

REVIEW

The gut microbiota-astrocyte axis: Implications for type 2 diabetic cognitive dysfunction

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Abstract

Background: Diabetic cognitive dysfunction (DCD) is one of the most insidious complications of type 2 diabetes mellitus, which can seriously affect the ability to self-monitoring of blood glucose and the quality of life in the elderly. Previous pathological studies of cognitive dysfunction have focused on neuronal dysfunction, characterized by extracellular beta-amyloid deposition and intracellular tau hyperphosphorylation. In recent years, astrocytes have been recognized as a potential therapeutic target for cognitive dysfunction and important participants in the central control of metabolism. The disorder of gut microbiota and their metabolites have been linked to a series of metabolic diseases such as diabetes mellitus. The imbalance of intestinal flora has the effect of promoting the occurrence and deterioration of several diabetes-related complications. Gut microbes and their metabolites can drive astrocyte activation.

Aims: We reviewed the pathological progress of DCD related to the “gut microbiota-astrocyte” axis in terms of peripheral and central inflammation, intestinal and blood-brain barrier (BBB) dysfunction, systemic and brain energy metabolism disorders to deepen the pathological research progress of DCD and explore the potential therapeutic targets.

Conclusion: “Gut microbiota-astrocyte” axis, unique bidirectional crosstalk in the brain-gut axis, mediates the intermediate pathological process of neurocognitive dysfunction secondary to metabolic disorders in diabetes mellitus.

KEYWORDS

astrocytes, brain-gut axis, diabetes cognitive dysfunction, gut microbiota

1 | INTRODUCTION

Diabetic cognitive dysfunction (DCD) refers to the impairment of cognitive functions such as language and visual memory, information processing speed, and executive functions caused by diabetes mellitus. The 2021 American Diabetes Association (ADA) guidelines have explicitly identified diabetic cognitive impairment as a common

complication of type 2 diabetes mellitus (T2DM) and indicate that the severity of cognitive impairment can deteriorate significantly over time.¹ As population aging trends and the prevalence of diabetes continue to increase, the number of potential patients with DCD will continue to increase. The Rotterdam study found that patients with T2DM had about twice the risk of developing dementia as normal individuals, with a relative risk of 1.9, and the 95% confidence

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interval was 1.3–2.8.² Many epidemiological studies have shown a close relationship between diabetes mellitus and cognitive impairment.^{3,4} A systematic review and meta-analysis of 144 prospective studies demonstrated that diabetes conferred a 1.25- to 1.91-fold excess risk for cognitive disorders. High 2-h postload glucose, glycosylated hemoglobin (HbA1c), and fasting plasma insulin levels were associated with an increased risk of dementia.⁵ In addition, studies suggest that mild cognitive impairment in diabetes exists in all age groups.^{6,7} Cognitive development in adolescents⁸ and neurodegenerativity^{9,10} in older adults show mild changes compared with controls, suggesting that the burden of cognitive dysfunction is also present in young patients.

Type 2 diabetes mellitus and Alzheimer's disease (AD) have significant overlap in risk factors and pathophysiological mechanisms. However, neuropathology studies from multiple cohort studies have suggested no association between DCD and the characteristic pathological β -amyloid ($A\beta$) deposits or neurofibrillary tangle of AD.^{11,12} Systemic alterations in T2DM are associated with pathophysiological mechanisms that lead to impairment of cognitive function.^{13,14} Peripheral insulin resistance (IR) is thought to directly induce brain IR, and insulin signaling exerts a variety of effects in the brain regulating synaptic plasticity and peripheral energy metabolism.¹⁵ IR in specific brain regions was associated with decreased function of the posterior cingulate cortex and right middle temporal gyrus.¹⁶ Chronic hyperglycemia can induce chronic low-grade inflammation by the accumulation of advanced glycation end products (AGEs). Nerve cell oxidative stress and inflammation are also important causes of neurodegeneration and lead to neuronal mitochondrial dysfunction. Neurons rely on the intact mitochondrial function to synthesize and secrete neurotransmitters, enhance synaptic plasticity, and maintain membrane potential. It should be noted that disorders of glucose and lipid metabolism, IR, mitochondrial dysfunction, and chronic inflammatory states are integral pathological links that together lead to endothelial damage in the cerebral microcirculation^{17,18} and neurodegeneration.¹⁹

Prior neuroimaging studies have shown that specific functional and structural brain changes in patients with DCD are associated with cognitive impairment.²⁰ T2DM accelerates the reduction of total brain volume in elderly patients.²¹ In multiple cohort studies and meta-analyses, differences in brain volumes related to diabetes emerge in young adulthood and increase with T2DM duration.^{22,23} In the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort study, T2DM was associated with decreased global brain volume and decreased uptake of 18F-fluodeoxyglucose (18F-FDG) in the frontal lobe, sensorimotor cortex, and striatum.²⁴ In a cohort study of 713 patients with magnetic resonance imaging (MRI) and cognitive testing, T2DM-related gray matter loss was thought to be primarily distributed in the medial temporal lobe, anterior cingulate gyrus, and medial prefrontal lobe. The white matter loss is mainly in the frontal and temporal lobes and is associated with poor visuospatial working memory (VSWM), planning capacity, and processing speed.²⁵ Reduced brain volume in T2DM is associated with complex factors,

including loss of neuroglia and axons, thinning and atrophy of white matter, arteriosclerosis, and venous collagen degeneration.²⁰

Diffusion tensor imaging (DTI) studies have found the presence of microstructural lesions linked to white matter tissue and neural functional networks in T2DM.²⁶ Decreased information processing speed in T2DM patients is associated with decreased measures of overall brain connection.^{27,28} In addition, studies have shown that resting-state functional connectivity is reduced in the default mode network and is strongly associated with HOMA-IR.²⁹ The studies of neural function networks promote the exploration of the cooperative changes among multiple functional brain areas of T2DM and further explain the effect of DCD on higher mental function.

