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Altered cognitive function in obese patients: relationship to gut flora

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Abstract

Obesity is a risk factor for non-communicable diseases such as cardiovascular disease and diabetes, which are leading causes of death and disability. Today, China has the largest number of overweight and obese people, imposing a heavy burden on China's healthcare system. Obesity adversely affects the central nervous system (CNS), especially cognitive functions such as executive power, working memory, learning, and so on. The gradual increase in adult obesity rates has been accompanied by a increase in childhood obesity rates. In the past two decades, the obesity rate among children under 5 years of age has increased from 32 to 42 million. If childhood obesity is not intervened in the early years, it will continue into adulthood and remain there for life. Among the potential causative factors, early lifestyle may influence the composition of the gut flora in childhood obesity, such as the rate and intake of high-energy foods, low levels of physical activity, may persist into adulthood, thus, early lifestyle interventions may improve the composition of the gut flora in obese children. Adipose Axis plays an important role in the development of obesity. Adipose tissue is characterized by increased expression of nucleoside diphosphate-linked molecule X-type motif 2 (NUDT2), amphiphilic protein AMPH genes, which encode proteins that all play important roles in the CNS. NUDT2 is associated with intellectual disability. Furthermore, amphiphysin (AMPH) is involved in glutamatergic signaling, ganglionic synapse development, and maturation, which is associated with mild cognitive impairment (MCI) and Alzheimer's disease (AD). All of the above studies show that obesity is closely related to cognitive decline in patients. Animal experiments have confirmed that obesity causes changes in cognitive function. For example, high-fat diets rich in long- and medium-chain saturated fatty acids may adversely affect cognitive function in obese mice. This process may be attributed to the Short-Chain Fatty Acid (SCFA)-rich high-fat diet (HFD) activating enterocyte TLR signaling, especially TLR-2 and TLR-4, altering the downstream MyD88-4 signaling, thereby impacting the downstream MyD88-NF-κB signaling cascade and up-regulating the levels of pro-inflammatory factors and lipopolysaccharide (LPS). These changes result in the loss of integrity of the intestinal mucosa and cause an imbalance in the internal environment. Obesity may lead to the disruption of the intestinal flora and damage the intestinal barrier function, causing intestinal flora dysbiosis. In recent years, a growing number of studies have investigated the relationship between obesity and the intestinal flora. For example, high-fat and high-sugar diets have been found to lead to the thinning of the mucus layer of the colon, a decrease in the number of tight junction proteins, and an increase in intestinal permeability in mice. Such changes alter the composition of intestinal microorganisms, allow endotoxins into the blood circulation, and induce neuroinflammation and brain damage. Therefore, obesity affects cognitive function and is even hereditary. This paper reviews the obesity-induced cognitive dysfunction, the underlying mechanisms, the research progress of intestinal flora dysregulation in obese patients, the relationship between intestinal flora and cognitive function changes, and the research progress on intestinal flora dysregulation in obese patients. We want to regulate the internal environment of obese patients from the perspective of intestinal flora, improving the cognitive function of obese patients, and prevent obesity-induced changes in related neurological functions.

Keywords Obesity-induced cognitive dysfunction · Intestinal flora · Neurological functions · Blood–brain barrier dysfunction · Systemic inflammation

Extended author information available on the last page of the article

Abbreviations

CNS	Central nervous system
NUDT2	Nucleoside diphosphate-linked molecule X-type motif 2
AMPH	Amphiphysin
MCI	Mild cognitive impairment
AD	Alzheimer's disease
SCFA	Short-chain fatty acid
HFD	High-fat diet
IL-4	Interleukin-4
TNF-α	Tumor necrosis factor
MCP1	Monocyte chemoattractant protein-1
BBB	Blood–brain barrier
c-JNK	C-Jun N-terminal kinase
NF-κB	Nuclear factor-κB
ATMs	Adipose tissue macrophage subtypes
IL-6	Interleukin-6
HS	Hyperinsulinemia
β-tau	Phosphorylated-tau protein
ERK 1/2	Extracellular signaling-associated protein kinase 1/2
ROS	Reactive oxygen species
Ccl2	C–C motif chemokine ligand 2
Nos2	Nitric oxide synthase 2
SRB	Sulfate-reducing bacteria
BMAA	β-N-methylamino-L-alanine
ENS	Enteric nervous system
LC	Lactobacillus casei
5-HT	5-Hydroxytryptamine
GABA	Gamma-aminobutyric acid
LSG	Laparoscopic sleeve gastrectomy
RYG	Jejunal Y-anastomosis

Types of obesity-induced cognitive alterations and their research progress

Mild cognitive impairment (MCI)

MCI is defined as a progressive decline in memory or other cognitive functions, which does not affect the ability to perform daily living tasks and does not meet the diagnostic criteria for dementia. The diagnostic criteria for MCI were proposed by Petersen in 1999 and revised by an international working group in 2003. MCI is classified into four subtypes, including single cognitive domain amnestic, multiple cognitive domain amnestic, single cognitive domain non-amnestic, and multiple cognitive domain non-amnestic [1]. In a large-sample clinical study, the prevalence of MCI in adults over the age of 65 years was 10–20% [2]. Obesity increases the risk of MCI and is not related to age [3]. MCI is mainly characterized by attention deficit, poor executive functioning, impaired decision-making, impaired language learning, and memory loss. The symptoms are more pronounced in patients with metabolic syndrome and tend to be more severe in men than in women, which may be attributed to the protective effect of estrogen in women, however, the role of obesity as a risk factor for dementia remains controversial. Studies have confirmed that patients with a BMI of more than 30 kg/m^2 showed the highest prevalence of dementia [4].

Obesity-induced MCI has also been demonstrated in animal experiments, as evidenced by increased anxiety-like behavior in mice [5, 6], increased central nervous aging process, neuroinflammation induction, and microglia activation [7]. This was confirmed in a study by Lei Y et al. [8]. In mice, microglia activation triggers the release of TNF-α and IL-1β, which impair spatial learning and recall and ultimately lead to cognitive dysfunction in mice. Hence, microglia may be an important target for obesity-induced cognitive changes [9]. HFD-induced obesity in mice leads to an increase in LPS and increased intestinal permeability; in addition, LPS in the blood circulation can cross the blood–brain barrier and directly affect microglia, triggering neuroinflammation [10]. Neuroinflammation is a precursor of MCI. Furthermore, obesity adversely affects hippocampal structure and function, which induces a decline in hippocampus-dependent learning and memory ability. Damage to the hippocampal structure is often accompanied by neuroinflammation, which is closely related to cognitive dysfunction.

Most importantly, the multiprotein complex NLRP3 is produced and activated, which induces microglia to produce the interleukins IL-1β and IL-18 under the mediation of caspase-1 [11].

In summary, the causes of obesity-induced mild cognitive impairment are multifaceted and involve multiple biological mechanisms. It is widely believed that fat accumulation may trigger chronic low-grade inflammation throughout the body, and its representative markers include C-reactive protein (CRP), tumor necrosis factor α (TNF-α), etc. Inflammatory factors cross the blood–brain barrier and affect the function of nerve cells. Secondly, insulin resistance is also involved in cognitive impairment in obese patients, because insulin may affect oxygen metabolism and energy utilization in the brain, which has a significant effect in functional brain regions with high glucose demand, such as the hippocampus, and further affects learning and memory functions in obese patients. Then, adipose tissue may also secrete adipokines (e.g., lipocalin, leptin) that impair synaptic plasticity, affect serotonin and dopamine transmission, and impair neurocognitive function. Finally, obese patients due to the accumulation of large amounts of fat in the nasopharynx, resulting in long-term, chronic hypoxia, the formation of obstructive sleep apnea syndrome. All four of these factors may be responsible for the development of mild cognitive function in obese patients.

Alzheimer disease (AD)

AD is a progressive neurodegenerative disease that manifests clinically as cognitive decline and its neuropathology is characterized by the early appearance of amyloid plaques across brain regions in the cerebral cortex [12], with the spreading of tau phosphate neurofibrillary tangles in the entorhinal cortex and hippocampus [13]. These changes are the pathologic basis for the development of AD. Middle-aged obesity is a high-risk factor for AD, which can increase the risk of AD by more than twofold [14]. The efficacy of several weight loss and diabetes drugs in improving the clinical symptoms of AD by reducing body weight is being investigated [15–17].

A number of clinical studies have explored the relationship between obesity and AD. A clinical study of 6582 older British adults showed a 31% increased risk of dementia in the obese group [18]. Regrettably, the exact cause of obesity-induced AD remains unknown. Relevant studies reported that obesity may lead to excessive release of insulin, causing systemic insulin resistance. As an active endocrine organ, the adipose tissue releases proinflammatory adipokines and cytokines (including leptin, lipocalin, TNF-α, and IL-6), producing a systemic, low-grade inflammatory internal environment. This state may lead to blood–brain barrier dysfunction, triggering a central inflammatory response, which may induce AD [19]. Moreover, leptin resistance may be involved in obesity-induced AD. Leptin is secreted by adipose tissue and acts on leptin receptors in the central nervous system, exerting a protective effect on the hippocampus to regulate feeding behavior and memory function in organisms. However, hyperleptinemia may lead to cognitive deficits [20].

