parnova, 2023). Evidence from GF mice underscores this regulatory role, as reduced expression of tight junction proteins like claudin and occludin results in increased BBB permeability from prenatal stages through adulthood (Braniste *et al*., 2014). Remarkably, reintroducing a diverse microbiota or monocolonizing with SCFA-producing bacterial strains in adult GF mice restores BBB integrity (Braniste *et al*., 2014). In an *in vitro* study utilizing cerebrovascular endothelial cells, propionate treatment was observed to counteract the permeability effects triggered by exposure to lipopolysaccharide (LPS), indicating a potential role for SCFAs in modulating BBB function (Hoyles *et al*., 2018). These effects could potentially be mediated through GPR109A, a receptor for butyrate, which contributes to the promotion of expressions of occludin, claudin-1, and ZO-1 in rats (Ibrahim *et al*., 2022).

Microglia play a crucial role in refining nervous system circuits during maturation by eliminating excessive synaptic connections (Wilton *et al*., 2019). Proper brain development relies heavily on controlling innate immune function in the CNS, with the gut microbiota emerging as a key influencer. Research using GF mice highlights how the microbiota impacts microglial maturation (Erny *et al*., 2015). In GF mice, which lack microbial colonization, microglia development is prevented while oral administration of key SCFAs promotes microglial maturation. Butyrate treatment, in particular, reduces microglial activation and pro-inflammatory responses both *in vitro* and *in vivo* (Wang *et al*., 2018). Similarly, acetate treatment diminishes inflammatory signaling by reducing the expression of IL-1β, IL-6, and TNF-α, along with the phosphorylation of p38 MAPK, JNK, and NF-κB in microglia cultures (Soliman *et al*., 2012). Although SCFAs can trigger anti-inflammation via GPR43, predominant anti-inflammatory effects occur through inhibiting HDACs (Fig. 1B). SCFAs, specifically acetate and butyrate, inhibited HDAC and NF-κB activities, reducing inflammation induced by LPS (Caetano-Silva *et al*., 2023). These effects occurred even without SCFA receptor expression in microglia and are independent of MCTs, suggesting direct diffusion across cell membranes. Furthermore, research indicated that HDAC inhibitors promote microglial branching and AKT activation, highlighting the importance of HDAC blockade in butyrate-induced process growth (Wang *et al*., 2018). Blocking AKT undermines butyrate's anti-inflammatory action, its prevention of microglial contraction, and its alleviation of behavioral disturbances induced by LPS. This underscores a novel anti-inflammatory mechanism of SCFAs through microglial morphology changes.

According to an *in vitro* study employing neuron progenitor cells, the investigation suggests the impact of SCFAs on the growth rate of human neural progenitor cells (hNPCs) derived from the HS980 human embryonic stem cell line (Yang *et al*., 2020). They observed that physiological concentrations (μM) of SCFAs—acetate, propionate, and butyrate—heightened the growth rate of hNPCs, promoting a higher number of cells to undergo mitosis. Moreover, the researchers found that SCFA treatments influenced the expression of genes associated with neurogenesis, proliferation, and apoptosis (such as ATR, BCL2, BID, CASP8, CDK2, E2F1, FAS, NDN, and VEGFA), indicating that SCFAs facilitate the proliferation of human neural progenitor cells (Fig. 1C).

In the neurons, GRP43 expression is relatively low compared to other SCFA receptors. It is primarily detected in glial cells and neurons of the caudate, with an additional presence in cortical neurons and the pituitary gland (Silva *et al*., 2020). Moreover, GPR41 is known to be expressed in neurons found within the brain and spinal cord (Brown *et al*., 2003; Nøhr *et al*., 2015). Studies focused on GPR41/GPR43 functions sug-