In recent years, expert consensus and professional guidelines have called for the strengthening of early screening for DCD^{30,31} and the promotion of common standardized management of cognitive impairment and glycemic control in patients with the disease,³² to avoid mild cognitive impairment to the deterioration of dementia. However, there is currently no evidence to support that intensive glucose control and specific Anti-diabetic medication can prevent the progression of cognitive impairment.³³ Emergent research directions in the gut-brain axis as a pathological and therapeutic target of cognitive dysfunctions.³⁴ Gut microbiota and astrocyte act as sensitive metabolic sensors in gut-brain interactions. The gut microbiota is also an important upstream factor in the activation of astrocytes, which in turn promotes neuroinflammation and neurodegenerative.³⁵ Large-scale proteomic studies have shown that astrocyte activation and high expression of glycolytic proteins in the brain tissue of patients with dementia may serve as an important pathological marker of early decline in brain energy metabolism and neuroinflammation.³⁶ In this review, we focus on gut microbiota and astrocyte along the gut-brain axis and attempts to elucidate the specific course of complications associated with impaired neurocognitive function secondary to peripheral metabolic disorders in T2DM.

2 | ASTROCYTE PLASTICITY MAINTAINS METABOLISM AND HOMEOSTASIS IN THE BRAIN

Astrocytes are the most abundant neuroglia in the brain and play important roles in maintaining brain energy metabolism, modulating cerebral blood flow, and regulating neuronal circuits. The role of astrocytes in neurocognitive function has also received considerable attention in recent years.³⁷ The astrocytes are connected through a gap junction-coupled network and its endfeet ensheath blood vessels as well as neuronal synapses. About 60% of the axon-dendritic synapses in the hippocampus are enveloped by astrocytic processes, forming a tripartite synapse. The astrocyte endfeet connects microvessels to the neurons composing the neurovascular unit and can release vasoactive molecules, thus regulating the cerebral blood flow and BBB permeability. Horng et al.³⁸ demonstrated that astrocytes in response to inflammatory signals, thus inducing tight junction (TJ) formation, limiting the number of activated T cells infiltrating the CNS.

The astrocyte, which serves as the main CNS glycogen storage cell, is coupled to the oxidative phosphorylation system (OXPHOS) metabolism of neurons through aerobic glycolysis.³⁹ The astrocyte mediates the expansion of regional cerebral arteries in response to synaptic energy demands, matching blood flow to neuronal activity.^{40,41} Astrocytes transfer glucose from the perivascular to the synapse to support the energy needs of neurons via glucose transporter 1 (GLUT1) and the endoplasmic reticulum pathway mediated by G6Pase- β , G6PT, and G6Pase- β .⁴² Under conditions of high energy demands such as glucose deprivation or intense nerve activity, and with limited energy availability such as hypoglycemia, astrocyte aerobic glycolysis can rapidly deliver pyruvate and lactic acid to maintain brain energy metabolism homeostasis.⁴³ The high glycolytic activity of astrocytes results in a significant increase in the flux of the pentose-phosphate pathway (PPP) to produce NADPH and glutathione, thus resisting neuronal oxidative stress.⁴⁴

Astrocyte to neuron's nutritional and energetic support is essential for long-term memory formation.⁴⁵ The astrocyte regulates brain neuroplasticity and neurogenesis by releasing glial transmitters such as brain-derived neurotrophic factor (BDNF) and astrocyte-derived neurotrophic factor (ADNF).⁴⁵ Astrocytes regulate synaptic plasticity via metabolic pathways with neurons, such as the glutamine-glutamate cycle^{46,47} and the astrocyte-neuron lactate shuttle (ANLS),^{48,49} thereby affecting memory formation. To maintain neural circuit homeostasis and thus support cognitive function, astrocytes eliminate unnecessary excitatory synaptic connections.⁵⁰ The astrocyte also works on neural network projections. Kol et al.⁵¹ demonstrated that astrocytes could modulate hippocampal-cortical communication in the anterior cingulate cortex during learning, thereby promoting the formation of remote memory.

Reactive astrocytes contribute to cognitive decline and metabolic homeostasis disorders.²⁷ Astrocyte proliferation and high expression of the activation marker protein glial fibrillary acidic protein (GFAP) are hallmarks of neuroinflammation that arise with the neurodegenerative state. Astrocyte activation has been observed in various animal models of diabetes (Table 1). Zhang et al.⁵² have demonstrated that a high-fat diet (HFD) induces upregulation of astrocyte I κ K/NF- κ B, which in turn impairs astrocytic processes' plasticity. The astrocyte led to changes in extracellular GABA and BDNF in the hypothalamus, thus contributing to weight gain and impaired glucose tolerance. García-Cáceres et al.⁵³ showed that hypothalamic astrocytes regulate glucose uptake rate at the BBB by modulating insulin signaling/GLUT1, which co-controls brain glucose sensing and systemic glucose metabolism. The potential immunometabolic mechanism makes the astrocyte activation accompanied by its metabolic plasticity damage, which leads to the attenuation of brain energy metabolism and its adaptive changes. Rahma et al.⁵⁴ showed that the hypothalamic neuroinflammatory response in T2DM is associated with the metabolic shift from glycolysis to OXPHOS. Specific inhibition of astrocyte pyruvate dehydrogenase kinase (PDK)-2 reduces hypothalamic inflammation and lactate levels, reversing the diabetes-induced increase in food intake.

3 | INTESTINAL DYSBACTERIOSIS IS A COMMON PATHOLOGICAL FEATURE OF T2DM AND COGNITIVE DYSFUNCTION

The interplay between gut microbiota and host metabolism predisposes to drive T2DM pathogenesis through gut permeability change, chronic metabolic inflammation, IR, and metabolic energy disorder. The commonly reported results are that the genera of *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and *Roseburia* have a potential role in preventing T2DM, whereas *Ruminococcus*, *Fusobacteria*, and *Blautia* genera are associated with T2DM pathogenesis.⁶⁸ A microbiome research of 123 nonobese and 169 obese Danish subjects showed that individuals with low gut microbiota abundance were more likely to be obese, IR and dyslipidemia, and the inflammatory phenotype is more pronounced.⁶⁹ A cross-sectional analysis of prospective cohorts from the Rotterdam study and Life Lines-DEEP suggests that higher microbial α -diversity and more butyrate (NaB)-producing bacteria are associated with lower T2DM incidence and lower levels of IR.⁷⁰

Microbial balance is essential for maintaining metabolic homeostasis and protecting cognitive function.⁷¹ Restoring intestinal flora balance can alleviate cognitive impairment and neuropsychiatric symptoms. A cross-sectional study of microbiome data from 597 young Cardia patients examined the association between β -diversity of the gut microbiota and multiple cognitive test results.⁷² A recent clinical study found a decrease in the abundance of *Bifidobacterium* and *unnamed bacteria RF39* and an increase in the abundance of *Peptidococcus* and *Leucococcus* in patients with DCD. The gut microbiota regulates calcium signaling and renin-angiotensin system in relation to DCD.⁷³ Given the wide variation in gut bacterial dysregulation in DCD, further studies are required to elucidate the underlying mechanisms, and restoration of gut microbiota would be a promising therapeutic avenue for DCD.