The link between obesity and AD has also been confirmed by animal experiments. High-fat and high-sugar diet feeding for 3 days was found to cause microglia activation and hypothalamic inflammation, which may be due to the transient increase of uncoupling protein 2 (UCP2) mRNA and changes in mitochondrial dynamics. Selective inhibition of UCP2 may improve the mitochondrial dynamics and functional changes, inhibit microglia activation and hypothalamic inflammation, and attenuate the degree of hypothalamic inflammation to ameliorate cognitive function changes in AD [21].

β-amyloid and tau protein phosphorylation are typical alterations in AD, and obesity can affect β-amyloid metabolism, resulting in the accumulation of the protein and the formation of plaques, which are neurotoxic and involved in the formation of AD. In addition, insulin resistance may affect the hyperphosphorylation of tau protein and the formation of neurofibrillary tangles, which is another key pathologic feature of AD. Nonetheless, further research on the relationship between obesity and AD is required, but the exact mechanism remains unknown. Future relevant scientific studies will bring additional therapeutic opportunities for AD patients.

Dementia

Dementia is a clinical syndrome characterized by intellectual impairment with cognitive deficits as the core symptom, including impaired cognitive functioning in memory, language, visuospatial, attention, analytical, and problem-solving skills, which may be accompanied by personality changes and psychiatric behavioral abnormalities, the condition affects people's ability to carry out daily activities independently, and early detection, diagnosis, and treatment may prevent further progression [22].

Obesity can cause neuroinflammation, which represents an important link between dementia and obesity [23]. In obese patients, adipose tissue secretes immune factors or metabolic mediators such as C-reactive protein, interleukin IL-1β, and leptin, which cross the blood–brain barrier and are involved in the development of neuroinflammation, ultimately impairing brain function and leading to the development of dementia. In addition, studies have also investigated adipokines secreted by adipose tissue, which modulate insulin resistance, contribute to the dysfunction of the gut-brain axis, exacerbate the systemic inflammatory response, and exacerbate neuroinflammation and the development of dementia [24].

Furthermore, insulin resistance and mitochondrial dysfunction represent another possible link between obesity and dementia. Excessive adipose tissue leads to fatty acid accumulation; consequently, inflammatory adipokines are released and insulin resistance occurs [25]. Insulin resistance leads to a reduction in brain insulin signaling, resulting in the impairment of neuronal metabolism and function [26]. Brain oxygen consumption accounts for 20% of the total body oxygen consumption, whereas neurons account for 80–90% of the brain oxygen consumption. In neuronal cells, mitochondrial dysfunction exacerbates neuronal degeneration and death as mitochondria influence neuronal transmission, Ca^{2+} homeostasis, neuronal plasticity, and maintenance of morphological stability [27]. Considering the strong association between mitochondrial energy supply and neurons, interventions targeting mitochondrial energy metabolism to attenuate insulin resistance and obesity-induced neuronal degeneration may ameliorate cognitive dysfunction in elderly obese patients.

Neuroinflammation, insulin resistance, and mitochondrial dysfunction are important mechanisms underlying cognitive function changes in obese patients, but there is still a lack of specific research to elucidate the underlying principles. We look forward to more related studies in the future.

Mechanisms of obesity-induced cognitive dysfunction: summarized as blood–brain barrier dysfunction, systemic inflammation, and insulin resistance (Fig. 1)

Blood–brain barrier dysfunction

Obesity causes dysfunction of the endothelial cells that form the capillary wall and act as the main components of the blood–brain barrier (BBB). Considering that obesity may gradually impair the BBB and activate neuroinflammation and degeneration, endothelial cells may be a key factor in obesity-associated cognitive deficits. A mouse model study in aged obese animals revealed that long-term HFD leads to increased perivascular, plasma-derived IgG permeability in the hippocampus, leading to chronic inflammation [7]. Reduced hippocampal microvessel density was observed in obese aged mice with hippocampus-dependent cognitive impairment compared to normal diet mice. In addition, obesity disrupts endothelial cell tight junction structures, resulting in increased blood–brain barrier permeability [28]. Topiramate (Topomax®; TPM) is an inhibitor of mitochondrial carbonic anhydrase (mCA) and reduces the level of reactive oxygen radicals, attenuates oxidative stress, and prevents BBB disruption in the brains of STZ-induced diabetic mice. Salameh T S et al. demonstrated that TPM prevented the loss of claudin-12 and ZO-1 in HFD mice while increasing the expression of tight junction proteins in the mouse hippocampus and restoring the integrity of the BBB [29].

Long-term high-fat and high-sugar diet stimulate the hypothalamic center to increase sensitivity to the inflammatory signaling intermediate c-Jun N-terminal kinase (c-JNK)/nuclear factor-κB (NF-κB) signaling molecules, leading to an increase in pro-inflammatory cytokines, impaired insulin, and leptin signaling. These changes result in inflammation, which is an important factor in aggravating blood–brain barrier dysfunction [30]. Finally, a high-fat and high-sugar diet can also trigger the proliferation and morphological transformation of microglia, which is a specific response of the hypothalamus to the HFD diet [31].

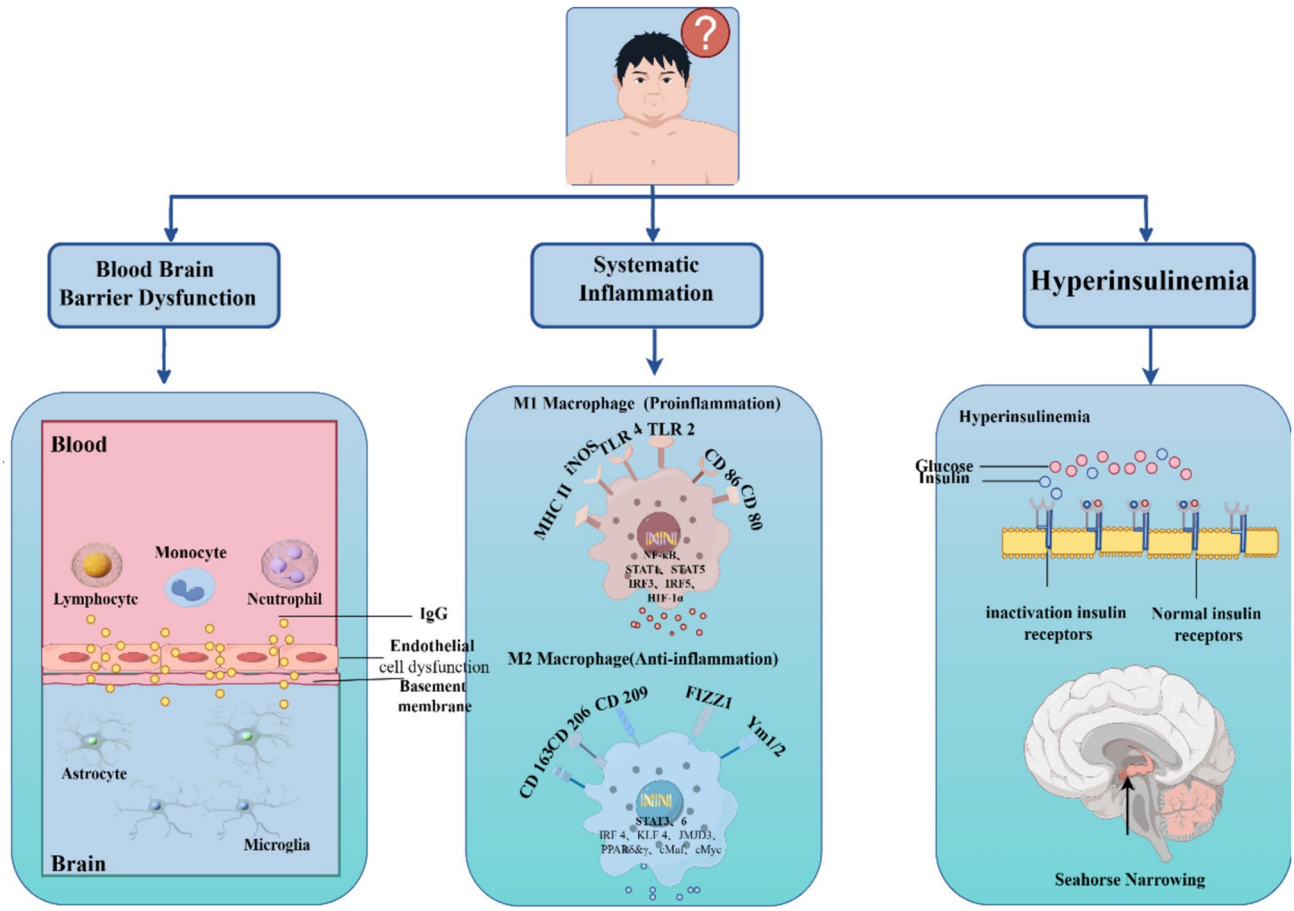

Fig. 1 Mechanisms of obesity-induced cognitive dysfunction. Obesity-induced cognitive dysfunction is primarily mediated by blood–brain barrier dysfunction, systemic inflammation, and insulin resistance

The above studies all suggest that obesity participates in the development of BBB by triggering neuroinflammation and activating related inflammatory pathways in different ways, thereby aggravating cognitive dysfunction.

