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БОЛЕЗНЬ АЛЬЦГЕЙМЕРА: ВЛИЯНИЕ МИКРОФЛОРЫ КИШЕЧНИКА И ПОЛОВЫХ РАЗЛИЧИЙ НА ПАТОГЕНЕЗ И СТРАТЕГИИ ЛЕЧЕНИЯ

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Alzheimer's Disease: The Impact of Gut Microbiota and Sex Differences on Pathogenesis and Treatment Strategies

Резюме

Болезнь Альцгеймера (БА) — глобальное заболевание. Наиболее важным в патогенезе БА является увеличение отложений амилоидного белка бета (Аβ) и патологическое скопление тау-белка. В развитии болезни принимает участие ряд этиологических факторов, таких как возраст, генетика, образ жизни, факторы окружающей среды и микрофлора кишечника (МК). Нарушение регуляции МК — один из факторов патогенеза БА, который способствует нарушению когнитивной функции, включая скопление Аβ и тау-белка, выработку нейромедиаторов и метаболитов, нарушение иммунной регуляции, нейровоспаление, нарушение гематоэнцефалитического барьера, оксидативный стресс и синдром раздраженного кишечника.

Половые различия могут быть важным фактором патогенеза БА. Около 75 % пациентов с БА являются женщинами. Преобладание БА у женщин связано с генетикой, структурой и функцией головного мозга, эстрогеном, образом жизни (например, образование, род деятельности, уровень физической активности и продолжительность сна) и случаями инфекционно-воспалительных заболеваний. Поскольку продолжительность жизни у женщин больше, чем у мужчин, женщины более склонны к БА.

В настоящей статье рассматривается роль МК и половые различия при БА. В начале статьи приводится краткое описание характеристик микрофлоры кишечника и половых различий при БА. В работе рассматриваются перспективные терапевтические стратегии при БА, направленные на МК.

Ключевые слова: *болезнь Альцгеймера, микрофлора кишечника, половые различия, амилоидный белок бета, тау-белок*

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Abstract

Alzheimer's is a global disease (AD). The most important pathogenesis of AD is the increase in the amyloid-β protein (Aβ) deposition, and abnormal phosphorylation aggregation of the microtubule-associated protein tau. Many etiological factors are implicated in the production of AD such as age, genetics, lifestyle, environmental factors, and gut microbiota (GM). Dysregulation of GM contributes to AD pathogenesis and cognitive impairment via several mechanisms, including Aβ and Tau protein aggregation, production of neurotransmitters and metabolites, immune dysregulation, neuroinflammation, blood-brain barrier disruption, oxidative stress, and leaky gut.

Sex differences might be an important factor for AD pathogenesis. About 75 % of AD patients are females. The higher prevalence of AD in females is due to their genetics, brain structure, and function, estrogen, lifestyle factors (e.g., education, occupation, exercise, and sleep), and incidences of infection and inflammations. Because women live longer than men do, they are more likely to get AD.

This article discusses the role of the GM and sex differences in AD. It begins with an overview of the gut-microbiota axis and sex differences in AD. It discusses promising therapeutic strategies for AD targeting GM.

Key words: *Alzheimer's disease, gut microbiota, sex differences, amyloid-β protein, tau protein*

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AD — Alzheimer's disease, Aβ — amyloid-β protein, APOE — apolipoprotein E, GM — gut microbiota, CNS — central nervous system, HPA — hypothalamic-pituitary-adrenal axis, GABA — gamma amino butyric acid, 5-HT — serotonin, LPS — lipopolysaccharide, TMAO — trimethylamine N- oxidase, SCFAs — short-chain fatty acids, NMDA — ionotropic glutamate receptor, BBB — blood-brain barrier, IL — interleukin, APP — amyloid precursor protein, FSH — follicle-stimulating hormone, BDNF — brain-derived neurotrophic factor, BADLs — Basic activities of Daily Living, IADLs — Instrumental Activities of Daily Living, MRI — magnetic resonance imaging, DASH — Dietary Approaches to Stop Hypertension, GSK — glycogen synthase kinase, FMT — fecal microbiota transplantation

Introduction

Alzheimer's disease (AD) is characterized by deterioration in memory, behavior, thinking, ability to perform daily activities, judgment, and language. It has become a global health epidemic problem. The total estimated prevalence is expected to reach 82 million by 2030 and 210 million by 2050 [1]. Per year, approximately 6 % is the rate of death from AD. The survival duration from the date of AD symptoms is about four years for males and six years for females [2].