4 | GUT MICROBIOTA AND ITS METABOLIC PRODUCTS TARGET ASTROCYTES

Intestinal microflora regulates the development and function of astrocytes through neural, endocrine, and immune pathways. The gut microbiota is regulated by genetic and environmental factors, referred to as the second brain, and is also an important shaper of the intestinal microenvironment. Microbial metabolites are important information mediators of the dialogue between gut and brain, most of which can cross the BBB and act directly on the neural microenvironment, and also drive the activation of peripheral immune cells and resident neuroglia of the brain.⁷⁴ By expressing pattern recognition receptor receptors (PRRs), such as toll-like receptors (TLRs) and nod-like receptors (NLRs), astrocyte constantly detects microbial-associated molecular patterns (MAMPs) in the neural microenvironment in response to gut bacteria-derived stimuli and initiate innate immune responses.^{75,76} Astrocytes express major histocompatibility

TABLE 1 Astrocyte phenotypes in experimental diabetes models.

				Astrocytes			
Species (sex), age/weight	Model establish	Location	Phenotype	Molecular mechanisms	References		
C57BL/6 mice (male), 4 weeks/20–25 g	STZ (MLDS for 5 days, 50 mg/kg)	Hippocampus	GFAP↑ GRP78↓ ROS ↑ HO-1↓	Akt↑	Wong et al. ⁵⁵		
C57BL/6J mice (male), 8–10 weeks/NM	STZ (MLDS for 5 days, 40 mg/kg) or (SIJ, 150 mg/kg)+ HFD	Hypothalamus	GFAP↑ Glycolytic shift↑ Lactate surge↑ TNF-α↑ IL-1β ↑ IL-6 ↑	PDK2 and p-PDH protein↑	Rahman et al. ⁵⁴		
C57BL/6J mice (male), 6 weeks/NM	HFHFD for 24 weeks	Hippocampus	GFAP↑ TNF-α ↑ IL-1β ↑ BBB integrity ↓	NM	Takechi et al. ⁵⁶		
C57BL/6N mice (male), 6 weeks/NM	HFD	Hippocampus	GFAP↑	NM	Yu et al. ⁵⁷		
db/db mice (male), NM/NM	Spontaneous diabetes	Hippocampus	GFAP↑	Synaptophysin↓ JAK2/STAT3↑	Zhang et al. ⁵⁸		
db/db mice (male), 8 weeks/NM	Spontaneous diabetes	Cortical gray matter	Astrocyte activation with detachment and retraction from mural cells	NM	Hayden et al. ⁵⁹		
KK-Ay mice (male), 3 months/NM	HFD	Hippocampus	Size of astrocytes reduced; GFAP↓ GLUT1↓ EAAT2-BDNF↓ GDNF↓ IL-1β ↑ TNF-α↑	NM	Shi et al. ⁶⁰		
Wistar rats (male), 3 months/200–250 g	STZ (SIJ, 45 mg/kg)	Hippocampus	GFAP ↑ S100β↑	NM	Nagayach et al. ⁶¹		
Wistar rats (male), NM/250 g	STZ (SIJ, 70 mg/kg)	Hypothalamus	GFAP↑	NM	Lechuga-Sancho et al. ⁶²		
WKY rats (male), 8 weeks/160–270 g	STZ (SIJ, 75 mg/kg)	Hippocampus	GFAP-S100B↓ GLUT1↑ GLT1-GLAST-GluN1↓	AGE-RAGE	Nardin et al. ⁶³		
SD rats (male), NM/190–240 g	STZ (SIJ, 45 mg/kg)	Hippocampus	GFAP↑ S100b↓	NM	Lebed et al. ⁶⁴		

TABLE 1 (Continued)

Species (sex), age/weight	Model establish	Astrocytes			References
		Location	Phenotype	Molecular mechanisms	
SD rats (male), NM/180–200 g	STZ (SIJ, 70 mg/kg)	MCx	GFAP↑ TNF-α↑ IL-1β↑	NM	Lu et al. ⁶⁵
SD rats (male), NM/200–220 g	STZ (SIJ, 60 mg/kg)	vIPAG	GFAP↑	NM	Liu et al. ⁶⁶
ICR mice (male), NM/18–22 g	STZ (SIJ, 150 mg/kg)	Hippocampus	GFAP↑ IL-1β↑ IL-4↑ IL-6↑ TNF-α↑	NM	Chu et al. ⁶⁷

Note: Compared with the nondiabetic group, J indicates reduction, ↑ indicates increase while – indicates no statistical change.

Abbreviations: AGE, advanced glycation end products; EAAT2, recombinant excitatory amino acid transporter 2; GFAP, glial fibrillary acidic protein; GLAST, glutamate/aspartate transporter; GLT1, glutamate transporter subtype 1; GluN1, anti-NMDA Receptor 1; GLUT1, glucose transporter 1; GRP78, glucose-regulated protein 78; HFFD, high-fat and high-fructose; HFrD, high-fructose diet; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; JAK2, janus tyrosine kinase 2; MCx, motor cortex; MLDS, multiple low doses; NM, not mentioned; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; RAGE, recombinant receptor for advanced glycation endproducts; SD, Sprague Dawley; SIJ, single intraperitoneal injection; STAT3, signal transducer and activator of transcription 3; STZ, streptozotocin; TNF, tumor necrosis factor; vIPAG, ventrolateral region of periaqueductal gray; WKY, Wistar-Kyoto.

complex class II antigens and costimulatory molecules that activate T cell, thus exacerbating neuroinflammation.⁷⁷ Short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and aryl hydrocarbon receptors (AhR) ligands are significantly related metabolites of T2DM, and also have the potential to activate astrocytes (Figure 1).