Systemic inflammation

Systemic inflammation caused by obesity primarily involves white adipose tissue hypertrophy and dysfunction. Multiple adipose tissue macrophage subtypes (ATMs) are present in white adipose tissue, Different subpopulations have different functions, such as the M1 phenotype being pro-inflammatory and the M2 type being anti-inflammatory [32]. Inflammatory factors produced by ATM include interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). With adipocyte hypertrophy, IL-6 secretion gradually increases and exerts multiple effects on inflammation and immune response. Clinical studies have shown that IL-6 and its receptor expression are upregulated in the subcutaneous adipose tissue of obese patients compared to normal-weight patients; IL-6 disrupts neural circuits responsible for cognitive function and task completion, inhibits neuron formation, and reduces synaptic plasticity, ultimately decreasing the ability to learn and remember. Moreover, the IL-6 receptor antagonist tocilizumab was found to reduce systemic inflammation and improve cognitive function [33].

TNF-α is another inflammatory factor produced by ATMs. It activates the phosphate pathway and improves insulin resistance. A study in obese patients on hemodialysis showed that TNF-α-receptor 1 knockout rats were resistant to diet-induced obesity [34]. Under physiological conditions, moderate concentrations of TNF-α in the hippocampus modulate synaptic plasticity; However, there was a significant correlation with cognitive impairment when TNF-α was elevated, TNF-α may modulate cognitive function through the endothelium of microvessels. A clinical study isolated perivascular tissue from obese patients and found that the tissue had a weak endothelium-dependent diastolic response, which may be attributed to the fact that the perivascular tissue around microvessels in obese patients was weakly responsive to endothelium-dependent diastole. This may be explained by obese patients' perivascular adipose tissue producing excessive TNF-α, leading to increased levels of oxidative stress and the loss of vasodilatory function. The mechanism may be related to endogenous oxidative stress signals induced by TNF-α [35], such as the upregulation of TNF-α and IL-1β, the downregulation of IL-6, and the activation of microglial cells that can activate the TLR4/MyD88/NF-κB signaling pathway and attenuate the cognitive dysfunction induced by hematoxylin in rats [36].

In summary, the systemic inflammation caused by obesity is mainly white adipose tissue hypertrophy, which activates macrophages to polarize into M1 type. This type mainly plays a pro-inflammatory role, secreting inflammatory factors such as TNF -α, IL-1 β, IL-6, further activating signaling pathways including TLR4/MyD88/NF κ B, reducing synaptic plasticity, aggravating neuroinflammation, and causing cognitive dysfunction. This pathway may be the main cause of obesity induced systemic inflammation, ultimately leading to cognitive dysfunction.

Hyperinsulinemia (HS)

Insulin is involved in energy metabolism in the brain, and insulin receptor signaling plays an important role in synaptic plasticity, neuronal survival, learning, and memory clocks. Dietary obesity-mediated HS is closely associated with central nervous system insulin receptor impairment, but the exact mechanism remains unknown. Naotaka Izuo et al. constructed insulin receptor knockout mice with P1195L mutation (IR-KI mice) and demonstrated that insulin resistance induces cognitive dysfunction; cognitive deficits developed significantly faster in IR-KI mice compared to AD mice [37]. Moreover, long-term high-fat and high-sugar diets may cause HS, leading to insufficient cerebral glucose metabolism and impaired recognition memory [38].

Furthermore, insulin affects amyloid β-peptide clearance and Tau phosphorylation, which are classical features of AD [39]. HS was found to interfere with downstream processes of amyloid β peptide in AD patients, such as inflammation and oxidative stress, dyslipidemia, mitochondrial and synaptic function, and impaired brain insulin signaling, which mediates the impaired cognitive function. Significant insulin dysfunction was observed in the peripheral tissues of AD patients, which may be caused by chronic HS reducing the permeability of the blood–brain barrier and preventing the transport of insulin receptors, resulting in a decrease in central insulin levels [40]. A large number of abnormal Tau proteins are present in the brains of AD patients, and the abnormal modification and content changes of Tau proteins play a crucial role in the pathogenesis of clinical AD. A study by Das-Earl et al. confirmed that metabolic syndrome increases phosphorylated-tau protein (β-tau) in rat hippocampus, activates the insulin/PI3K/Akt signaling pathway [41], upregulates β-tau protein expression, including cortical β-tau, tau epitope, and insoluble or human β-tau [42], and exacerbates peripheral inflammation. These changes result in the deterioration of Aβ pathology in the mouse hippocampal cortex [43], and can collectively lead to cognitive dysfunction in AD patients.

In summary, the impact of hyperinsulinemia on cognitive function mainly involves insulin resistance in brain regions. When insulin levels increase, except for the neural features related to vigilance, attention, and memory, namely cortical activity, is enhanced, all other cortical activations are weakened. Long term hyperinsulinemia will reduce the

number of insulin receptors, thereby reducing the amount of insulin entering the brain, leading to a decrease in brain insulin uptake and affecting insulin action, which is a typical neuropathological feature of AD. In addition, mitochondrial dysfunction is also an important change in hyperinsulinemia, which can hinder the brain insulin signaling pathway and affect cognitive function, the same change also involves disturbances in glucose and lipid metabolism, synaptic plasticity, and neuronal signaling. The above factors collectively contribute to the cognitive function changes caused by hyperinsulinemia.

Advances in the study of gut flora dysbiosis in obese patients

The gut-brain axis influences various physiological processes, including glucose homeostasis, regulation of feeding processes, gut motility, and appetite, it is closely related to the formation of obesity [44]. Intestinal flora can alter the secretion of gut hormones such as GLP-1, gastrin, PYY, and leptin, which affect appetite and satiety through the hypothalamic neuroendocrine pathway [45]. Short-chain fatty acids (SCFA) bind to receptors on enteroendocrine cells (EECs) and alter the release of gut hormones into the systemic circulation [46]. In addition, various taste receptors (bitter, fatty, fresh, and sweet) in EECs are activated, resulting in the release of GLP-1, gastrin, and cholecystokinin, which suppresses appetite function through the hypothalamic centers [47].

Dysbiosis of the intestinal flora leads to an increase in acetate concentration, which activates the parasympathetic nervous system and promotes the release of glucose, causing an increase in glucagon [48], long term hyperglycemia can promote glycogen breakdown and gluconeogenesis in the liver, causing the body to remain in a hyperglycemic state for a long time and triggering insulin resistance, which is an important development process of obesity [49]. Furthermore, the intestinal flora can stimulate the release of neuroactive metabolites such as 5-hydroxytryptamine and GABA, which affect the appetite center [50]. Among them, 5-hydroxytryptamine is affected by melanocortin neurons and can reduce appetite and ultimately lower body weight [51]. In addition, GABA is an inhibitory neurotransmitter in the central nervous system and is involved in energy regulation.

Obesity-associated microflora can influence the rate of calorie intake from food [52]. A previous study reported that obese populations have elevated primary fermentative enzyme production and nutrient translocation rates by gut microbes compared to lean populations, which may provide more energy to the host [53]. Therefore, modifying the gut flora of obese people represents a potential therapeutic option to treat obesity and its associated metabolic diseases.

The changes in gut microbiota of obese patients mainly include: (1) Changes in intestinal microbial diversity: for example, Megamonas, Prevotella and Bacteroides strains, among which Megamonas dominated clustering is associated with a higher obesity rate and severe metabolic dysfunction [54], the proportion of Firms/Bacteroides is higher in diabetes patients, and Lactobacillus is more in obese individuals. (2) The relationship between gut microbiota and metabolite levels: for example, the content of glutamate in obese individuals is significantly higher than that in normal weight individuals, and is inversely proportional to the number of Bacteroides thetaiotaomicron. (3) The gut microbiota can also affect host metabolism through various mechanisms, including the synthesis of amino acids SCFA. The above factors collectively lead to changes in the gut microbiota of obese patients, resulting in impaired cognitive function.

Gut flora and altered cognitive function

In addition to the gut-brain axis, the gut microbiota affects brain function via inflammation and oxidative stress, neurological substances, and diet. Recent studies have investigated the effects of metabolites produced by the gut microbiota on neurodevelopment and formation. These metabolites were found to connect neuronal cells and gut microbes to influence cognitive functions [55]. The research progress of several pathways mentioned previously is summarized to provide a reference for researchers (Fig. 2).

Gut-brain axis

The gut-brain axis is a network of bidirectional information exchange between the brain and the gut, which is primarily mediated by metabolites produced by gut microbes and cells in the central nervous system, including neuronal cells and astrocytes.