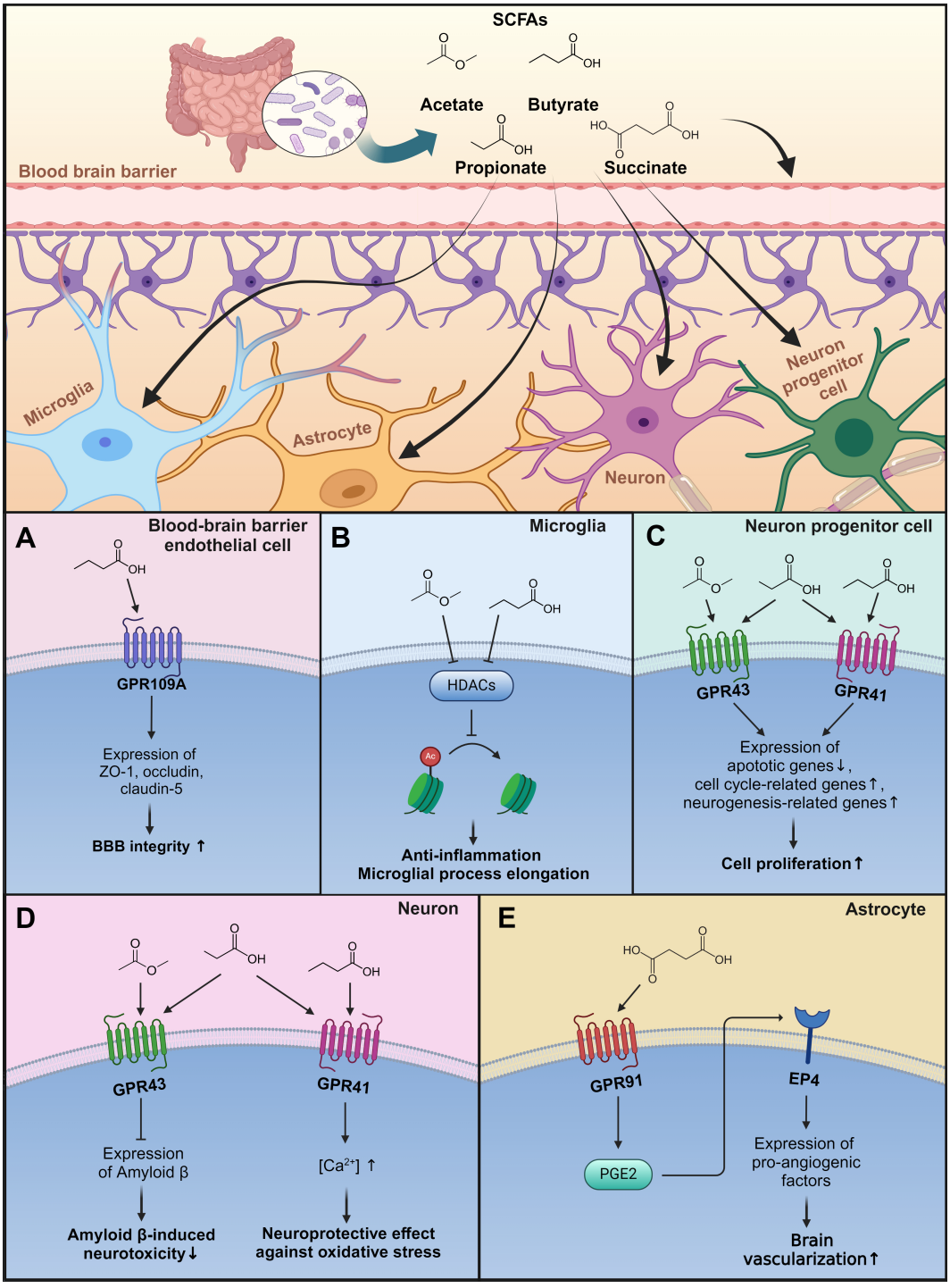

Fig. 1. Molecular Mechanisms of Short-Chain Fatty Acids (SCFAs) in Diverse Brain Cell Types. The gut microbiome plays a crucial role in producing short-chain fatty acids (SCFAs) such as acetate, butyrate, propionate, and succinate. These SCFAs traverse the BBB through the monocarboxylate transporter 1 (MCT1) expressed in the BBB. (A) Blood-Brain Barrier (BBB). Within the BBB, the GPR109A receptor, specifically responsive to butyrate, contributes to the upregulation of key proteins like occludin, claudin-1, and ZO-1, reinforcing BBB integrity. (B) Microglia. Although microglia express few GPCRs, SCFAs function as HDAC inhibitors, fostering an anti-inflammatory environment and promoting the elongation of microglial processes. (C) Neuronal Progenitor Cells. GPR41 and GPR43 mediate crucial processes in neuronal progenitor cells, influencing the regulation of apoptotic genes, cell cycle-related genes, and genes related to neurogenesis, thereby supporting the proliferation of neuronal progenitor cells. (D) Neurons. Activation of GPR43 by SCFAs leads to decreased amyloid-beta (Aβ) expression, thereby reducing neurotoxicity. GPR41-mediated signaling in neurons elevates calcium ion efflux, exhibiting a neuroprotective effect against oxidative stress. (E) Astrocytes. The activation of succinate receptor GPR91 in astrocytes induces the expression of PGE2. PGE2 binds to EP4 receptors and enhances the expression of pro-angiogenic factors, promoting brain vascularization.

gest their role in modulating oxidative stress and inflammation in various tissues, including neuronal cells. Some studies investigated the protective role of SCFAs and GPR41 activation against oxidative stress-induced neuronal cell injury (Saikachain *et al*., 2023) (Fig. 1D). Researchers' findings suggest that physiological SCFA levels could shield neurons from H_2O_2-induced damage. Similarly, a study demonstrated that GPR43 inhibition exacerbates Aβ-induced neurodegeneration, while GPR43 activation by Fenchol mitigates these abnormalities by promoting Aβ clearance and reducing cellular senescence (Razazan *et al*., 2021) (Fig. 1D). Additionally, other study demonstrated the accumulation of succinate in the hypoxic retina of rodents (Sapieha *et al*., 2008). They highlighted succinate's role, acting through its receptor GPR91, as a potent mediator of vessel growth in both normal retinal development and proliferative ischemic retinopathy. This effect of GPR91 is modulated by retinal ganglion neurons (RGCs), which, upon encountering heightened succinate levels, regulate the production of various angiogenic factors, including VEGF. Notably, succinate did not exhibit proangiogenic effects in RGC-deficient rats, suggesting a metabolite signaling pathway in which succinate, through GPR91, regulates retinal angiogenesis. This highlights the role of RGCs as sensors of ischemic stress (Sapieha *et al*., 2008).

Conversely, there's limited research exploring the functional mechanisms of SCFAs in astrocytes. In a study on brain vascularization and recovery mechanisms following post-hypoxia-ischemia, succinate, a minor component of SCFAs, played a role through the modulation of GPR91 (Hamel *et al*., 2014). The researchers observed the accumulation of succinate in the cerebral cortex expressing GPR91, with GPR91 regulating the expression of various angiogenic factors. Notably, the succinate/GPR91-induced expression of key proangiogenic factors, particularly VEGF, was found to be modulated through a prostaglandin E2 (PGE2)/prostaglandin E receptor 4 (EP4)-dependent mechanism (Fig. 1E).

BILE ACID AND THE SECONDARY METABOLITES AFFECTING THE BRAIN

Bile acids, also known as bile salts, are amphipathic molecules composed of both hydrophilic and hydrophobic regions. It is synthesized in hepatocytes and stored in the gallbladder until it is secreted into the intestine. The main role of bile acid is the emulsification of dietary fats for efficient digestion and absorption to our body. Dietary fat forms large droplets in the aqueous environment of our body, making digestive enzymes hard to access and break it down. Bile acid with its amphipathic nature, can break down these droplets and form small droplets. After aiding in fat digestion and absorption, almost 95% of bile acids are reabsorbed in the small intestine and returned to the liver through a process called enterohepatic circulation. The remaining 5% of bile acid interacts with the intestinal bacteria flora to produce secondary bile acid (Winston and Theriot, 2020). It will create secondary bile acids deoxycholic acid (DCA) from cholic acid(CA), lithocholic acid (LCA), and ursodeoxycholic acid (UDCA) from chenodeoxycholate (CDCA) for humans (Thomas *et al*., 2008).

Synthesis of bile acid can be largely divided into primary synthesis in our body and secondary synthesis by intestinal bacteria flora. The primary synthesis of bile acid comprises two distinct pathways. The classical pathway and alternative pathway (Ramirez-Perez *et al*., 2017). In the classical route of bile acid synthesis within liver hepatocytes, cholesterol undergoes transformation into 7α-hydroxycholesterol by the enzyme 7α-hydroxylase (CYP7A1). Further enzymatic actions by 12α-hydroxylase (CYP8B1) and sterol 27-hydroxylase (CYP27A1) lead to the formation of CA and CDCA, respectively. In the alternative or acidic pathway, cholesterol is converted into 27-hydroxycholesterol by mitochondrial CYP27A1 in extrahepatic tissues (Chiang, 2013). Another alternative bile acid synthesis is in the brain. In the brain, cholesterol homeostasis is maintained through specific metabolic processes. Neuronal sterol 24-hydroxylase (CYP46A1) plays a pivotal role by transforming cholesterol into 24(S)-hydroxycholesterol. This conversion increases the solubility of the compound, facilitating its movement out of neural tissues. The efflux across the BBB is then mediated by the lipoprotein transport mechanism involving ATP-binding cassette transporter 1 (ABCA1) (Ferrell and Chiang, 2021). CDCA and CA may be conjugated to amino acids taurine or glycine through BA-CoA synthase and BA-amino acid N-acetyl transferase to gain more solubility to water and less cytotoxicity (Yang and Qian, 2022).

Secondary bile acid production, which is mediated by intestinal bacteria modifies secreted primary bile to form other metabolites. Deconjugation is a process of removing glycine or taurine conjugates in CA or CDCA. Microbial bile salt hydrolase (BSH) modifies and deconjugates taurocholic acid (TCA) and taurochenodeoxycholic acid (TCDCA) to CA and CDCA. Then microbial 7α-dehydroxylase (7α-HSDH) dehydroxylates them, which converts them to DCA and LCA respectively (Kuhn *et al*., 2020). Bacteria with BSH activity mainly include *Firmicutes* and phyla *Bacteroidetes*. Gram-positive bacteria are *Clostridiodes*, *Bacteroidetes*, *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Escherichia*, and *Listeria* (Winston and Theriot, 2020). Gram-negative bacteria are primarily *Methanobrevibacter smithii* and *Methanosphera stadtmanae* of the domain Archaea (Ridlon *et al*., 2016). DCA and LCA are the most abundant forms of secondary bile acid. Due to various possible modifications, numerous types of secondary bile acids have been reported to date (Winston and Theriot, 2020).