4.1 | Short-chain fatty acids

Short-chain fatty acids generated by colonic digestion and fermentation of dietary fiber have several roles within in gut microbiota-astrocyte axis, including maintaining energy and glucose homeostasis, relieving inflammation of CNS, and regulating the secretion of neurotransmitters to ameliorate neurodegeneration. SCFAs regulate central satiety and insulin secretion through AMPK signaling, GPCR-dependent pathway, and histone deacetylase inhibition, and influence immune cells and neuroglia to exert beneficial metabolic modulation.⁷⁸ The regulation of short-chain fatty acid on astrocytes is gender-related.⁷⁹ A decrease in acetate (AC)-producing bacteria was found in streptozocin (STZ)-induced mice, resulting in a decrease in hippocampal synaptophysin and learning and memory.⁸⁰

A variety of short-chain fatty acids cause different changes in astrocyte metabolism and immune function. According to Cuervo-Zanatta et al.,⁸¹ the ratio of propionate (PA) and NaB was altered in Tg mice but recovered to control values after plant-based diet rich in soluble fiber feed intake, inhibiting astrocyte activation, and ameliorated neuroinflammation. PA promotes higher glycolysis and mitochondrial respiration in astrocytes further, promoting neuroinflammation, whereas NaB induces more quiescent metabolism with anti-inflammatory actions. Sodium NaB promotes astrocyte differentiation into the neuroprotective A2 subtype, improves astrocyte mitochondrial function, and promotes the ANLS.⁸² PA treatment recuperated the astrocyte-microglia bidirectional interplay impairment, thereby increasing the level of GFAP and restoring ZO-1 protein increased to the level of the control group.⁸³ AC serves as a specific energy substrate and metabolic marker for astrocyte.⁸⁴ Studies using acetate 1-c-11 electron emission tomography have shown that activation of astrocytes is closely tied with demyelination and loss of neuron axons.⁸⁵

4.2 | Trimethylamine N-oxide

Trimethylamine N-oxide is an influential mediator of gut-brain metabolic interaction. Multiple evidence supports TMAO as a common risk factor for cognitive function^{86,87} and metabolic syndrome.⁸⁸ The nutrients such as l-choline, carnitine, and betaine in the high-choline diet are decomposed into trimethylamine (TMA) by intestinal flora Trimethylamine lyase, flavin-containing monooxygenase 3 (FMO3) is oxidized to TMAO by the liver after entering the portal vein. Meanwhile, a high-fat diet indirectly increases circulating TMAO concentrations by causing intestinal mucosal inflammation,

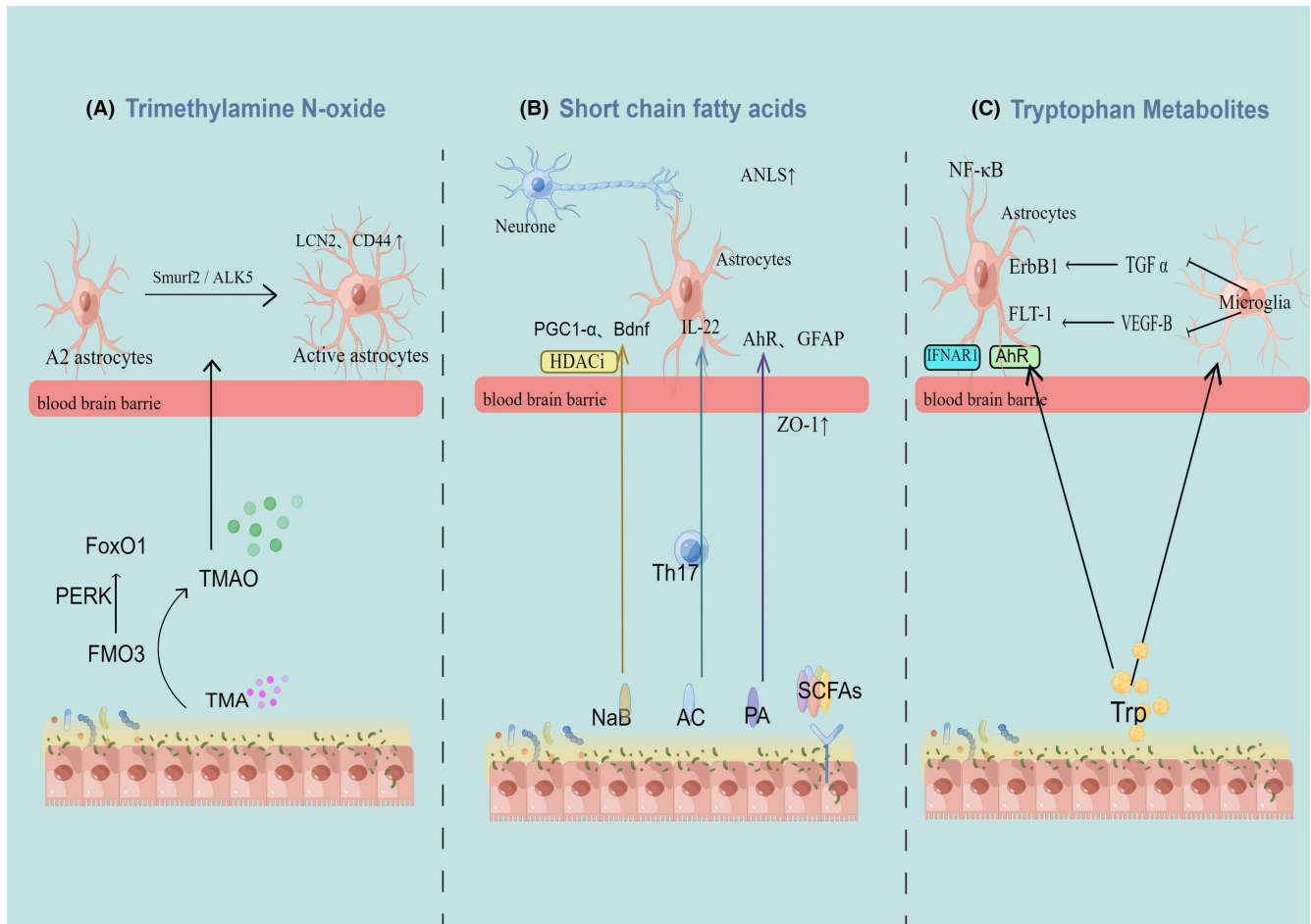


FIGURE 1 Gut microbiota metabolites drive astrocyte phenotypes. Trimethylamine N-oxide could increase the number of reactive astrocytes and change the marker of reactive activated LCN2 and CD44 protein through the Smurf2/ALK5 axis. Improvement of short-chain fatty acids ratio inhibited astrocytic activation and proinflammatory phenotype. The expression of PGC1- α and brain-derived neurotrophic factor in female mice was increased by HDACi, while the function of astrocyte mitochondria and ANLS were improved by butyrate (NaB). A significant correlation between acetate and aryl hydrocarbon receptors (AhR) and GFAP expression was observed in male mice, and the BBB structure was improved. Propionate promotes higher glycolysis and mitochondrial respiration in astrocytes and increases IL-22 expression in male mice. AhR promotes the production of TGF- α and VEGF-B by microglia to indirectly regulate the transcriptional program of astrocytes. In combination with tryptophan-derived metabolites, IFN-I signaling activates in astrocytes and inhibits neuroinflammation.