Mitochondria-dependent neuronal signaling plays a central role in neuronal activity in the mammalian brain, and neuronal loss can lead to memory loss, depression, and anxiety [56]. Microbiota can produce SCFAs, including propionate and butyrate, which upregulate mitochondrial oxidative stress levels and activate extracellular signaling-associated protein kinase 1/2 (ERK 1/2) by increasing the levels of reactive oxygen species (ROS) to promote neuronal differentiation and formation [57]. Therefore, the SCFAs-mediated increase in mitochondrial content could have a positive effect on neuronal development.

Indole is a metabolite of gut microbes and is also an important mediator between neurons and gut microbes.

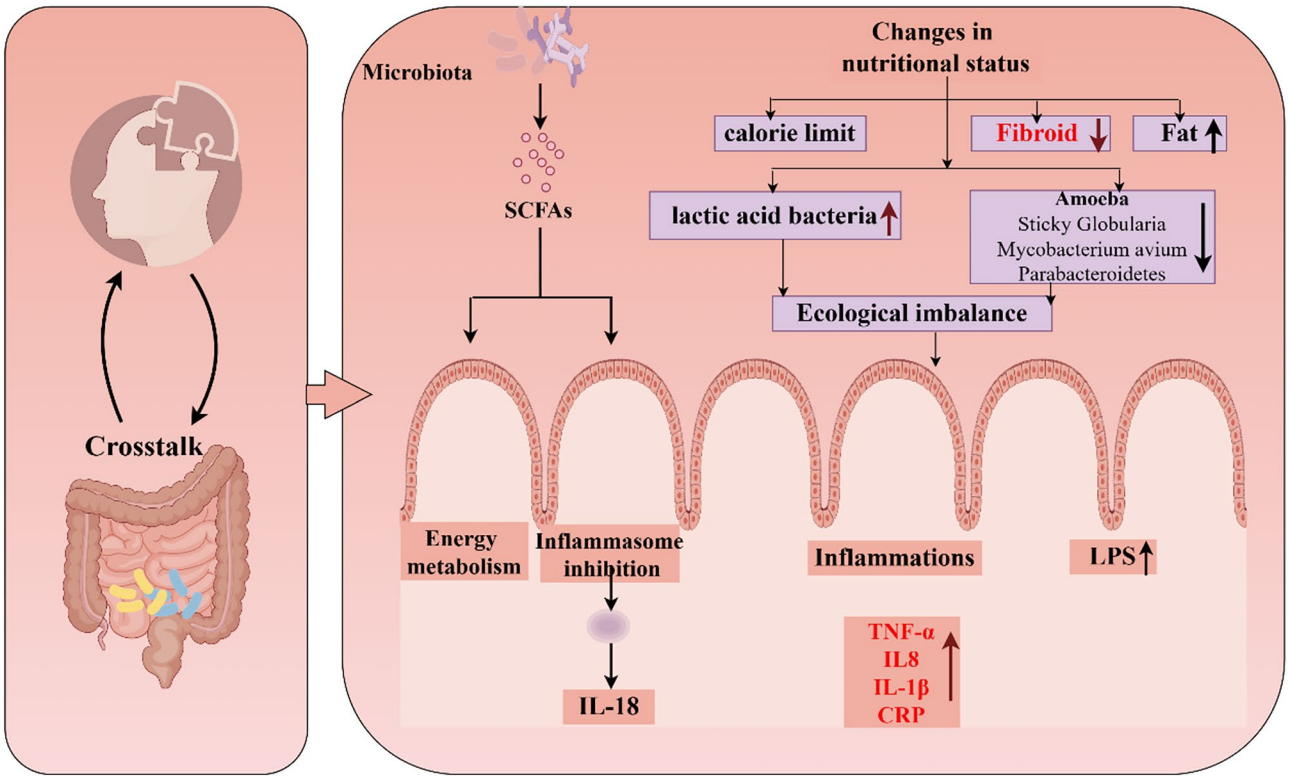

Fig. 2 Pathways of intestinal flora and altered cognitive functions. The gut-brain axis acts as a link between the gut flora and cognitive function, mediating cognitive changes through inflammation, oxidative stress, flora metabolites, and neurological substances

The oral administration of indole promotes the development of hippocampal neurons in adult mice by activating the AHR signaling pathway and increasing the expression of β-connexin, neuroligin 2, and vascular endothelial growth factor α at both the mRNA and protein levels. Furthermore, indole also increases the expression of pre and post-synaptic densities of hippocampal dystrophin 95 to stimulate the integration of neuronal function; this effect has been demonstrated in AHR-knockout mice [58].

In addition to the gut-brain axis, astrocytes and microglia in the central nervous system participate in neuronal activities in the brain. In particular, astrocytes are involved in neuronal development, neural circuit formation and metabolism, and neuronal repair. For example, SCFAs and indole can reduce neuroinflammation by down-regulating the expression of pro-inflammatory factors such as C–C motif chemokine ligand 2 (Ccl2) and nitric oxide synthase 2 (Nos2) in astrocytes [59]. Moreover, the metabolite tryptophan was found to affect astrocyte morphology and suppress CNS inflammation, whereas the gut flora bile acid metabolite TUDCA was reported to protect astrocytes from inflammation and neurodegeneration [60].

Gut-brain axis causes cognitive dysfunction through inflammatory and oxidative stress pathways

The destruction of gut microorganisms causes oxidative stress, which is a key step in the development of neuroinflammation and a prerequisite for cognitive changes in obese patients [61]. Some studies have shown that gut dysbiosis can elevate blood LPS levels, inducing elevated serum inflammation and exacerbating neuroinflammation, while elevated endotoxin levels activate the TLR4/NF-κB signaling pathway and exacerbate neuroinflammation in AD mice [62]. Furthermore, inflammation can lead to increased blood pressure and increased neuroinflammation in AD mice. Inflammation can also lead to the disruption of the tight junction proteins of the blood–brain barrier, enabling leukocytes and T cells to reach the brain parenchyma, resulting in neuronal death and cognitive dysfunction. In the CNS, $CD4^+$ Th17 and Th1 lymphocytes produce IL-27 and IFN-γ, resulting in neuronal axonal damage and oligodendrocyte death [63]. More importantly, a high-fat, high-sugar diet is strongly associated with blood–brain barrier permeability, contributing

to the development of neuroinflammation and cognitive dysfunction.

However, no gold standard has been established regarding the evaluation of blood–brain barrier permeability. Some scholars have proposed the use of the phenolphthalein excretion test and circulating D-lactic acid to determine the permeability of the intestinal barrier, or the use of time-domain near-infrared imaging to evaluate the permeability of the blood–brain barrier of mice. These assessment methods can confirm the role of the intestinal barrier induced alterations in cognitive function.

Cognitive dysfunction of the gut-brain axis via flora metabolites and neurologic substances

In addition to inflammatory pathways, gut flora metabolites and neurological substances can also impact cognitive function. Gut flora metabolites can be categorized into two groups based on their positive or negative effects on cognitive function. The Richenobacteriaceae, Desulfovibrio, Cyanobacteria, Aspergillus, Desulfovibrio, Helicobacter, and Escherichia coli have been shown to be detrimental to cognitive function [64]. Vibrio desulfuricans, also known as sulfate-reducing bacteria (SRB) belong to the phylum Aspergillus; these bacteria induce intestinal permeability and promote toxin leakage, impairing brain function [65]. The bacteria are known to produce the neurotoxin β Cyanobacteria produce the neurotoxin β-N-methylamino-L-alanine (BMAA). This neurotoxin promotes nervous system disorders and increases the formation of Aβ plaques and tangle deposits of phosphorylated tau neural progenitor fibers that can lead to progressive neuronal and synaptic loss, which is a pathognomonic feature of AD, aspergillus induces neuroinflammation and microglia activation, leading to cognitive decline [66]. Desmodium was found to increase inflammation production [67]. In addition, Bacteriophage de Ferris can increase inflammation production, and Helicobacter induces several cytokines, such as IL-6 and TNF-α, leading to blood–brain barrier disruption and neurodegeneration [68]. Ehrlichia produces extracellular amyloid that binds to Toll-like receptor 2 and triggers a downstream inflammatory response, which ultimately affects cognitive functions [69].

In contrast, Rumococcus spp, Ackermannia mucilaginosa, Mucilaginous bacilli, Negative bacilli, Clostridium perfringens, Eubacterium spp, and Heterobacterium spp exert beneficial effects on cognitive function. Ruminococcus spp. produce butyrate, which inhibits histone deacetylase, reduces the secretion of pro-inflammatory cytokines, and improves cognitive functions [70]. In patients with low butyrate levels, LPS induces a decrease in BBB and an increase in IL-1β expression, exacerbating cognitive dysfunction in mice [71]. Mucormycetophilic Ackermannia was found to attenuate intestinal barrier dysfunction, reducing Aβ plaque deposition in the brain, and attenuating cognitive dysfunction [72, 73]. On the other hand, negative bacilli had a positive effect on cognitive function [74]. Clostridium difficile can synthesize the strong oxidant 3-indolepropionic acid, which protects the brain from oxidative damage, reduces neuronal apoptosis, attenuates pathological histological changes and blood–brain barrier permeability, and improves cognitive function [75]. Moreover, Eubacterium spp. and Heterobacterium spp. can also improve cognitive function. In addition to the species present in the gut microbiota, their proportion also affects cognitive function; over-transplantation of Ackermannia mucophilus exacerbated intestinal inflammation, and an increased proportion of Ackermannia mucophilus was observed in patients with AD [76].