There are many hypotheses for describing the pathogenesis of AD including amyloid-β protein (Aβ) deposition, abnormal phosphorylation aggregation of the microtubule-associated protein tau, accumulation of apolipoprotein E (APOE), microglia dysfunction, oxidative stress, neuroinflammation, and astrocyte activation in the gut [3]. Any infections or traumatic brain injury can interfere with central immune homeostasis and accelerate the progression of the disease [4].

A complex combination of aging, genetics, lifestyle, and environmental factors can cause AD. The strongest risk factors for AD are at advanced ages [5]. It affects 50 % of individuals older than 85 %. A strong and statistically significant positive genetic correlation has been observed between AD and family history [6]. Among the environmental factors implicated in AD pathogenesis, rapidly growing evidence from animal and human data suggests an important role of the gut microbiota (GM) in the onset and progression of AD pathology [7]. Additionally, Tan et al., [8] reported that the increasing AD prevalence in recent years was highly correlated with unhealthy diets and environmental exposures that affect the GM composition [9].

There are about 100 trillion commensal microbial communities that colonize the human gut and are constituted by bacteria, fungi, archaea, viruses, and protozoans living in symbiotic relationships with our intestines [10]. The human intestines contain approximately 1000 species and 7000 strains of bacteria which constitute the gut flora [11].

The flora of the intestinal tract is not pathogenic and has numerous beneficial effects on the body's physiological functions and nutrition. For example, intestinal flora participates in energy metabolism, reduces inflammatory response, stimulates systemic immunity, and promotes intestinal motility and nutrient absorption [12].

Animal studies have shown that gut flora regulates memory and learning [13]. Dysregulation of the GM has been associated with abnormal brain protein aggregation, inflammation, immune dysregulation, and impaired neuronal and synaptic activity in animal and human studies of AD [14].

The human GM is influenced by various factors, including genetics, race, mode of delivery (vaginal vs. cesarean), early dietary intake (breastfeeding vs. formula feeding), age, body mass index, medical conditions, psychological factors, acidic pH of the gut, diet, physical activity, stress, lack of sleep and environmental factors [15].

Sex differences may also be a significant factor in addition to these well-known confounding factors. The microbiota compositions before and after puberty were different in the male mice, suggesting male sex hormones may play an important role in the sex differences in GM [16]. When the androgen source was removed by castration, the GM of the castrated male was similar to that of a female mouse. Also, bilateral ovariectomy causes microbial dysbiosis in mice [17] and humans [18]. The GM of postmenopausal women is more similar to that of men than that of premenopausal women [19].

Because there is no treatment for AD, only symptomatic measures, all studies aim to clarify the pathogenesis of the disease for future prevention of the progressive neurodegeneration caused by AD [3].

While there have been extensive studies on GM, research specifically focusing on sex differences and GM in AD is relatively limited with conflicting results. Therefore, this review summarizes the current knowledge of

the mechanistic role of sex differences, GM in the development of AD, and potential gut microbiome-targeting therapies in managing the disease.

Understanding the Microbiota Gut-Brain axis

The gut-brain axis allows a two-way communication network between the intestine and the brain, including the central nervous system (CNS), autonomic nervous system, enteric nervous system, neuroendocrine system, and neuroimmune system [20]. It encompasses several pathways, including the nervous system, endocrine system — hypothalamic-pituitary-adrenal axis (HPA)- and immune system, that work together to regulate various physiology, such as digestion, immune function, mood, cognition, and anxiety [21]. HPA activation leads to a release of cortisol which can cause changes in both GM composition and cognition [22].

The CNS affects intestinal motility, sensory, permeability, and secretion. The GM regulates CNS neurons, astrocytes, microglia, and the blood-brain barrier by the production of a variety of neurotransmitters and metabolites and regulation of inflammation and immune systems [23]. Intestinal flora produces neurotransmitters such as glutamate, gamma amino butyric acid (GABA), serotonin (5-HT), acetylcholine, and dopamine [24]. While gut dysbiosis produces metabolites such as lipopolysaccharide (LPS), trimethylamine N- oxidase (TMAO), short-chain fatty acids (SCFAs) (such as butyrate and acetate), amino acids, and bile acids. It also produces inflammatory cytokines, directly affecting neuro-inflammation or activating peripheral immune cells [25].