disrupting the hypoxic environment of the colon, increasing the abundance of gut bacteria, and promoting the catabolism of choline by the microbiota.⁸⁹

The deterioration of insulin sensitivity and glucose homeostasis in T2DM was correlated with the increase in plasma TMAO concentration. Meta-analysis results showed that for every 5 $\mu\text{mol/L}$ increase in TMAO in plasma, the prevalence of diabetes increased by 54%.⁹⁰ Hepatic FMO3 expression is increased in animal models of obesity and IR in human samples. IR can increase plasma TMAO concentration by promoting the FMO3 pathway.⁹¹ TMAO binds the liver PERK, which induces the transcription of FOXO1, leading to hyperglycaemia.⁹²

Pathological concentrations of TMAO are upstream factors that activate the proinflammatory phenotype of astrocytes, impair their aerobic glycolytic metabolic plasticity, cause abnormalities in brain energy metabolism, and result in cognitive dysfunction.

The 27-month-old mice had higher concentrations of TMAO in their plasma and brains, performed worse on new object recognition tests, and were associated with higher proinflammatory cytokine and astrocyte activation markers. Primary human astrocytes co-cultured with TMAO exhibited morphological proliferation and hypertrophy, as well as increased reactive activation of LCN2 and CD44 protein markers.⁹³ TMAO promotes microglia and astrocyte activation in mice with intracerebral hemorrhage and promotes a cellular inflammatory response.⁹⁴ TMAO exacerbates ischemic nerve damage by activating astrocytes and forming glial scars via the Smurf2/ALK5 axis.⁹⁵ In addition, chronic low-dose long-term exposure to TMAO protected the BBB from inflammatory challenges and preserves cognitive function. LPS exposure was associated with a significant decrease in endothelial GFAP+ astrocytes and IBA1+ microglia, which was effectively reversed with TMAO treatment.⁹⁶

4.3 | Aryl hydrocarbon receptors ligands

The microbial metabolism of dietary tryptophan can be decomposed into various biologically active molecules that bind directly to AhR as hydrocarbon receptor ligands. Through the gut microbiota, tryptophan metabolites may also affect CNS inflammation and contribute to neuropsychiatric disorders. As diabetes severity increases in the PREDIMED cohort, plasma tryptophan levels are likely to rise first and then deplete.⁹⁷ The AhR pathway promotes microglia to produce TGF- α and VEGF-B to indirectly regulate the astrocyte transcriptional program. Microglia TGF- α exerts its neuroprotective function through the ErbB1 receptor, promoting beneficial astrocyte activity. VEGF-B triggers vascular endothelial growth factor receptor 1 (Flt-1) signaling in the astrocyte.⁹⁰ Conversely, Type I interferons (IFN-I) signaling in combination with gut microbiota metabolites derived from dietary tryptophan activates AhR in astrocytes. Interferon alpha receptor 1 (IFNAR1-1) plays an important role in anti-neuroinflammation and preventing neurodegeneration.⁹⁸

5 | GUT MICROBIOTA-ASTROCYTE AXIS CONNECTS T2DM WITH COGNITIVE DYSFUNCTION

Diabetes-related cognitive impairment is secondary to metabolic disturbances via the gut-brain axis. Gut microbiota disturbance is the key link of metabolic inflammation, immune barrier damage, and energy metabolism. The astrocyte is an important regulator of the immune and metabolic balance of the brain. Gut microbiota, which drives astrocyte activation via neuroimmune pathways, is a target for the treatment and diagnosis of cognitive impairment in diabetes (Figure 2).

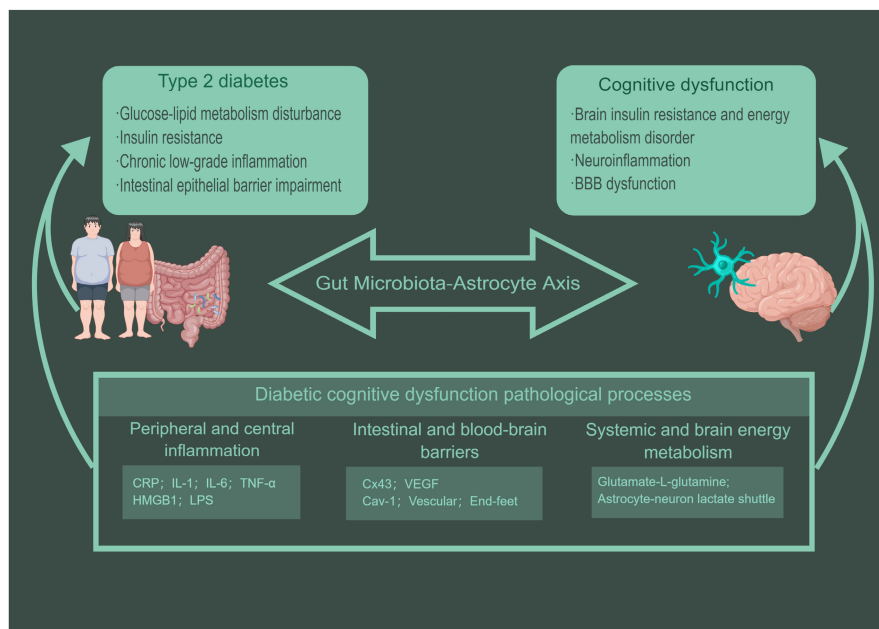
5.1 | Gut microbiota and astrocyte co-regulate central and peripheral inflammation

Chronic low-grade inflammation is a hallmark of type 2 diabetes, leading to impaired β cell islet structure and function, inducing hepatic IR, and impairing glucose tolerance by blocking glucose-stimulated insulin secretion (GSIS). Through dysbiosis of the gut microbiota, pathogen-associated molecular patterns, damage-associated and microbial-associated patterns enter the circulatory system, inducing systemic inflammation and immune responses.^{68,99} A cell wall component of gram-negative bacteria, lipopolysaccharide (LPS), has been reported to be a source of metabolic inflammation. By activating macrophages through the inflammatory cytokine TLR4-MyD88 pathway, LPS induces macrophages, dendritic cells, and other inflammation-causing cells to form a worsened inflammatory microenvironment in metabolic tissues.^{99,100}