Neurotransmitters released in the digestive tract can participate in the enteric nervous system and influence vagal activity, forming a complete neural pathway. Such neurotransmitters mainly include GABA, serotonin, melatonin, histamine, acetylcholine, and catecholamines, which are involved in vagal regulation via afferent sensory neurons [77]. Additionally, these neurotransmitters can also influence the activation of the gastrointestinal immune system by altering the response of mast cells and macrophages to the intestinal flora. Furthermore, the intestinal flora regulates intestinal function through the enteric nervous system (ENS), which is independent of the central nervous system but can control both CNS and autonomic nervous system communication. Long-term feeding of Lactobacillus casei (JB-1) to rats with increased intrinsic excitability of intestinal muscular AH cells and inhibitory time was shortened after slow hyperpolarization. This represents a potential information transfer pathway between gut microbes and the nervous system [78].

In summary, the gut brain axis is an important pathway for cognitive function changes in obese patients, which caused by gut microbiota. Interactive signals along the gut brain axis can regulate inflammatory injury perception, inflammatory response, and immune homeostasis. The reason may be intestinal inflammation and oxidative stress causing intestinal ecological imbalance, leading to an increase in blood LPS levels, inducing serum inflammation, and the elevated endotoxin levels, which could activated the TLR/NF-KB signaling pathway, exacerbating neuroinflammation in obese mice. Secondly, the gut microbiota can secrete dopamine, 5-HT, norepinephrine, etc. 5-HT is a key signaling molecule in the gut brain axis and plays an important role in cognitive processing. Finally, dietary intake, particularly high-fat, meat, butter, etc., can cause a decrease in serum concentrations of chromium, magnesium, and zinc, as well as an increase in the abundance of Eggerthella and Faecalibacterium bacterial communities. The above are all related studies on the relationship between gut brain axis and cognitive function changes in obese patients,

but unfortunately, the specific mechanism is still unclear. However, we look forward to more research on gut axis in the future to clarify the mechanism in detail.

Advances in the study of cognitive alterations due to gut flora dysbiosis in obese patients (Fig. 3)

Mechanism

Changes in bacterial species and systemic inflammation

Obesity leads to an increased relative abundance of the thick-walled phylum Firmicutes, and a decrease in the abundance of the phylum Mycobacterium. Furthermore, a lower number of bacterial genes (i.e., < 480,000 gene counts) [79] was associated with obesity, as well as reduced alpha diversity, species richness, and beta diversity [80]. A study involving obese mice revealed that high-fat, high-sugar diets increased the abundance of thick-walled bacillus phylum in the gut, showing greater changes in gut microbial abundance compared to plant-based diets. This resulted in increased turnover of G^- bacilli, increased production of LPS, dysbiosis of the microbial ecology, increased intestinal permeability, and increased passage of opportunistic pathogens, thereby triggering inflammation and altering cognitive function. In addition, a long-term high-fat diet increases the formation of celiac particles and accelerates the entry of LPS into the body's circulation [81]. Moreover, the expression of the TOLL-like receptor TLR4 is upregulated in the gut, which recognizes LPS on the cell wall of Gram-negative bacteria, activates the TLR4 signaling pathway, releases pro-inflammatory factor and chemokines, and leads to chronic systemic low-grade inflammation [82]. Vascular endothelial dysfunction is a risk factor for cerebrovascular disease and may be caused by the dysregulation of microbial ecology and relative abundance, increased LPS levels, and inflammation. This may be attributed to inadequate perfusion altering the structure and function of the brain, leading to cognitive decline. Thus, increased LPS can lead to dysregulated gut ecology and systemic inflammation, activating immune responses and endothelial dysfunction and affecting cognitive function.

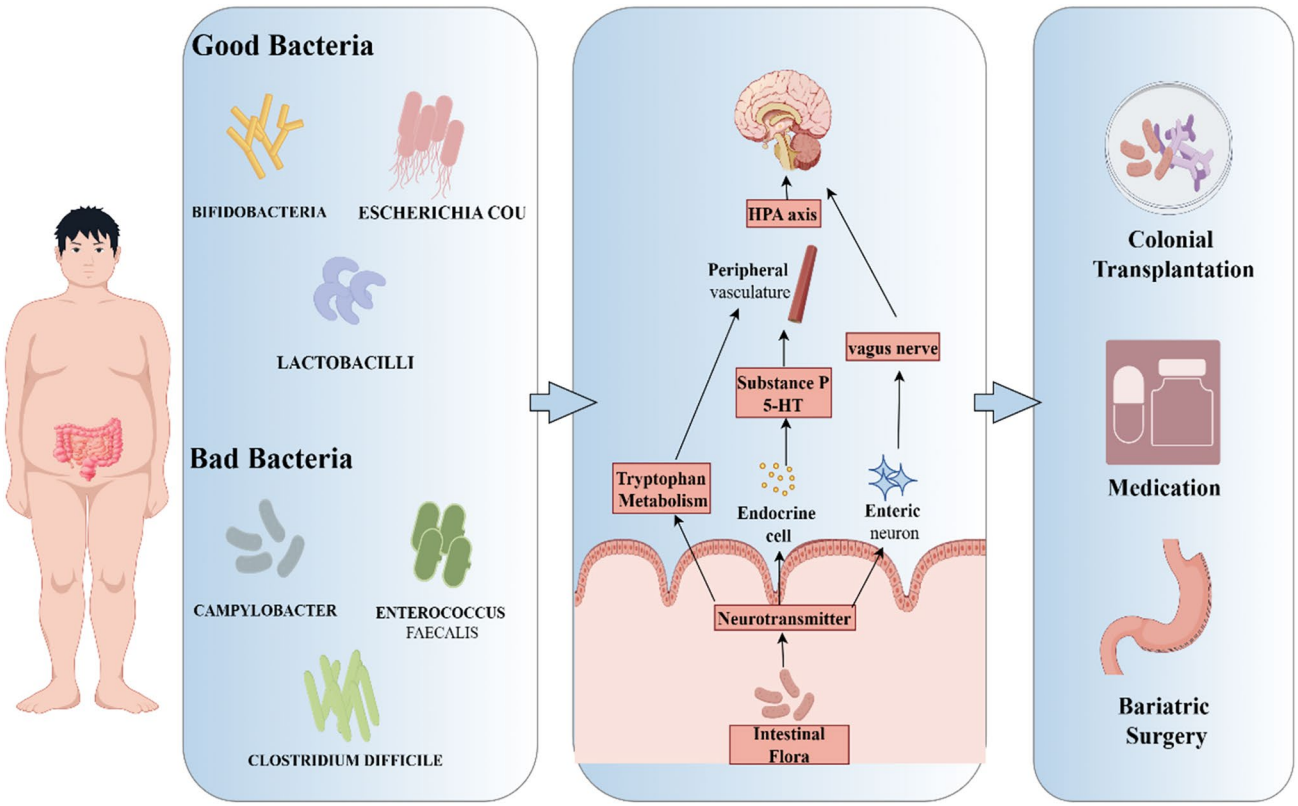

Fig. 3 Progress in the study of cognitive alterations caused by dysbiosis in the gut flora of obese patients. Changes in gut flora species, systemic inflammation, and neuroactive substances can lead to altered cognitive function in obese patients; changes in gut flora species and relative abundance, pharmacological treatments, and surgical weight-loss procedures may potentially improve cognitive function in obese patients

Therefore, inhibiting the inflammatory response, influencing the composition of the gut microbiota, or targeting specific strains of bacteria may potentially improve obesity or diet-induced alterations in cognitive function. Interventions with gut flora may be developed to improve cognitive function in obese patients.

Neuroactive substances

The gut microbiota secretes several neuroactive substances, which are closely related to cognitive function changes in obese patients [83]. These substances can influence neurodevelopment, cognition, and behavior by modulating bidirectional communication between the intestinal tract and the central nervous system [84]. For example, the gut flora can produce neuroactive metabolites such as 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA), propionate, and short-chain fatty acids.