Mechanisms of action of GM in driving AD progression

Gut dysbiosis contributes to AD pathogenesis and cognitive impairment via several mechanisms, including Aβ and Tau protein aggregation, production of neurotransmitters and metabolites, immune dysregulation, neuroinflammation, blood-brain barrier disruption, oxidative stress, and leaky gut.

Aβ and Tau protein aggregation

It is widely believed that an increase in the production of Aβ plaques and Tau protein is the most important pathogenesis of AD. The imbalance between production and clearance of Aβ leads to accumulation of it. Aβ is produced by neurons and secreted into the interstitial fluid of the brain. The major clearance system for Aβ and tau proteins is the glymphatic system [26]. Tau protein is a microtubule protein that has a role in neuronal stability. There is a relationship between tau and Aβ. Tau is essential for Aβ action and also Aβ is necessary for tau hyperphosphorylation [27].

Most microorganisms in the human body, including bacteria and fungi, secrete functional amyloid [28]. Bacterial amyloid protein can cross the blood-brain barrier into the blood flow to the CNS, deposit in the brain, and promote Aβ plaques and tau protein accumulation [29]. Furthermore, GM dysbiosis reduces the clearance of Aβ by affecting the gut mucosal barrier and energy homeostasis [30]. GM-induced tau protein aggregation through the TMAO formation and activation of the glycogen synthase kinase 3 beta pathway [31].

Production of Neurotransmitters

1. Glutamate

The excitatory neurotransmitter glutamate is responsible for memory and learning. It has two receptors: metabotropic and ionotropic. The ionotropic glutamate receptor (NMDA) has a role in the AD [32]. Furthermore, the hippocampal NMDA level decreased significantly after antibiotic treatment, indicating that intestinal flora was involved in the metabolic activity of NMDA [33].

2. GABA

Lactobacillus and *Bifidobacterium* are components of normal intestinal microbiota, which can convert sodium glutamate into GABA [34]. There is cognitive and memory impairment when the function of the GABA system is impaired. GABA also participates in the proliferation of precursor neurons, synaptic formation, and inhibition of inflammation *in vivo* [35].

3. 5-HT

It is a neurotransmitter produced by the gastrointestinal tract chromaffin cells [36]. *Candida*, *Streptococcus*, *E. coli*, and *Enterococcus* indirectly stimulate intestinal cells to store and release 5-HT [35].

It influences mood, memory, and overall bodily functions as a stimulant. Thus, disturbances in 5-HT metabolism coming about because of uneven characteristics in the gastrointestinal microbiota may assist the movement of neurodegenerative problems [37].

4. Acetylcholine

The expression and functioning of acetylcholine are closely associated with AD [38]. Acetylcholine is a commonly occurring metabolite in bacteria, specifically in *Lactobacillus plantarum*, *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus* [39]. Nevertheless, acetylcholine is unable to traverse the blood-brain barrier (BBB); however, its precursor choline can be transported to the brain through a carrier present on the capillary endothelial cells. Once in the brain, choline can contribute to the biosynthesis of acetylcholine [40].

5. Dopamine

Dysregulation of the dopamine system significantly contributes to the pathological progression of AD [41]. Staphylococcus bacteria residing in the human gut produce substantial quantities of dopamine via the enzymatic activity of aromatic amino acid decarboxylase [42]. The disruption of the dopamine system due to alterations in the GM has the potential to expedite the pathological progression of CNS disorders, including AD [37].

Production of Metabolites

As discussed before, GM can produce bioactive metabolites. These metabolites can cross the BBB to affect cognition directly or indirectly through immune, neuroendocrine, or vagal mechanisms [25].

1. LPS

It is the glycolipid formed by the combination of lipids and polysaccharides. Contrasted and the age-matched control bunch, the typical LPS level of the cerebral neocortex in old Promotion patients expanded multiple times. Neuroinflammation of AD patients may be determined by LPS [43].