As a relatively immune-privileged site, the neuroinflammation of the brain mostly results from the stimulation of circulating and gut-derived inflammatory factors. The central recruitment and migration of metabolic inflammatory factors across the BBB promote astrocyte activation and transition to a responsive proinflammatory phenotype. It enhances inflammatory signaling and exacerbates neurodegeneration.¹⁰¹

Systemic chronic low-grade inflammation is a common pathological mechanism of diabetes and dementia and is an important factor in accelerating central nerve damage in diabetes.¹⁰² Chronic inflammation within the peripheral and central nervous systems underlies cognitive dysfunction associated with metabolic syndrome.¹⁰³ A prospective cohort study showed that plasma levels of C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF- α) are associated with cognitive difficulties in older adults with T2DM.¹⁰⁴ In a meta-analysis of 40 clinical studies, elevated IL-6, CRP, SVCAM-1, and AGEs levels were suggested

FIGURE 2 The “gut microbiota-astrocyte” axis is coupled to the pathogenesis of cognitive dysfunction secondary to type 2 diabetes mellitus. Gut microbes and astrocytes are critical factors in the gut-brain axis, leading to diabetic cognitive dysfunction through peripheral and central inflammation, gut and blood–brain barriers, and systemic and brain energy metabolism. Gut microbiota and its metabolites as upstream drivers of astrocytic activation. The reactive astrocytes' morphology and function changes result in blood–brain barrier injury, neuroinflammation, and brain energy metabolic disorder.



in cognitively impaired T2DM patients.¹⁰⁵ Besides these peripheral markers of inflammation, CNS inflammation is also present in obese and T2DM patients, which manifests as neural immune cell infiltration, microglia, and astrocyte activation.

Astrocyte activation is a significant feature of neuroinflammation. Activated astrocyte gene expression switches to a proinflammatory and cytotoxic state, producing a variety of proinflammatory molecules, including cytokines, chemokines, complement factors, and ROS.⁹⁷ The synthesis of LacCer in astrocytes promotes CNS-infiltrating monocytes and microglia.¹⁰⁶ The metabesity factor HMG20A is increased under mild inflammation induced by obesity and IR, inducing reactive astrocyte hyperplasia, protecting neurons from metabolic stress, and re-establishing glucose homeostasis.¹⁰⁷ Regulating COX-mediated oxylipin synthesis in astrocytes as a novel potential target in the treatment of hyperglycemia-associated brain injury.¹⁰⁸

The Proinflammatory cytokine produced by dysbacteriosis is an important immune signal that directly activates astrocytes. The db/db mice have significantly increased escape latency at 6, 18, and 26 weeks of age, and their senescence-associated cognitive decline is associated with the gut microbiome.^{109,110} Phulwani et al.¹¹¹ have shown that LPS induces astrocyte TLR2 via TNF- α and NF- κ B pathways. Fecal microbiota transplantation (FMT)¹¹² and vancomycin¹¹³ can inhibit the TLR4/TNF- α and alleviate astrocyte-related neuroinflammation. FMT treatment was involved in reducing depressive behavior by inhibiting astrocyte dysfunction in CIRCHIP2-expressing good mice.¹¹⁴ Recent studies have shown that gut microbes regulate the expression of Interferon- γ in meningeal NK cells, thereby promoting the expression of astrocyte TRAIL, limiting CNS inflammation through induction of T-cell apoptosis by Lamp1+ TRAIL+ astrocyte.¹¹⁵

5.2 | Gut microbiota and astrocyte are critical hubs to the intestinal and blood-brain barrier

The TJs of the BBB are similar to those of the intestinal immune barrier, including Claudin-5, occludin, and ZO-1. An energetically favorable change in the gut barrier and BBB is an important pathway for interaction between the gut-brain axis. The results showed that BBB dysfunction preceded early biomarkers of cognitive decline other than the accumulation of amyloid and tau proteins.¹¹⁶ Increased BBB permeability is one of the key pathologies of cognitive impairment in diabetes.^{117,118} The accumulation of lipid peroxidation by-products, advanced glycation end products, and mitochondrial superoxide production in diabetes mellitus, causing neovascularization abnormalities and increased capillary density in the CNS.

Blood-brain barrier damage varies in different types of diabetic animals. Increased BBB permeability in more than 84% of brain regions was found in BBZDR/WOR rats, whereas no significant changes were observed in the cerebellum and midbrain.¹¹⁹ In STZ-induced diabetic rats, BBB permeability to small molecules gradually

increased over a 28 to 90-day period, and these changes were mainly observed in the midbrain, basal ganglia, cortex, and hippocampal regions.¹²⁰ In the HFD diet-induced model of obese T2DM rats, BBB damage predates cognitive impairment and occurs predominantly in the hypothalamus and hippocampus, and continues to deteriorate with the course of the disease.¹²¹ High-fat and high-fructose (HFHF) diet-induced prediabetes mice experienced significant cognitive deterioration, accompanied by the permeability of the BBB and enhanced neuroinflammation in the cortex and hippocampus.⁵⁶

Astrocyte is required for the maintenance of BBB integrity in the adult brain, and BBB regulators secreted by other cell types are insufficient to compensate for the loss of astrocyte.¹²² In addition to its role in vascularization, astrocytes exert synergic action with endothelial cells via paracrine and extracellular vesicle pathways to regulate TJ protein expression to control BBB integrity.¹²³ For instance, astrocyte-derived Wnt maintains the activity of Wnt/ β -catenin, thereby controlling Cav-1 expression, vesicle abundance, and terminal integrity of the foot in NVU cells.¹²⁴ During sustained inflammation, microglia phagocytose astrocytic endfeet and impair BBB function.¹²⁵ Impaired BBB is accompanied by elevated GFAP and serves as a biomarker of cognitive impairment in diabetes.¹²⁶ The co-culture system of astrocyte and cerebral microvascular (CMEC) suggests that high glucose concentrations alter the expression of astrocyte Cx43 and increase VEGF secretion, resulting in impaired CMEC barrier properties.¹²⁷