5-HT is an important neurotransmitter synthesized in the gut and central nervous system and plays an essential role in the gut-brain axis, where its activity is mainly determined by the 5-HT transporter SERT, which exerts its signaling function through the specific neuroreceptor 5-HTR to regulate functions such as mood, cognition, and inflammation [84]. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter involved in multiple physiological and metabolic processes. GABAergic neurons in the brain produce the enzyme glutamic acid decarboxylase, which converts glutamic acid to GABA. Specific species of bacteria in the gut produce GABA, including Lactococcus lactis, Pseudomonas fragilis, Parabacillus spp, Eubacterium spp, and Bifidobacterium spp [85]. In addition, another study revealed that Bifidobacterium bifidum in the intestinal tract of adolescents also contained this compound; moreover, the strains PRL2019 and HD17T2H showed higher GABA production, and Bifidobacterium bifidum may be positively associated with neuropsychiatric disorders in adolescents [86]. GABA imbalance or reduced activity can lead to mood disorders such as anxiety and depression, schizophrenia, and autism; hence, GABA may be a therapeutic target for psychiatric-related disorders.

SCFAs are derived from microbial fermentation that is indigestible. The site with the highest SCFA concentration in the human gut is the colon, where SCFAs act as an energy substrate for enterocytes and colonocytes, affecting intestinal epithelial barriers and defenses. In addition, they exert anti-inflammatory effects by regulating the recruitment and migration of immune cells, T-cell and B-cell differentiation, and gene expression of some inflammatory chemokines and cytokines [87]. Therefore, SCFAs play a crucial role in the health status of the host and promote lipid metabolism, glucose utilization, and immune homeostasis. SCFAs also affect the structure and function of the mammalian brain and improve learning, memory, mood, neurodevelopment, cognitive function, and stress response, among others [88]. Considering the close relationship between the gut microbiota and the host, dysbiosis has been associated with several extra-intestinal disorders of metabolic, behavioral, and neurological origins. SCFAs may be a potential target for the treatment of such disorders [89].

The types of gut microbiota, systemic inflammation, and neuroactive substances are the three major pathways through which gut microbiota affects cognitive function changes in obese patients. In the gut microbiota, Clostridium, Ruminococcus, and Bifidobacterium are positively correlated with memory scores, while Bacteroides and Proteobacteria are negatively correlated with memory scores, SCFA producing bacteria are responsible for producing tight junction proteins, improving intestinal permeability, preventing brain damage, and peripheral inflammation caused by cytokine leakage. These microbiota are closely related to cognitive function changes in obese patients. Systemic inflammation involves the imbalance of intestinal ecology and systemic inflammation caused by an increase in LPS, which can activate immune response and endothelial dysfunction, affecting cognitive function. Neuroactive substances include 5-hydroxytryptamine (5-HT), gamma aminobutyric acid (GABA), propionate, and short chain fatty acids. The above three factors can both influence each other and jointly affect the cognitive function of obese patients.

Potential approaches to modulate gut flora to improve cognitive function in obese patients

Altering the strain type and relative abundance of the gut flora:

Zhao T et al. treated obese patients and their lipid metabolism disorders by modulating the structure, relative abundance, and function of the gut microbiota [90]. The results from animal experiments by Uaasr et al. suggest that transplantation of the gut microbiota from obesity-resistant mice into germ-free obesity-susceptible mice improves specific metabolic consequences of obesity [91]. Furthermore, Nicolucci A C et al. found that the use of prebiotics reduced body mass index Z-scores, percent body fat, percent trunk fat, and serum IL-6 levels [92]. Therefore, gut flora transplantation and oral prebiotics may be therapeutic tools to improve cognitive function in obese patients.

Pharmacotherapy

Pharmacotherapeutic drugs, including atorvastatin, melatonin, and natural supplements such as beluga, have been shown to alleviate LPS-induced neuroinflammatory, behavioral, and cognitive dysfunction in animal studies [93].

LPS-derived TLR4 agonists, gut ecological modulators, and vagus nerve stimulation and its associated treatment to inhibit inflammatory pathways may potentially prevent cognitive decline. The leucine-restricted diet can reshape the structure of the microbiota, e.g., by down-regulating the ratio of fungi/mycobacteria, decreasing the relative abundance of bacteria associated with inflammation (e.g., Acetobacter, Helicobacter, Mucor sphaericus, and short-chain fatty acid-producing genera), and, finally, decreasing the cognitive deficits induced by LPS [94]. Currently, numerous studies have investigated the mechanism underlying the inflammatory effects of increased LPS, leading to dysregulation of gut ecology [95–97]. These findings may provide evidence for targeted drug development for obese patients.

Bariatric surgery

The two main types of bariatric surgery for the treatment of obesity include laparoscopic sleeve gastrectomy (LSG) and jejunal Y-anastomosis (RYG) [98]. Studies have shown that bariatric surgery not only reduces body weight but also improves neurocognitive function in obese individuals, but the exact mechanism remains unclear. In obese individuals, an increased proportion of thick-walled phyla was observed, accompanied by a lower abundance of anamorphic phyla, leading to ecological dysregulation of the intestinal flora. Bariatric surgery results in increased diversity and composition of the intestinal flora, including anamorphic phyla and clostridial phyla, and a decrease in thick-walled phyla, anamorphic phyla, and actinomycetes. The decrease in the thick-walled phyla increases the host metabolism and decreases caloric absorption, which ultimately leads to a decrease in body weight [99]. In addition to altering the number and diversity of fecal microorganisms, bariatric surgery can also improve serum biomarkers [100]. Under normal physiological conditions, pro-inflammatory cytokines are unlikely to cross the blood–brain barrier, but the neural signals they send may cross the blood–brain barrier, triggering blood–brain-barrier-deficient hypothalamic disorders such as autism. Furthermore, LSG was found to decrease IL-1β and TNF-α levels, while increasing IL-4 levels, which correlates with serum biomarkers or with bacterial abundance in diseases such as diabetes mellitus, obesity, and bulimia nervosa. Elevated levels of IL-1β can have a negative impact on neuronal cell death and cognitive function, but IL-4 may have a protective effect on cognitive function [101]. In order to fully understand the mechanisms associated with the bariatric surgery-microbiota-brain-gut axis, further studies are required to explore changes in relevant regions of the brain postoperatively and to determine the effects of obesity on the integrity of the blood–brain barrier. Future longitudinal studies are required to evaluate the multifactorial changes following bariatric surgery to provide more solid evidence. Regrettably, research on the effects of long-term changes in gut microbiota on cognitive function is currently lacking, and the effects of obesity on blood–brain barrier integrity and its associated neurostructural changes remain incompletely understood.

Changing the type and abundance of gut microbiota, drug therapy, and Bariatric Surgery are the three methods that can regulate gut microbiota and improve cognitive function in obese patients. In the future, there may more effective, simple and non-invasive methods.

Summary and outlook

Gut flora is associated with altered cognitive function in obese patients, mainly changes in the composition, abundance, and metabolic products of the gut microbiota, which can affect energy absorption and metabolism in the human body, leading to the formation of obesity, and obesity ultimately triggers cognitive changes. Possible mechanisms underlying this association include the following points. **1 Inflammatory Reaction:** The inflammatory response is often elevated during obesity, and imbalances in some flora may lead to intestinal inflammation.Inflammatory state is linked to cognitive decline, as inflammatory factors can cross the blood–brain barrier and affect brain function. **2 Product of metabolism:** Gut flora metabolites, such as SCFA and neuroactive substances, can affect neurological function. SCFAs are thought to impact cognitive function by affecting neurotransmission, modulating inflammatory responses, and apoptosis. **3 Neurotransmitter:** Gut flora synthesize a variety of neurotransmitters, such as 5-hydroxytryptamine and dopamine, which have modulatory effects on mood and cognitive function. An imbalance in gut flora may lead to altered levels of these neurotransmitters, which may affect cognitive function.

Therefore, the association between gut flora and altered cognitive function in obese patients may result from a combination of factors. Although current research is still exploring these mechanisms, advances in this area may help to develop new therapeutic approaches, such as improving cognitive function by modulating gut flora. We look forward to the early realization of this intervention.