After active or passive transportation through the intestinal membrane, secondary bile is either subjected to enterohepatic circulation or acts as a signaling molecule circulating through the blood. The brain is one of the organs that secondary bile can affect. Several secondary bile acid receptors are known to exist in the brain composing cells such as neurons, astrocytes, microglia, and oligodendrocyte cells (Hurley *et al*., 2022). Several transporters such as Apical sodium-dependent bile acid transporter (ASBT) (McMillin *et al*., 2016) and Organic anion transport polypeptides (OATP) (Ose *et al*., 2010) are reported to transfer peripheral secondary bile acid to the brain. Also, some bile acids can go through BBB due to their hydrophobic nature (Grant and DeMorrow, 2020). Several bile acid receptors are reported in peripheral organs as well as in the brain which will be further elucidated below.

RECEPTORS OF SECONDARY BILE ACID IN THE BRAIN

Secondary bile acid can act as a signaling molecule and interact with various receptors and enzymes. In this review,

the most well-known targets of secondary bile acid will be introduced.

FXR

The Farnesoid X receptor (FXR) is a bile acid-activated nuclear receptor (BAR) that plays a significant role in regulating bile acid synthesis, transport, reabsorption, and metabolism, as well as carbohydrates and lipids metabolism. Primarily expressed in the liver and intestines, FXR regulates key genes involved in these metabolic processes upon ligand binding (Jiang *et al*., 2021a). This receptor is a member of the nuclear hormone receptor superfamily, indicating its crucial role in various biological and metabolic processes (Tian *et al*., 2022). FXR plays a crucial role in the synthesis and transport of bile acids (BAs), as well as in their enterohepatic circulation. Additionally, it is significantly involved in various metabolic pathways related to glucose and lipids (Wei *et al*., 2020). Wu *et al*. (2023) found that induced spared nerve injury (SNI) of the sciatic nerve causes neuropathic pain accompanied by downregulation of bile acid and upregulation of CYP7A1 exclusively in microglia in the spinal dorsal horn. Moreover, the expression of bile acid receptors TGR5 and FXR increased in glial cells and GABAergic neurons in the spinal dorsal horn. Treatment with TGR5 and FXR agonist alleviated established mechanical allodynia in mice by inhibiting ERK pathway (Wu *et al*., 2023) (Fig. 2A). FXR activation by its ligand and CDCA showed increased expression of small heterodimer partner (SHP) gene in mouse neuron. However, the function of SHP gene in neuron needs further research (Huang *et al*., 2016) (Fig. 2C). According to research done by Huang *et al*. (2015), knocking out of FXR in mice resulted in impaired memory and reduced motor coordination. Also, the concentration of secondary bile such as TCA, TDCA, tauro-ω-muricholic acid (TωMCA), tauro-β-muricholic acid (TβMCA), DCA, and LCA increased as well. Although the exact effect needs more elucidation, bile acids present in the brain appear to be partially related (Huang *et al*., 2015).

VDR

The vitamin D receptor (VDR) is a nuclear hormone receptor that mediates the physiological functions of the calcemic hormone 1α,25-dihydroxyvitamin D3 [1,25$(OH)_2D_3$]. LCA and DCA are also effective ligands of VDR (Makishima *et al*., 2002; Thompson *et al*., 2023). VDR is under a ligand-dependent conformational change to bind with retinoid X receptor and form heterodimers. This heterodimer binds to vitamin D responsive elements in DNA regions controlled by [1,25$(OH)_2D_3$] (Haussler *et al*., 2013). The presence of VDR is also reported in astrocytes and microglia. Although brain cell-specific signaling pathways need more clarification, there are few phenotype-based reports on VDR. VDR-mediated signaling via vitamin D3 could inhibit the activation of hippocampal astrocytes, increase BDNF expression and protect hippocampal neurons from external toxins (Zou *et al*., 2022) (Fig. 2B). Also, tauroursodeoxycholic acid (TUDCA) injection in a spinal cord injury (SCI) model showed anti-inflammatory effect, significantly improving motor functions and lesions. TUDCA treatment group had decreased pro-inflammatory cytokine levels and suppressed p-ERK, and p-JNK in the MAPK pathway (Han *et al*., 2020).

TGR5

TGR5, also known as G protein-coupled bile acid receptor 1 (GPBAR1), is a membrane-bound receptor and a member of the GPCR family. TGR5 is mainly activated by LCA and DCA of the secondary bile (Wahlstrom *et al*., 2016). TGR5 is fairly known for its anti-inflammatory role in astrocytes and microglia. In an experimental autoimmune encephalomyelitis (EAE) multiple sclerosis (MS) mouse model, treatment of TUDCA improved EAE mediated astrocytic neuroinflammation. Activated TGR5 suppressed AKT/NF-κB signaling pathway and the nuclear translocation of NFκB (Xu *et al*., 2023) (Fig. 2B). Activation of microglia and astrocytes in the spinal dorsal horn can lead to neuroinflammation and increased pain sensitivity. When TGR5 or FXR agonist was injected intrathecally, the established mechanical allodynia was alleviated in mice. The agonists inhibited the activation of glial cells and ERK pathway in the spinal dorsal horn (Wu *et al*., 2023) (Fig. 2A). TGR5 is also located in the hypothalamus of the brain. Ashley Castellanos-Jankiewicz *et al*. (2021) reported that diet-induced obese mice had altered bile acid content. Also, central administration of TGR5 agonist decreased body weight and fat mass by activation of sympathetic nervous system. Significant alteration of secondary bile acid such as TUDCA and TDCA shows that microbiome metabolite can affect the homeostasis of the host (Castellanos-Jankiewicz *et al*., 2021).

S1PR2

S1PR2 is one of five different S1PRs (S1PR1-5) (Takabe and Spiegel, 2014). S1P is a ligand of S1PR2 which can be easily implicated from the name. S1P is an important bioactive lipid molecule that regulates multiple cellular responses (Qiu *et al*., 2022). In ischemic brain injury, S1P mediates brain injury through activation of microglia and M1 polarization of microglia through binding with S1PR2. Suppressing S1PR2 attenuated M1-relevant ERK1/2 and JNK in post-ischemic brain or lipopolysaccharide-driven M1 microglia (Sapkota *et al*., 2019). Also, in the scope of metabolic disorders, cognitive deficit in type 2 diabetic mice is mediated by activated microglia. S1PR2 inhibition increased p-AKT and TP53-induced glycolysis and apoptosis regulator (TIGAR) levels and reduced p53 in the prefrontal cortex and hippocampus of type 2 diabetic mice (Sood *et al*., 2024). In the case of secondary bile acid, S1PR2 is expressed in neurons and activated by TCA treatment. Activated neurons secrete chemokine ligand 2 (CCL2) leading to microglial activation and neuroinflammation (McMillin *et al*., 2017) (Fig. 2C).