Gut microbiota-associated metabolites promote peripheral immune cells to alter the structural integrity of the BBB.¹²⁸ Gut microbiota-BBB communication begins during pregnancy and spreads throughout life. Germ-free mice showed increased BBB permeability and a consistent reduction in TJ protein expressions such as occludin and Claudin-5 after birth and adulthood.¹²⁹ Dysregulation of gut metabolites and disruption of the intestinal barrier caused by microbial perturbations promote the entry of deleterious metabolites into the circulatory system. Yu et al.⁵⁷ showed that intestinal dysbiosis caused by a high-fructose diet (HFrD) reduces SCFAs and damages the intestinal epithelial barrier, thus promoting astrocyte activation and BBB damage. In mouse models of obesity and diabetes, hyperglycemia entrains the permeability of the intestinal barrier. High glucose levels lead to retrograde glucose transport to intestinal epithelial cells via GLUT2, which subsequently alters intracellular glucose metabolism and transcriptional reprogramming, altering intestinal mucosal compactness and adhesion junction integrity.¹³⁰ Microbiome and altered intestinal permeability increase circulating high mobility group protein 1 (HMGB1) and LPS, leading to systemic inflammation and disruption of the BBB.¹³¹ HMGB1 induces the production of proinflammatory cytokines and promotes neuroinflammation by activating TLR4 and RAGE in the astrocyte. Astrocyte's endfeet swelling, detachment from the basement membrane, and opening of the TJ between endothelial cells were strongly inhibited by the anti-HMGB1 monoclonal antibody.¹³² The induction of astrocyte proliferation and activation by LPS promotes high expression of proinflammatory and cytotoxic genes, which may be related to BBB destruction.¹³³

5.3 | The gut microbiota-astrocyte axis couples systemic and brain energy metabolism disorders

The brain uses glucose as its primary energy substrate, consuming 20 percent of the body's glucose and oxygen, to support the energy-dependent synaptic activity of neurons. Brain energy metabolism decline is a hallmark event of cognitive decline, restoring energy metabolism as a novel therapeutic Neurodegeneration.¹³⁴

Blood glucose fluctuation, frequent hypoglycemia events, IR, and other metabolic disorders are all risk factors for regional energy metabolism decline in the brain. Diabetes has been found in existing studies to reduce cerebral glucose utilization and cause nerve damage, possibly by altering BBB glucose transport uptake, neurotransmitter metabolism, and the ability to regulate cerebral blood flow.^{135,136} According to a study including 323 adults with prediabetes, hyperglycemia was negatively associated with 18F-FDG uptake in the prewedge lobe and occipital cortex.¹⁰⁴ The brain is inefficient at energy acquisition after glucose loading in obese men, which could be due to abnormalities in glucose transport across the BBB or downregulation of energy synthesis during mitochondrial oxidation.¹³⁷

The adaptive changes in brain energy metabolism were also observed in different animal models of diabetes. A recent multi-omics analysis in 4-month-old db/db mice of cognitive impairment has identified disturbances in cerebral and circulatory mitochondrial metabolism.¹³⁸ Huang et al.¹³⁹ found that 26-week-old db/db mice had significantly reduced mitochondrial function and ATP content in the hippocampus. Andersen et al.¹⁴⁰ found glucose hypometabolism in the cortex and hippocampal slices of db/db mice. The hippocampus showed enhanced ketone metabolism, and mitochondria in the cerebral cortex showed enhanced OXPHOS. These metabolic changes may be adaptive changes associated with low brain energy metabolism.

Astrocytes generate abundant mitochondrial reactive oxygen species, including lactic acid and serine, during glycolysis, which is coupled to neuronal OXPHOS to maintain brain energy requirements and relieve oxidative stress, and regulate the activity of neurotransmitter receptor.³⁹ Astrocytes' glucose uptake and glycolytic plasticity play an essential role in maintaining brain energy metabolic balance. Astrocyte metabolic disorders have been observed in various animal models of diabetes. Girault et al.¹⁴¹ examined GK rats using ¹³C magnetic resonance spectroscopy and found that T2D impairs glutamate-L-Glutamine circuits in the brain between neurons and astrocytes, increasing the rate of TCA astrocytes.

Biological communication between the gut and brain is mediated by the gut microbiome, regulating the system and cerebral energy balance. C57BL/6J mice treated with HFD antibiotics altered the gut microbiota and multiple metabolites and improved insulin signaling and energy metabolism in the brain.¹⁴² Intermittent fasting (IF) can reconstitute the gut microbiota and metabolites of db/db mice, which in turn improves mitochondrial metabolism in the hippocampus and enhances genes associated with the OXPHOS pathway.¹⁴³

Akkermansia muciniphila CIP107961 and environmental enrichment has been shown to reverse the metabolic abnormalities in the brain induced by the high-fat, high-cholesterol diet.¹⁴⁴

Gut microbiota drives astrocyte activation along with metabolic switching, which in turn improves brain energy metabolism. Gut microbiota promotes the expression of PFKFB3 and ATP1A2, key proteins of hippocampal ANLS.¹⁴⁵ STZ-induced diabetic SD rats have cognitive impairment and intestinal flora disturbance. Disturbances in Glu/GABA-Gln cycling and astrocyte energy metabolism in the rat hippocampus are thought to be associated with changes in *Clostridium_sensu_stricto_1*, *Romboutsia* and *Turicibacter*.¹⁴⁶

6 | THERAPEUTIC STRATEGIES OF GUT MICROBIOTA AND ASTROCYTE

Clinical guidelines on DCD emphasize the management of glucose and other metabolic homeostasis, reducing glucose fluctuations and avoiding hypoglycemic events.¹⁴⁷ However, the benefits and mechanisms of anti-diabetic drugs for DCD remain unclear. Cholinesterase inhibitors improve some dementia symptoms but fail to reverse the ongoing deterioration of cognitive impairment. The overlapping risk factors and the close pathophysiological relationship between diabetes and cognitive impairment have prompted interest in the role of anti-diabetic drugs for cognition. There have been many excellent reviews suggesting the effects of sodium-glucose co-transporter 2 (SGLT2),¹⁴⁸ dipeptidyl peptidase-4 (DPP-4) inhibitors,¹⁴⁹ metformin,¹⁵⁰ and glucagon-like peptide-1 receptor (GLP-1R) agonist¹⁵¹ on cognitive function. But conflicting and divergent findings remain between the current studies, and the benefits and mechanisms of anti-diabetic drugs on DCD remain unclear.¹⁵²

Preclinical studies have observed that many anti-diabetic drugs drive astrocyte phenotypic transformation. IR deficiency in astrocytes leads to impaired glucose tolerance and increases anxious-depressive behavior. Intranasal insulin administration improves cognitive function.¹⁵³ Astrocytes express IR and GLP-1R, which activation affects brain glucose uptake and neurocognitive function. As an intestinal hormone, GLP-1R agonists selectively block A β protein-induced microglia activation and inhibits astrocyte-responsive activation.¹⁵⁴ GLP-1R agonists also reduce astrocyte-derived activators to protect the BBB and inhibit neuroinflammation.¹⁵⁵ In addition, thiazolidinediones act as peroxisome proliferator-activated receptor- γ (PPAR γ) agonists and exert neuroprotective effects by inhibiting GFAP expression and morphological proliferation of astrocytes.^{156,157}

Currently, new drug developments such as the seaweed derivative sodium oligomannate (GV-971), have gone beyond neuronal centers and act by targeting the gut-brain axis.¹⁵⁸ Based on the broad utility of astrocytes and gut microbiota in neuroendocrinology, we take a step back and discuss those dietary interventions and natural compounds with considerable therapeutic potential.