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Declarations

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References

1. Yuan M, Rong M, Long X et al (2024) Trajectories of cognitive decline in different domains prior to AD onset in persons with mild cognitive impairment. Arch Gerontol Geriatr 122:105375
2. Petersen RC (2011) Mild cognitive impairment. N Engl J Med 364(23):2227–2234
3. Dahl AK, Hassing LB, Fransson EI et al (2013) Body mass index across midlife and cognitive change in late life. Int J Obes 37(2):296–302
4. Whitmer RA, Gustafson DR, Barrett-Connor E et al (2008) Central obesity and increased risk of dementia more than three decades later. Neurology 71(14):1057–1064
5. Zhuang H, Yao X, Li H et al (2022) Long-term high-fat diet consumption by mice throughout adulthood induces neurobehavioral alterations and hippocampal neuronal remodeling accompanied by augmented microglial lipid accumulation. Brain Behav Immun 100:155–171
6. Kesby JP, Kim JJ, Scadeng M et al (2015) Spatial cognition in adult and aged mice exposed to high-fat diet. PLoS ONE 10(10):e0140034
7. Tucsek Z, Toth P, Sosnowska D et al (2014) Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. J Gerontol Series A, Biol Sci Med Sci 69(10):1212–1226
8. Lei Y, Chen Y, Zhang S et al (2024) Qingzhuan dark tea Theabrownin alleviates hippocampal injury in HFD-induced obese mice through the MARK4/NLRP3 pathway. Heliyon 10(5):e26923
9. Evans AK, Saw NL, Woods CE et al (2024) Impact of high-fat diet on cognitive behavior and central and systemic inflammation with aging and sex differences in mice. Brain Behav Immun 118:334–354
10. Zhang Y, Luo C, Huang P et al (2024) Diosmetin ameliorates HFD-induced cognitive impairments via inhibiting metabolic disorders, mitochondrial dysfunction and neuroinflammation in male SD rats. Molecular Neurobiol. https://doi.org/10.1007/s12035-024-04083-x
11. Fu J, Wu H (2023) Structural mechanisms of NLRP3 inflammasome assembly and activation. Annu Rev Immunol 41(1):301–316
12. 2022 Alzheimer's disease facts and figures[J]. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 2022, 18(4): 700–789.
13. Hyman BT, Van Hoesen GW, Damasio AR et al (1984) Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 225:1168–1170
14. Nianogo RA, Rosenwohl-Mack A, Yaffe K et al (2022) Risk factors associated with alzheimer disease and related dementias by sex and race and ethnicity in the US. JAMA Neurol 79(6):584–591
15. Pszczołowska M, Walczak K, Miśków W et al (2024) Mitochondrial disorders leading to Alzheimer's disease—perspectives of diagnosis and treatment. GeroScience. https://doi.org/10.1007/s11357-024-01118-y
16. Diz-Chaves Y, Maastor Z, Spuch C et al (2024) Glucagon-like peptide 1 receptor activation: anti-inflammatory effects in the brain. Neural Regen Res 19(8):1671–1677
17. Złotek M, Kurowska A, Herbet M et al (2023) GLP-1 Analogs, SGLT-2, and DPP-4 inhibitors: a triad of hope for alzheimer's disease therapy. Biomedicines 11(11):3035
18. Ma Y, Ajnakina O, Steptoe A et al (2020) Higher risk of dementia in English older individuals who are overweight or obese. Int J Epidemiol 49(4):1353–1365
19. Patel V, Edison P (2024) Cardiometabolic risk factors and neurodegeneration: a review of the mechanisms underlying diabetes, obesity and hypertension in Alzheimer's disease. J Neurol Neurosurg Psychiatry 95(6):581–589
20. Amorim MR, Aung O, Mokhlesi B et al (2022) Leptin-mediated neural targets in obesity hypoventilation syndrome. Sleep. https://doi.org/10.1093/sleep/zsac153
21. Kim JD, Yoon NA, Jin S et al (2019) Microglial UCP2 mediates inflammation and obesity induced by high-fat feeding. Cell Metab 30(5):952-962.e5
22. Khan S, Barve KH, Kumar MS (2020) Recent advancements in pathogenesis, diagnostics and treatment of alzheimer's disease. Curr Neuropharmacol 18(11):1106–1125
23. Ge X, Hu M, Zhou M et al (2024) Overexpression of forebrain PTP1B leads to synaptic and cognitive impairments in obesity. Brain Behav Immun 117:456–470
24. Wong Zhang DE, Tran V, Vinh A et al (2023) Pathophysiological links between obesity and dementia. NeuroMol Med 25(4):451–456
25. Rolfe DF, Brown GC (1997) Cellular energy utilization and molecular origin of standard metabolic rate in mammals. Physiol Rev 77(3):731–758
26. Guo H, Xin Y, Wang S et al (2024) Hypothalamic POMC neuron-specific knockout of MC4R affects insulin sensitivity by regulating Kir2.1. Molecular Med 30(1):34
27. Sharma VK, Singh TG (2020) Insulin resistance and bioenergetic manifestations: targets and approaches in Alzheimer's disease. Life Sci 262:118401

28. Zlokovic BV (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 57(2):178–201
29. Salameh TS, Mortell WG, Logsdon AF et al (2019) Disruption of the hippocampal and hypothalamic blood-brain barrier in a diet-induced obese model of type II diabetes: prevention and treatment by the mitochondrial carbonic anhydrase inhibitor, topiramate. Fluids Barriers CNS 16(1):1
30. Posey KA, Clegg DJ, Printz RL et al (2009) Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. Am J Physiol-Endocrinol Metabol 296(5):E1003–E1012
31. Milanski M, Degasperi G, Coope A et al (2009) Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci 29(2):359–370
32. Buie JJ, Watson LS, Smith CJ et al (2019) Obesity-related cognitive impairment: the role of endothelial dysfunction. Neurobiol Dis 132:104580
33. Sindhu S, Thomas R, Shihab P et al (2015) Obesity is a positive modulator of IL-6R and IL-6 expression in the subcutaneous adipose tissue: significance for metabolic inflammation. PLoS ONE 10(7):e0133494
34. Beberashvili I, Azar A, Abu Hamad R et al (2019) Abdominal obesity in normal weight versus overweight and obese hemodialysis patients: associations with nutrition, inflammation, muscle strength, and quality of life. Nutrition 59:7–13
35. Virdis A, Duranti E, Rossi C et al (2015) Tumour necrosis factor-alpha participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue. Eur Heart J 36(13):784–794
36. Wei X, Zhang F, Cheng D et al (2024) Free heme induces neuroinflammation and cognitive impairment by microglial activation via the TLR4/MyD88/NF-κB signaling pathway. Cell Commun Signal 22(1):16
37. Izuo N, Watanabe N, Noda Y et al (2023) Insulin resistance induces earlier initiation of cognitive dysfunction mediated by cholinergic deregulation in a mouse model of Alzheimer's disease. Aging Cell 22(11):e13994
38. Al-Onaizi M, Braysh K, Alkafeef S S, et al. Glucose intolerance induces anxiety-like behaviors independent of obesity and insulin resistance in a novel model of nutritional metabolic stress[J]. Nutritional Neuroscience, 2024: 1–19.
39. Saraya AW, Tunvirachaisakul C, Sonpee C et al (2023) Serum proinsulin levels as peripheral blood biomarkers in patients with cognitive impairment. Sci Rep 13(1):22436
40. Kellar D, Craft S (2020) Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol 19(9):758–766
41. Das-Earl P, Schreihofer DA, Sumien N et al (2024) Temporal and region-specific tau hyperphosphorylation in the medulla and forebrain coincides with development of functional changes in male obese Zucker rats. J Neurophysiol. https://doi.org/10.1152/jn.00409.2023
42. Valentin-Escalera J, Leclerc M, Calon F (2024) High-fat diets in animal models of alzheimer's disease: how can eating too much fat increase alzheimer's disease risk? J Alzheimer's Dis: JAD 97(3):977–1005
43. Mengr A, Strnadová V, Strnad Š et al (2023) Feeding high-fat diet accelerates development of peripheral and central insulin resistance and inflammation and worsens AD-like pathology in APP/PS1 mice. Nutrients 15(17):3690
44. Asadi A, Shadab Mehr N, Mohamadi MH et al (2022) Obesity and gut-microbiota-brain axis: a narrative review. J Clin Lab Anal 36(5):e24420
45. Torres-Fuentes C, Schellekens H, Dinan TG et al (2015) A natural solution for obesity: bioactives for the prevention and treatment of weight gain. A review. Nutr Neurosci 18(2):49–65
46. Nøhr MK, Pedersen MH, Gille A et al (2013) GPR41/FFAR3 and GPR43/FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes. Endocrinology 154(10):3552–3564
47. Frost G, Sleeth ML, Sahuri-Arisoylu M et al (2014) The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat Commun 5:3611
48. Perry RJ, Peng L, Barry NA et al (2016) Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. Nature 534:213–217
49. Sacks DB, Arnold M, Bakris GL et al (2023) Guidelines and recommendations for laboratory analysis in the diagnosis and management of Diabetes Mellitus. Diabetes Care 46(10):e151–e199
50. Delgado TC (2013) Glutamate and GABA in appetite regulation. Front Endocrinol 4:103
51. Xu Y, Jones JE, Kohno D et al (2008) 5-HT2CRs expressed by pro-opiomelanocortin neurons regulate energy homeostasis. Neuron 60(4):582–589
52. Turnbaugh PJ, Ley RE, Mahowald MA et al (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444(7122):1027–1031
53. Krajmalnik-Brown R, Ilhan ZE, Kang DW et al (2012) Effects of gut microbes on nutrient absorption and energy regulation. Nutr Clin Pract: Off Publ Am Soc Parenter Enteral Nutr 27(2):201–214
54. Wu C, Yang F, Zhong H et al (2024) Obesity-enriched gut microbe degrades myo-inositol and promotes lipid absorption. Cell Host Microbe 32(8):1301-1314.e9
55. Kim CS (2024) Roles of diet-associated gut microbial metabolites on brain health: cell-to-cell interactions between gut bacteria and the central nervous system. Adv Nutrition 15(1):100136
56. Liu L, Cheng S, Qi X et al (2023) Mitochondria-wide association study observed significant interactions of mitochondrial respiratory and the inflammatory in the development of anxiety and depression. Transl Psychiatry 13(1):216
57. Ribeiro MF, Santos AA, Afonso MB et al (2020) Diet-dependent gut microbiota impacts on adult neurogenesis through mitochondrial stress modulation. Brain Commun. https://doi.org/10.1093/braincomms/fcaa165
58. Kim CS, Jung S, Hwang GS et al (2023) Gut microbiota indole-3-propionic acid mediates neuroprotective effect of probiotic consumption in healthy elderly: a randomized, double-blind, placebo-controlled, multicenter trial and in vitro study. Clin Nutr 42(6):1025–1033
59. Ahmed H, Leyrolle Q, Koistinen V et al (2022) Microbiota-derived metabolites as drivers of gut-brain communication. Gut Microbes 14(1):2102878
60. Liddelow SA, Guttenplan KA, Clarke LE et al (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541(7638):481–487
61. Loffredo L, Ettorre E, Zicari AM et al (2020) Oxidative stress and gut-derived lipopolysaccharides in neurodegenerative disease: role of NOX2. Oxid Med Cell Longev 2020:1–7
62. Fasina OB, Wang J, Mo J et al (2022) Gastrodin From *Gastrodia elata* enhances cognitive function and neuroprotection of AD Mice via the regulation of gut microbiota composition and inhibition of neuron inflammation. Front Pharmacol 13:814271
63. Wang Q, Li D, Cao G et al (2021) IL-27 signalling promotes adipocyte thermogenesis and energy expenditure. Nature 600:314–318
64. Wu L, Han Y, Zheng Z et al (2021) Obeticholic acid inhibits anxiety via alleviating gut microbiota-mediated Microglia