NEUROTRANSMITTER RECEPTOR-MEDIATED MODULATION OF BILE ACID IN BRAIN FUNCTION

In addition to conventional bile acid receptors, other targets are known to be present in the brain that are affected by secondary bile acid. The neurological functions of secondary bile can be generated from interaction with ligand-gated ion channels such as N-methyl-D-aspartate (NMDA) receptor and γ-aminobutyric acid ($GABA_A$) receptor. NMDA is a glutamate receptor and ion channel found in neurons that plays a crucial role in synaptic plasticity, learning, and memory formation (Li and Tsien, 2009), and the $GABA_A$ receptor is an ionotropic receptor and ligand-gated ion channel that mediates the majority of inhibitory neurotransmission in the central nervous system

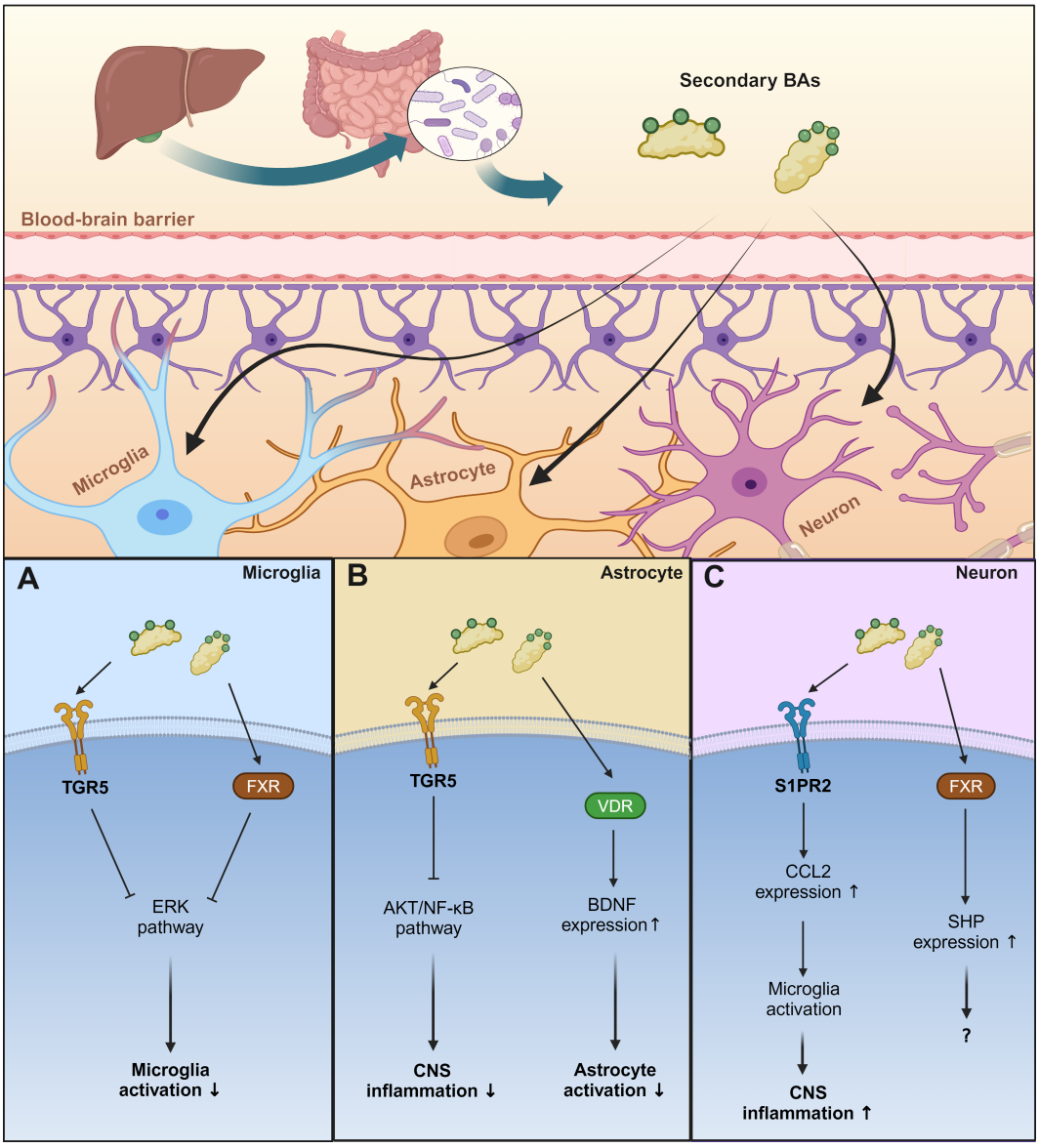

Fig. 2. Secondary bile acid produced by gut microbes can circulate through blood and pass through BBB to affect microglia, astrocytes, and neurons in distinct ways. (A) In microglia, bile acid can either activate TGR5 or FXR to inhibit microglial activity for an anti-inflammatory effect via attenuation of ERK pathway. (B) Activated TGR5 suppressed the AKT/NF-κB pathway which reduces CNS inflammation. VDR activation via specific ligands inhibits activation of hippocampal astrocytes. Leading to suppressed inflammatory effect. (C) Neurons can also be activated by bile acid mediated by S1PR2 and FXR. When bile acid binds to S1PR2, CCL2 is expressed and secreted to induce microglia activation and CNS inflammation. Activation of the nuclear receptor FXR induced expression of SHP.

(Ghit *et al*., 2021). According to the research by Schubring *et al*. (2012), CDCA and CA can act as antagonists of NMDA and $GABA_A$ receptors which reduced the firing of hypothalamic neurons and synchronized the network activity (Schubring *et al*., 2012). Although much more research is necessary, direct interaction of CDCA and CA with neurotransmitter receptors suggests a neuromodulatory role of microbe-derived bile acid.

TRYPTOPHAN AND TRYPTOPHAN DERIVATIVES

Tryptophan (Trp) is one of the essential amino acids which is a building block for proteins. Also, it functions as a precursor of some biochemicals through several metabolic pathways. Trp metabolism includes indole pathway, kynurenine (Kyn) pathway, and serotonin pathway (Lee *et al*., 2018; Sun *et al*., 2020b). Many metabolites from these three major Trp metabolism pathways are known for working as ligands for aryl hydrocarbon receptor (AhR) (Natividad *et al*., 2018). AhR has been shown to participate in a variety of physiological processes including intestinal homeostasis by regulating functions of several immune cells (Rothhammer and Quintana, 2019).

When AhR is activated by ligand binding, AhR is localized from the cytoplasm into the nucleus, where it is dimerized with

AhR nuclear translocator (ARNT). This heterodimer is then translocated to the promoters of AhR target genes and induce gene expression. Some inflammatory cytokines, including IL-6, IL-10, and IL-22, and CYP genes such as CYP1 and CYP3A are associated with AhR activation and play crucial roles in maintaining host homeostasis (Schiering *et al*., 2018; Ma *et al*., 2020).