6.1 | Dietary interventions and probiotics

Restructuring the dietary structure is a direct way to modulate the gut microbiota and explore its effects. Intensive lifestyle interventions have been recognized as an essential clinical approach to reversing the course of diabetes and delaying the development of complications.¹⁵⁹ Researchers' interest in nutritional psychiatry has driven many studies of specific dietary approaches such as the ketogenic diet,¹⁶⁰ the Mediterranean diet,¹⁶¹ and Intermittent fasting¹⁴³ to improve neurocognitive function. Genomic and proteomic sequencing reveals extensive immune and metabolic shifts in arcuate nucleus astrocytes in response to a high-fat, high-sugar diet.¹⁶² The ketogenic diet affects the metabolic plasticity of neurons and astrocytes,¹⁶³ and research has shown that gut microbiota is necessary and sufficient for the neuroprotective effects.¹⁶⁴ The calorie-restricted diet reduces astrocyte glycolysis thereby limiting neuroinflammation.^{165,166}

Probiotics and synbiotics have been proposed as dietary supplements to intervene in metabolic disorders and cognitive impairment. Several research studies in vitro and in vivo have demonstrated that intake of probiotics can protect the intestinal mucosal barrier and promote the release of beneficial intestinal hormones and gut microbiota metabolites in patients with diabetes, thereby improving glycemic control and insulin resistance.^{167,168} Probiotic supplementation increased the ratio of *Lactobacillus/Clostridium* and *Lactobacillus/Bacteroidetes*, promoted the BDNF/TrkB/CREB signaling pathway in diabetic rats, decreased the level of neuronal apoptosis, and effectively reversed the synaptic long-time enhancement.^{169,170}

6.2 | Traditional herbals and their active ingredients

Herbs and their active ingredients are potential treasures for targeting gut microflora dysbiosis and thereby improving cognitive function. A wealth of contemporary evidence supports its important role in preventing diabetic complications.^{171,172} With the advancement of multi-omics and genome sequencing technologies, in-depth biological mechanisms have elaborated the holistic systemic concept of governance and multi-targeted efficacy of TCM.^{173,174} Focusing on the "gut microbiota-astrocyte" axis, we screened the five most potentially therapeutic herbs and their derivatives. Ginsenosides are ginseng's main active pharmacological components.

Ginsenoside Rh4 inhibits astrocyte overactivation by promoting the enrichment of beneficial gut microbiota and increasing SCFAs content, thereby reducing hippocampal neuronal apoptosis and synaptic structural damage.¹⁷⁵

Astragalus polysaccharide (APP) possesses hypoglycemic and cognitive protective effects on both db/db mice¹⁷⁶ and STZ-induced diabetic models of rats.¹⁷⁷ APP increases the diversity of the gut microbiota, inhibits the potential intestinal pathogen *Shigella*, and enriches the beneficial bacteria *Homococcus* and *Lactobacillus*.¹⁷⁸ APP

improves insulin resistance status in metabolically stressed mice and reduces astrocyte proliferation and activation around neuronal amyloid plaques.¹⁷⁹

Berberine (BBR) is characterized by low oral utilization and significant regulation in the intestinal microflora. It has been found in many plants, such as *Coptis chinensis* Franch and *Phellodendron chinense* Schneid.¹⁸⁰ BBR reduced hyperglycemia in diabetic rats while reducing oxidative stress in the hippocampus and preventing excessive activation of GFAP.^{181,182}

Curcumin and its analogs attenuate DCD by modulating inflammation and oxidative stress, and reduce aberrantly activated astrocytes in the hippocampus.^{183,184} Curcumin reverses gut microbiota dysbiosis in diabetic rats, and increases *Bacteroides* and *Bifidobacterium* but inhibits *Enterobacteriaceae* and *Thicketella phylum*.¹⁸⁵ In vitro studies have shown that curcumin modulates the binding of endogenous ligands to AhR, promotes AhR activation, and decreases LPS-induced NF- κ B activation, thereby regulating inflammatory astrocyte proliferation.¹⁸⁶ In addition, herbal active substances such as forsythoside B, rhubarb phenol, chrysin, resveratrol, and paeoniflorin have the effect of ameliorating DCD over gut microbiota and astrocytes, but direct and complete research evidence is still lacking.

Overall, the study of the gut-brain axis in traditional medicine still needs to shift from analyzing correlations to establishing cause-effect relationships. Observations on astrocytes have been mostly limited to neuroinflammation. Further enrichment of the modulatory effects of herbs on astrocyte phenotypes will help to uncover potential treatment of DCD and provide insight into the clinical efficacy of traditional herbals.

7 | CONCLUSION

Though there is much evidence for cognitive impairment in patients with diabetes, the pathogenesis of DCD as a complication of diabetes is unclear and it is difficult to differentiate DCD from AD. Out of the multiple pathological factors, gut microbiota and its metabolites are important mediators to couple visceral and central environment, through the gut-brain axis neuroimmune pathway, the unique two-sided relationship between metabolic health and cognitive mind is highlighted. Unique anatomical and functional characteristics of astrocytes serve as intermediary glia in contact with circulating substances and brain microenvironment, maintaining immune and metabolic brain homeostasis and providing a continuous supply of energy-dependent neuronal activity. With the development of genomics and cell sequencing technology, "gut microbiota-astrocyte" axis research using the concept of system biology will help to deepen the understanding of the pathological mechanism of metabolic cognitive disorders, to explore an accurate and comprehensive treatment plan.

AUTHOR CONTRIBUTIONS

All authors read, revised, and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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