accumulation in the brain of high-fat high-sugar diet mice. Nutrients 13(3):940
65. Murros KE, Huynh VA, Takala TM et al (2021) Desulfovibrio bacteria are associated with Parkinson's disease. Front Cell Infect Microbiol 11:652617
66. Silva DF, Candeias E, Esteves AR et al (2020) Microbial BMAA elicits mitochondrial dysfunction, innate immunity activation, and Alzheimer's disease features in cortical neurons. J Neuroinflammation 17(1):332
67. Carabotti M, Scirocco A, Maselli MA et al (2015) The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 28(2):203–209
68. Wu M, Wang Q, Li X et al (2024) Gut microbiota-derived 5-hydroxyindoleacetic acid from pumpkin polysaccharides supplementation alleviates colitis via MAPKs-PPARγ/NF-κB inhibition. Int J Biol Macromol 264:130385
69. Qiu C, Yuan Z, He Z et al (2021) Lipopolysaccharide preparation derived from *Porphyromonas gingivalis* induces a weaker immuno-inflammatory response in BV-2 microglial cells than *Escherichia coli* by differentially activating TLR2/4-mediated NF-κB/STAT3 signaling pathways. Front Cell Infect Microbiol 11:606986
70. Jiang Y, Li K, Li X et al (2021) Sodium butyrate ameliorates the impairment of synaptic plasticity by inhibiting the neuroinflammation in 5XFAD mice. Chem Biol Interact 341:109452
71. Marizzoni M, Cattaneo A, Mirabelli P et al (2020) Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. J Alzheimer's Dis 78(2):683–697
72. Ou Z, Deng L, Lu Z et al (2020) Protective effects of Akkermansia muciniphila on cognitive deficits and amyloid pathology in a mouse model of Alzheimer's disease. Nutr Diabetes 10(1):12
73. Higarza SG, Arboleya S, Arias JL et al (2021) *Akkermansia muciniphila* and environmental enrichment reverse cognitive impairment associated with high-fat high-cholesterol consumption in rats. Gut Microbes 13(1):1880240
74. Sadovnikova IS, Gureev AP, Ignatyeva DA et al (2021) Nrf2/ARE activators improve memory in aged mice via maintaining of mitochondrial quality control of brain and the modulation of gut microbiome. Pharmaceuticals (Basel, Switzerland) 14(7):607
75. Obrenovich M, Jaworski H, Tadimalla T et al (2020) The role of the microbiota–gut–brain axis and antibiotics in ALS and neurodegenerative diseases. Microorganisms 8(5):784
76. Megur A, Baltriukienė D, Bukelskienė V et al (2020) The microbiota-gut-brain axis and Alzheimer's disease: neuroinflammation is to blame? Nutrients 13(1):37
77. Prescott SL, Liberles SD (2022) Internal senses of the vagus nerve. Neuron 110(4):579–599
78. McVey Neufeld KA, Mao YK, Bienenstock J et al (2013) The microbiome is essential for normal gut intrinsic primary afferent neuron excitability in the mouse. Neurogastroenterol Motil 25(2):183-e88
79. Le Chatelier E, Nielsen T, Qin J et al (2013) Richness of human gut microbiome correlates with metabolic markers. Nature 500(7464):541–546
80. Geisler C, Pankoke J, Schlicht K et al (2021) BMI, alcohol consumption and gut microbiome species richness are related to structural and functional neurological abnormalities. Nutrients 13(11):3743
81. Lei C, Wu G, Cui Y et al (2024) Development and validation of a cognitive dysfunction risk prediction model for the abdominal obesity population. Front Endocrinol 15:1290286
82. Mandle HB, Jenab M, Gunter MJ et al (2024) Inflammation and gut barrier function-related genes and colorectal cancer risk in Western European populations. Mutagenesis. https://doi.org/10.1093/mutage/geae008
83. Kuijer EJ, Steenbergen L (2023) The microbiota-gut-brain axis in hippocampus-dependent learning and memory: current state and future challenges. Neurosci Biobehav Rev 152:105296
84. Buey B, Forcén A, Grasa L et al (2023) Gut microbiota-derived short-chain fatty acids: novel regulators of intestinal serotonin transporter. Life (Basel, Switzerland) 13(5):1085
85. Strandwitz P, Kim KH, Terekhova D et al (2019) GABA-modulating bacteria of the human gut microbiota. Nat Microbiol 4(3):396–403
86. Duranti S, Ruiz L, Lugli GA et al (2020) Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Sci Rep 10(1):14112
87. Yao Y, Cai X, Fei W et al (2022) The role of short-chain fatty acids in immunity, inflammation and metabolism. Crit Rev Food Sci Nutr 62(1):1–12
88. Silva YP, Bernardi A, Frozza RL (2020) The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol 11:25
89. O'Riordan KJ, Collins MK, Moloney GM et al (2022) Short chain fatty acids: microbial metabolites for gut-brain axis signalling. Mol Cell Endocrinol 546:111572
90. Zhao T, Zhan L, Zhou W et al (2021) The effects of Erchen decoction on gut microbiota and lipid metabolism disorders in zucker diabetic fatty rats. Front Pharmacol 12:647529
91. Ussar S, Griffin NW, Bezy O et al (2015) Interactions between gut microbiota, host genetics and diet modulate the predisposition to obesity and metabolic syndrome. Cell Metab 22(3):516–530
92. Nicolucci AC, Hume MP, Martínez I et al (2017) Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. Gastroenterology 153(3):711–722
93. McFarland AJ, Davey AK, Anoopkumar-Dukie S (2017) Statins reduce lipopolysaccharide-induced cytokine and inflammatory mediator release in an in vitro model of microglial-like cells. Mediators Inflamm 2017:2582745
94. Wang D, Wang L, Han L et al (2023) Leucine-restricted diet ameliorates obesity-linked cognitive deficits: involvement of the microbiota-gut-brain axis. J Agric Food Chem 71(24):9404–9418
95. Hu X, Zhen W, Bai D et al (2024) Effects of dietary chlorogenic acid on cecal microbiota and metabolites in broilers during lipopolysaccharide-induced immune stress. Front Microbiol 15:1347053
96. Sun Y, Wang Y, Lin Z et al (2024) Irisin delays the onset of type 1 diabetes in NOD mice by enhancing intestinal barrier. Int J Biol Macromolecules 265:130857
97. Chang BT, Wang Y, Tu WL et al (2024) Regulatory effects of mangiferin on LPS-induced inflammatory responses and intestinal flora imbalance during sepsis. Food Sci Nutr 12(3):2068–2080
98. Chen W, Song J, Cheng Y et al (2023) Changes in gut microbiota and cytokines following laparoscopic sleeve gastrectomy are associated with cognitive function improvement. Heliyon 9(9):e19245
99. Campisciano G, Palmisano S, Cason C et al (2018) Gut microbiota characterisation in obese patients before and after bariatric surgery. Beneficial Microbes 9(3):367–373
100. Tabasi M, Eybpoosh S, Siadat SD et al (2021) Modulation of the gut microbiota and serum biomarkers after laparoscopic sleeve gastrectomy: a 1-year follow-up study. Obes Surg 31(5):1949–1956
101. Shen F, Gao C, Wang M et al (2024) Therapeutic effects of the Qingre-Qushi recipe on atopic dermatitis through the regulation of gut microbiota and skin inflammation. Heliyon 10(4):e26063

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