Although most of the Trp obtained from ingested protein can be absorbed in the small intestine, tryptophan can still reach the large intestine, where it would be metabolized by various microbes (Kaluzna-Czaplinska *et al*., 2019). Certain bacteria, such as *Clostridiodes*, *Ruminococcus*, *Blautia*, and *Lactobacillus*, have been identified as capable of converting tryptophan to Trp in a TrpD-dependent manner (Williams *et al*., 2014). Additionally, many Gram-negative and Gram-positive bacterial species, including Escherichia coli, Clostridiodes sp., and Bacteroides sp. have been reported to metabolize Trp in Tryptophanase (TnaA)-dependent manner.

In this section, we discussed the latest findings on Trp metabolites within the "microbiome-gut-brain" axis, highlighting the role of AhR as a crucial node in the signaling pathway from microbiota to the brain. Recent research showed that AhR can decrease inflammatory cytokines in astrocytes (Rothhammer *et al*., 2016) and microglia (Rothhammer *et al*., 2018), which may be novel aspects to consider in several brain diseases (Jain *et al*., 2014). Additionally, the vagal nerve system is mentioned as a key pathway for gut microbiota to modulate brain function.

Metabolic pathways of tryptophan

The Kyn pathway is the dominant Trp metabolic pathway. Approximately 90% of ingested Trp is degraded along this pathway in both immune cells and epithelial cells (Clarke *et al*., 2013; Vecsei *et al*., 2013). Kyn and its metabolites, specifically 3-hydroxykynurenine (3HK), have the ability to penetrate the BBB. This characteristic holds great significance due to their specific targeting and significant implications in the pathogenic activities of neurological disorders, as well as their role in neurotransmitter metabolism (Garrison *et al*., 2018). When Astrocytes absorbed 3HK, microglia and neurons are activated by astrocytes and start to produce neuroprotective kynurenic acid (KYNA). On the other hand, microglia are responsible for generating neurotoxic metabolites of the kynurenine pathway (KP), such as quinolinic acid (QA) (Wu *et al*., 2023). The manifestation of neuroactive function relies not only on the downstream products of the Kyn pathway through AhR but also on the coevolution of IDO1, TDO2, and AhR. The breakdown of Trp via the Kyn pathway is facilitated by IDO and TDO, which are recognized as enzymes that regulate the rate of the process and generate Kyn as an agonist for AhR (Pantouris *et al*., 2014).

Indole and its derivatives such as 3-acetic acid (IAA), indoleacrylic acid (IA), indole-3-aldehyde (I3A), and indole-3-propionic acid (IPA) also can work as AhR ligands. Certain microbiota produces some indole derivatives and affect microglia activation. These activated microglia then transfer signals through the AhR in astrocyte cells. This signaling helps mediate responses to CNS inflammation and ultimately reduces CNS autoimmunity (Nicolas and Chang, 2019).

AhR signaling by microbial tryptophan metabolites

The combination of IFN-I signaling in astrocytes and Trp microbial metabolites triggers the activation of AhR (Rothhammer *et al*., 2016). This activated AhR then inhibits the activation of NF-κB by inducing the expression of suppressor of cytokine signaling 2 (SOCS2) (Marsland, 2016). The transcription factor NF-κB plays a crucial role in controlling immune activities and acts as a central mediator in inflammatory responses. Several researches demonstrate that NF-κB activates neuroinflammation (Shih *et al*., 2015; Nguyen *et al*., 2022; Sun *et al*., 2022). Additionally, AhR is shown to mediate the effective anti-inflammatory and neurodegeneration-arresting properties of interferon-alpha receptor-1 (IFNAR-1) (Rothhammer *et al*., 2016). Therefore, the IFN-I-AhR-SOCS2-NF-κB pathway provides a molecular mechanism for the protective effects of AhR ligands against CNS autoimmunity (Marsland, 2016).

Microglia, in addition to astrocytes, is a type of immune cell found in the CNS and has been found to express AhR (Lee *et al*., 2015; Salter and Stevens, 2017). Certain astrocytes receive signals from microglia, and these two cell types communicate at a molecular level to regulate responses to inflammation in the CNS (Liddelow *et al*., 2017) (Fig. 3A). The activation of microglia is regulated by microbial metabolites of Trp, which leads to the production of TGFα and Vascular endothelial growth factor B (VEGF-B) (Rothhammer *et al*., 2018). These molecules play a role in regulating CNS-associated diseases and the transcriptional program of astrocytes through AhR. Extensive research has demonstrated that TGFα derived from microglia acts through the ErbB1 receptor in astrocytes, exerting neuroprotective functions and promoting astrocyte activities (Anderson *et al*., 2016; Rothhammer *et al*., 2018) (Fig. 3B).

Tryptophan metabolites in brain function

One of the major Trp metabolites, KYNA, plays a key role in brain cognitive function. In animal models, systemic administration of KYNA causes impairments in spatial working memory (Chess *et al*., 2007), auditory sensory gating (Shepard *et al*., 2003), and reduction in all behaviors linked to glutamatergic and dopaminergic neurotransmission (Rassoulpour *et al*., 2005; Amori *et al*., 2009; Konradsson-Geuken *et al*., 2010). In contrast, deletion of KAT-II which is a main biosynthetic enzyme of KYNA results in a decrease of KYNA level in rat CNS and improved cognitive performance in behavioral experiments (Potter *et al*., 2010; Pocivavsek *et al*., 2011). These researches showed that fluctuation of brain KYNA levels have a distinct relationship with cognitive behavior.

Tryptophan metabolites in Oligodendrocyte cell

In Oligodendrocyte cells, the role of AhR is related to myelination. Gene regulation via AhR ablation in mice leads to defects of myelin sheath structure and composition. Pro-inflammatory cytokines such as TNF-a and IFN-r are elevated in the impaired CNS and a signal transducer STAT1 is causally linked to an AhR-dependent decreased expression of myelin-associated genes (Juricek *et al*., 2017). The physical interaction between STAT1 and AhR has been demonstrated in several immune cells. AhR-dependent inflammatory regulation of STAT1 in oligodendrocytes leads to its interaction with AhR (Kimura *et al*., 2009).

Tryptophan metabolites in the amygdala region

Microbial-derived Trp metabolites have been found to be linked to the connectivity of crucial regions within the brain's

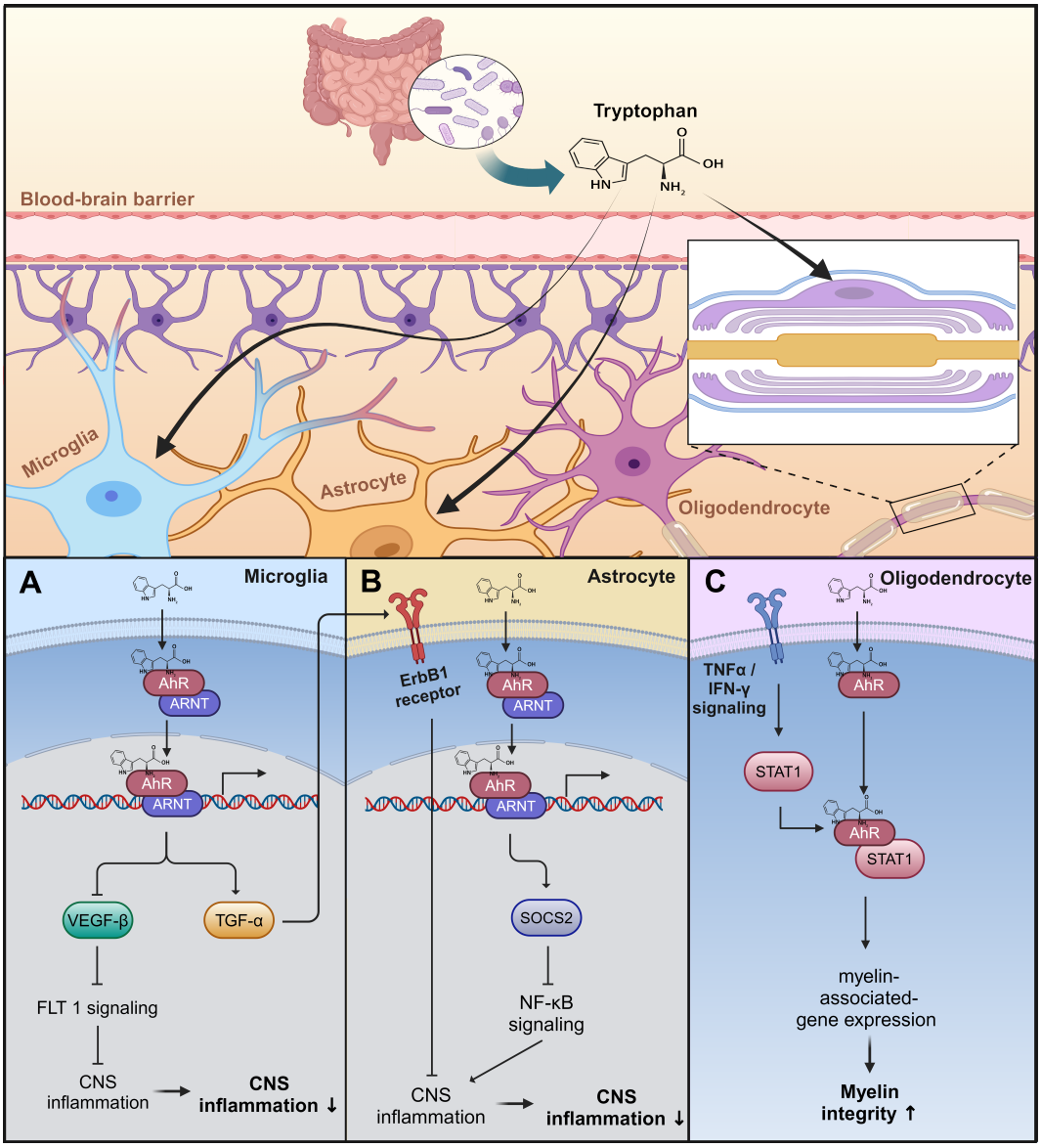

Fig. 3. Modulation of brain cell activity by gut microbe-derived tryptophan metabolites. The Aryl hydrocarbon Receptor (AhR) plays a crucial role as a central point in the signaling of tryptophan metabolites to the brain. The impact of tryptophan metabolites, facilitated by gut microbes, extends beyond the intestine and may have implications for central nervous system (CNS) inflammation in various types of brain cells. (A) Tryptophan metabolites, including indole derivatives, activate microglia, which then transmit signals (activating TGF-α or suppressing VEGF-β) through AhR in astrocytes to suppress CNS inflammation. TGF-α then affects astrocyte through ErbB1 receptor which also modulates CNS inflammation. (B) In astrocytes, SOCS2 gene is expressed via AhR-tryptophan metabolites signaling. SOCS2 blocks activation of NF- κB signaling and finally decreases inflammation response of CNS. (C) In oligodendrocyte cells, AhR binds to STAT1 which works as a transcription factor of myelin genes and AhR stabilizes activation of stat1. Following ligand binding to AhR, increased expression of myelin associated gene helps to maintain myelin integrity.

extended reward network. Specifically, the circuitry involving the amygdala-nucleus accumbens (NAcc) and the amygdala-anterior insula (aINS) plays a vital role in the microbial-gut-brain signaling that influences non-homeostatic food intake (Mayer, 2011). The activation of the AhR by indole-3-acetic acid (IAA) signal may provide an explanation for the positive correlation observed between indoles, the amygdala-aINS circuit, and food addiction scores (Osadchiy *et al.*, 2018). In this region, AhR acts as a transcription factor and regulates the rate-limiting enzymes involved in Trp metabolism along the kynurenine pathway (Jaronen and Quintana, 2014).

Vagus pathways modulation of tryptophan metabolites

Despite the potential involvement of metabolic and immune pathways in the microbiome-gut-brain communication, the hijacking of vagus nerve (VN) signaling remains the most efficient and expeditious means by which the gut microbiota influences brain function (Fulling *et al.*, 2019). The vagus nerve plays a role in maintaining body homeostasis by controlling hunger, satiety, neurotransmitter levels, and inflammation in

the brain (Browning *et al*., 2017).

Rather than direct interaction with the gut microbiota, the vagal afferents detect signals from microbial metabolites or products that diffuse across the gut barrier (Bonaz *et al*., 2018). Neuro-modulatory metabolites, derived from the microbiota, consist of GABA, catecholamines, Trp precursors, and metabolites like serotonin (Bravo *et al*., 2011).

The metabolism of Trp results in the production of indole or serotonin, which has a significant impact on host biosynthesis and alters the levels of neurotransmitters in the host (Yano *et al*., 2015). The increased expression of the c-Fos in the dorsal vagal complex can serve as an indication of vagus nerve activation (Covasa and Ritter, 2005). Therefore, the increased expression of c-Fos following indole treatment suggests the activation of vagal afferent fibers in the intestinal mucosa caused by indole (Jaglin *et al*., 2018). Activated vagal nerve system by microbial metabolites affects a vast array of crucial bodily functions, including control of mood, immune response, digestion, and heart rate.

GUT MICROBIOTA METABOLITES AND BRAIN DISORDERS

The recognition of gut microbiota's influence on brain function has prompted extensive research into neurological disorders (Cryan *et al*., 2019). This concept is bolstered by experimental and clinical evidence, which demonstrates correlations between changes in microbiota and these conditions. These alterations could either contribute to these diseases or hold potential to prevent and ameliorate the progression of CNS pathologies (Fan and Pedersen, 2021; Madhogaria *et al*., 2022). Furthermore, there's a growing body of evidence emphasizing the critical role of metabolites produced by the gut microbiota in signaling along this gut-brain axis (Rahman *et al*., 2023). Disruptions in this signaling pathway may underpin disturbances in the CNS, ranging from conditions in neurodevelopment to those in neurodegeneration (Sochocka *et al*., 2019; Warner, 2019; Wu *et al*., 2021b; Andoh and Nishida, 2022).

Alzheimer's disease (AD)

AD is characterized by amyloid-beta (Aβ) aggregation, tau hyperphosphorylation, neuroinflammation, and metabolic disruptions (Gong and Iqbal, 2008; Chen, 2018; Ryu *et al*., 2019). Gut dysbiosis is increasingly associated with AD, evidenced by altered gut microbiota in AD transgenic mice and patients (Zhang *et al*., 2017a; Zhuang *et al*., 2018). In a human study, researchers observed reduced levels of *Bacteroides* in individuals with AD (Zhuang *et al*., 2018), aligning with prior research indicating lower *Bacteroides fragilis* levels in individuals with cognitive decline and brain amyloidosis (Cattaneo *et al*., 2017). Conversely, AD patients showed an increase in *Ruminococcus* species, which was associated with lower levels of N-acetylaspartate, which is an indicator of neuronal health (Zhuang *et al*., 2018). This dysbiosis links to neuroinflammatory processes (Sochocka *et al*., 2019) particularly microglial activation (Cerovic *et al*., 2019), and compromises intestinal barriers (Honarpisheh *et al*., 2020; Heston *et al*., 2023). This allows inflammatory substances into circulation, contributing to brain inflammation. In comparison to healthy controls, individuals with mild cognitive impairment exhibited decreased fecal levels of SCFAs (Nagpal *et al*., 2019; Wu *et al*., 2021a). Among these, patients diagnosed with AD displayed the lowest concentrations of SCFAs in their fecal samples. Additionally, an alteration in gut microbiota diversity was observed in mice models of AD (Zhang *et al*., 2017a), mirroring findings in human studies. Notably, this shift included a reduction in the population of butyrate-producing bacteria, aligning with similar trends identified in human research. In the pursuit of potential therapeutics for AD, researchers have been exploring the efficacy of SCFAs. Oral administration of *Bifidobacterium breve* strain A1, capable of generating acetate, demonstrated significant alleviation of Aβ-induced cognitive decline (Kobayashi *et al*., 2017). Similarly, *Clostridiodes butyricum*, a producer of butyrate, exhibited the capability to ameliorate cognitive impairment, diminish Aβ accumulation, and mitigate neuroinflammation by reducing both microglial activation and the release of proinflammatory cytokines (Sun *et al*., 2020a). Moreover, the transplantation of fecal matter from wild-type mice into APP/PS1 mouse model, which is a dual-gene knockout used to study AD showed promising results in improving pathological markers, primarily by augmenting SCFA production (Sun *et al*., 2019). In an *in vivo* investigation involving germ-free mice with AD, notable findings emerged. Germ-free APP/PS1 mice displayed significantly reduced levels of Aβ plaque accumulation alongside significantly decreased concentrations of SCFAs in their plasma (Colombo *et al*., 2021). Intriguingly, supplementing SCFAs to germ-free AD mice led to an increase in Aβ plaque load, reaching levels comparable to conventionally colonized (specific pathogen-free) animals. These suggest that SCFAs act as crucial mediators influencing Aβ deposition, likely by modulating the microglial phenotype in the context of AD.

In the case for secondary bile acid, VDR has a role in reducing cerebral soluble and insoluble Aβ peptides. Treatment with a VDR ligand induced P-gp and reduced both soluble and insoluble Aβ peptides, particularly in the hippocampus, which has a high expression of VDR (Durk *et al*., 2014). MahmoudianDehkordi *et al*. (2019) observed significantly lower serum concentrations of CA and increased levels of DCA, as well as its glycine and taurine conjugates, in individuals with AD compared to the normal group. An increased ratio of DCA to CA, which reflects 7α-dehydroxylation of CA by gut bacteria, showed a strong correlation with cognitive decline (MahmoudianDehkordi *et al*., 2019). Nho *et al*. (2019) reported that altered ratios of 23 serum bile acids have been associated with cerebrospinal fluid biomarkers of AD (Nho *et al*., 2019; Hurley *et al*., 2022). Additionally, plasma levels of lithocholic acid (LCA) were found to be higher in AD patients compared to controls. Moreover, plasma levels of glycochenodeoxycholic acid (GCDCA), glycodeoxycholic acid (GDCA), and glycolithocholic acid (GLCA) were significantly elevated in AD patients compared to those with mild cognitive impairment.

Bile acids have been shown to impact AD, as demonstrated by the fact that TUDCA, a specific bile acid, can inhibit apoptosis caused by Aβ in neuron cell cultures and primary rat neurons. This effect is achieved by blocking the E2F-1/p53/Bax pathway (Schepetkin *et al*., 2016). Additionally, in the APP/PS1 mouse model, it was observed that consuming a diet enriched with TUDCA for six months led to a decrease in the accumulation of Aβ aggregates and enhanced memory performance when compared to mice fed a standard control diet (Nunes *et al*., 2012). Utilizing the identical double-knock-

out model, Dionísio PA, *et al* discovered that administering TUDCA through intraperitoneal injection decreased the accumulation of Aβ, the activity of glycogen synthase kinase 3β, tau phosphorylation, and neuroinflammation (Dionisio *et al*., 2015).

Lastly, two Trp metabolites, 5-hydroxyindole-acetic acid (5-HIAA) and KYNA, activate neprilysin (NEP) which is a metalloproteinase regulating the brain clearance of Aβ peptides (Yoon and Jo, 2012; Howell and Cameron, 2016). Moreover, the tryptophan metabolite 3-hydroxyanthranilic acid has been reported to inhibit Aβ aggregation by directly binding to Aβ (Meek *et al*., 2013).

Parkinson's disease (PD)

PD is a progressive neurological disorder primarily affecting movement control. The disease is marked by the degeneration of dopamine-producing neurons in the substantia nigra, a region of the brain crucial for regulating movement (Calabresi *et al*., 2023). The loss of these neurons leads to the hallmark symptoms of PD: tremors, stiffness, bradykinesia (slowness of movement), and postural instability. Additionally, the presence of Lewy bodies, and abnormal aggregates of the protein α-synuclein, is a key pathological feature in the affected brain cells (Calabresi *et al*., 2023). Levodopa (L-DOPA) which is a precursor of dopamine and serotonin is the gold standard for treatment with PD. But because of adverse effect for long time L-DOPA treatment, 5-Hydroxytryptophan (5-HTP) which is also a precursor of serotonin can be considered to substitute L-DOPA treatment (Choi *et al*., 2023). Secondary metabolites are being explored as a potent modulator of PD through numerous research.

Alterations in the gut microbiota producing SCFAs may drive dopaminergic neuronal degeneration linked to PD. PD is associated with a decrease in various SCFA-producing bacteria, including *Roseburia*, *Eubacterium*, *Ruminococcus*, *Blautia*, *Faecalibacterium prausnitzii*, and *Coprococcus*, many of which generate butyric acid (Keshavarzian *et al*., 2015; Wallen *et al*., 2022). In a study involving patients, it was observed that acetic, propionic, and butyric acids, which are products of gut microbiota, exhibited reduced levels in fecal samples. Paradoxically, these SCFAs showed an increase in plasma among individuals with PD. This discrepancy could potentially result from intestinal wall permeability, possibly exacerbated by constipation, leading to wall leakage (Yang *et al*., 2022). Moreover, the decline in SCFAs coincided with alterations in the composition of the gut microbiota, suggesting an interplay between SCFA levels and changes in gut microbial communities in individuals with PD (Unger *et al*., 2016). This reduction in SCFA levels results in decreased colonic motility and mucin production, coupled with heightened inflammation and permeability in the intestinal mucosa (Soret *et al*., 2010; Forsyth *et al*., 2011; Ganapathy *et al*., 2013; Yang *et al*., 2022). Consequently, this exposure to bacterial components leads to systemic inflammation, neuroinflammation, and neurodegeneration, leading to increased expression, misfolding, and impaired clearance of α-synuclein, thus exacerbating PD symptoms (Clairembault *et al*., 2015; Sampson *et al*., 2016). Conversely, augmenting gut bacteria that produce butyric acid could reinforce the damaged intestinal barrier and elevate striatal dopamine levels (Qiao *et al*., 2020). Butyric acid, derived from the fermentation of prebiotic fibers by gut bacteria, holds promise as a potential therapeutic agent for PD by restoring gut health and potentially mitigating PD-related symptoms (Cantu-Jungles *et al*., 2019).

Metatranscriptomic analysis between PD patients and control showed microbial alteration related to secondary bile acid synthesis. Bile acid analysis revealed an increase in DCA and LCA in PD patients (Li *et al*., 2021). Also, an analysis of 18 bile acids in the serum of prodromal mouse model identified three bile acid signatures in PD model mice. These include ω-murichoclic acid (MCA), tauroursodeoxycholic acid (TUDCA), and ursodeoxycholic acid (UDCA). All were down-regulated in prodromal PD mice with TUDCA and UDCA at significantly lower levels (17-fold and 14-fold decrease, respectively) (Graham *et al*., 2018). In line with this finding, UDCA treatment in the rotenone treated mouse model of PD showed restoration in striatal dopamine level and normalized markers of inflammation and apoptosis (Abdelkader *et al*., 2016).

Pathological α-synuclein accumulation initiated in the gut is well known for its association with PD. α-synuclein can reach the brain through the vagus nerve (Kubicova *et al*., 2019). Constipation, which is a non-motor PD symptom, is linked to α-synuclein accumulation and neurodegeneration with elevated signs of inflammation, oxidative stress and intestinal permeability (Forsyth *et al*., 2011; Bottner *et al*., 2012). A recent study has suggested that excess level of quinoline due to mutated KP enzymes can lead to the formation of metabolite assemblies that causes α-synuclein aggregation (Wikoff *et al*., 2009). Two kynurenine enzymes, Kynurenine-3-monooxygenase and amino-carboxymuconate semialdehyde decarboxylase (ACMSD) genes have been reported to be mutated in PD patients (Marti-Masso *et al*., 2013; Torok *et al*., 2015). Mutation of ACMSD in PD leads to excess quinoline which has excitotoxic property and contributes to the progression and modification in the inflammatory response in PD (Gurling *et al*., 2001).

Amyotrophic lateral sclerosis (ALS)

ALS, also known as Lou Gehrig's disease, is a progressive neurodegenerative disease that primarily affects motor neurons in the brain and spinal cord. Misfolded protein aggregations, including superoxide dismutase 1 (SOD1), chromosome 9 open reading frame 72 (C9orf72), transactive response DNA binding protein 43 (TDP-43), and RNA-binding protein Fused in Sarcoma/Translocated in Sarcoma (FUS/TLS), are characteristic features of this disease (Erber *et al*., 2020). The disease leads to the gradual degeneration and death of motor neurons, which are essential for initiating and controlling muscle movement. As these neurons die, patients experience weakness and wasting in muscles, leading to a loss of voluntary movement and eventually paralysis.

Several studies have highlighted the functional potential of predicted metagenomics (Fang *et al*., 2016; Erber *et al*., 2020), revealing a significant link between ALS and dysbiosis of butyrate-producing bacteria in humans and *in vivo*. For example, investigations using mouse models discovered reduced levels of butyrate-producing bacteria in ALS (Fang *et al*., 2016; Zhang *et al*., 2017b; Erber *et al*., 2020). Zhang *et al*. (2017b) demonstrated that administering 2% butyrate in the drinking water of ALS mouse models restored gut integrity and prolonged survival, suggesting its therapeutic potential (Zhang *et al*., 2017b). Moreover, *in vivo* models over-expressing the $SOD1^{G93A}$ mutation exhibit bacterial dysbiosis and reduced butyrate-producing bacteria, particularly before ALS onset (Wu

et al., 2015; Sun, 2017; Zhang *et al*., 2017b). This dysbiosis correlates with delayed ALS onset and extended lifespan following butyrate administration (Zhang *et al*., 2017b). Butyrate and its producing bacteria are also thought to exert beneficial effects through anti-inflammatory mechanisms (Duncan *et al*., 2002). Further investigation into other short-chain fatty acids in ALS patients is necessary.

In the main mouse model of ALS which is $SOD1^{G93A}$ mice, significant elevations of CDCA, UDCA, β-MCA, TCA, TCDCA, TDCA, TUDCA, GCA and GDCA were identified in the spinal cord of end-stage $SOD1^{G93A}$ mice compared to wild type (Dodge *et al*., 2021). Also in ALS, increased levels of quinoline than normal condition have been observed in both the CSF and serum (Chen *et al*., 2010). These elevated levels of quinoline can cause significant neuronal damage via activation of N-methyl-d-aspartate (NMDA) receptor which is one of the glutamate receptors (Connick and Stone, 1986). Quinoline can lead to human neuronal death via several mechanisms including cytoskeleton destabilization (Pierozan *et al*., 2010), inducing oxidative stress (Aguilera *et al*., 2007; Braidy *et al*., 2009) and releasing excitotoxic glutamate (Lugo-Huitron *et al*., 2013).

CONCLUSION

There is compelling evidence indicating that the gut microbiota plays a crucial role in the bidirectional communication between the gut and the nervous system. Microbiota related metabolites act as a form of chemical communication, playing a crucial role in the "gut-brain" axis and influencing the progression or treatment of various neurodegenerative diseases. By uncovering the molecular mechanisms through which these metabolites regulate host physiology, significant advancements can be made in translating microbiome-gut-brain axis research into clinical applications. This will enhance our comprehension of CNS diseases and aid in the development of effective therapeutic interventions.

In this paper, we reviewed the up-to-date researches that verified the connectivity of gut metabolite and brain. Additionally, we focused on gut microbiota-derived metabolites and how they affect brain function and pathology through their receptors and enzymes. Gut microbiota metabolites such as SCFAs, bile acids, tryptophan metabolites have demonstrated the ability to modulate neurodegenerative disorders. This includes promoting neurogenesis, inhibiting neural inflammation, and reducing oxidative stress. Strategies like adjusting metabolite levels through the control of dietary sources or external supplementation have proven effective in bringing about notable changes, whether in ameliorating or exacerbating symptoms. In conclusion, gut microbiota metabolite can be promising targets for innovative treatment approaches.

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