LPS causes neuroinflammation, microglia activation, an increase in the permeability of the intestine, and changes in BBB [44]. Animal experiments also confirmed that intraperitoneal injection of LPS could increase the Aβ protein level in the hippocampus of mice, resulting in learning disabilities [45].

2. TMAO

It promotes neuro-inflammation and the accumulation of Aβ and tau proteins by inducing the imbalance of intestinal microorganisms. Additionally, it induces the release of proinflammatory mediators [46].

TMAO causes neurodegeneration by affecting fragile neurons, brain, and neuronal aging, increases oxidative stress damages mitochondrial function [47], and can lead to cognitive impairment. Therefore, anti-TMAO preparations can inhibit the course of AD [48].

3. SCFAs

SCFAs participate in nerve conduction and regulate cognition and behavior. Butyric acid and propionic acid can promote tyrosine and tryptophan hydroxylase expressions, which are involved in synthesizing dopamine, norepinephrine, and 5-HT [49].

4. Amino acid

Neural function in the AD brain is greatly impacted by glutamate metabolism [50]. The decrease of Tryptophan reduces 5-HT and leads to cognitive decline [51].

Similarly, gut bacteria have an effect on tyrosine and valine metabolism in the diet. Tyrosine is a precursor of the catechol neurotransmitters dopamine, norepinephrine, and epinephrine. These tyrosine-dependent neurotransmitters affect various central and peripheral functions, which are involved in stress response and working memory [52]. Reduced plasma valine concentrations are linked to faster cognitive loss, and individuals with AD have much lower valine concentrations. On the other hand, as the brain absorbs valine more readily than other branched-chain amino acids, higher valine concentrations can lower the risk of AD [53].

5. Bile acid (BA)

It can also be produced in the brain or transferred from the peripheral circulation to the brain via BA transporters via the BBB. BA influences cognition, memory, and motor skills [54]. Kiriyama and Nochi [55] investigated the relationship between intestinal microbiota, BA distribution, and genetic variation in AD etiology. Conjugated BA Tauroursodeoxycholic acid (TUDCA) has been found in tests to decrease Aβ peptide buildup in the hippocampus and frontal cortex, leading to improved memory. Therefore, they have protective effects on nervous system diseases [55].

Immune Dysregulation

Activated astrocytes are supportive cells that affect neuroinflammation in AD and supply nutrients and metabolic support for neurons [56]. To remove the accumulated Aβ, astrocytes also release chemokines and pro-inflammatory cytokines. A positive feedback loop is created by the extra Aβ deposition, which encourages astrocyte activation and increases the release of pro-inflammatory cytokines. Massive pro-inflammatory cytokine production can harm microglia, impair their capacity to remove toxic Aβ, hinder their capacity to repair synapses and cause irreparable brain damage [57].

The creation of gut-associated lymphoid tissue plays a role in priming the innate immune system, and the gut microbiota also regulates adaptive local and systemic immune responses. Alterations to the gut microbiome are associated with increased penetration of peripheral T-helper1 immune cells into the BBB, increased microglial activation, Aβ aggregation, and cognitive decline in AD mouse models [58].

Gut and Neuroinflammation

AD is characterized by systemic and gut inflammation. It is associated with an increase in inflammatory markers such as interleukin1 (IL1), IL6, IL12, and IL18, interferon, and tumor necrosis factor leading to neuronal cell death and ultimately Aβ and tau protein deposition [59].

On the other hand, intestinal flora is closely associated with gut and neuroinflammation [60]. Microbiota-host immune interactions in the gut lead to the release of proinflammatory mediators, e.g., cytokines such as IFN-γ, IL-1β, IL-6, and TNF-α and other inflammatory

mediators, and specific antibodies involved in the regulation of brain immunity [61]. The increase in gut pro-inflammatory is accompanied by enhanced systemic inflammation and neuroinflammatory processes [48].

In addition, microbial disorders at the intestinal level may damage intestinal permeability and induce systemic activation of the immune system [46]. Patients with AD have markedly higher levels of calprotectin in their brains and CSF, a marker of intestinal inflammation. It implies that intestinal permeability could be associated with AD pathogenesis [62]. Gut inflammation might also have sex differences concerning the GM. In a mouse model of colitis induced with 2,4,6-trinitro benzenesulfonic acid, the males exhibited more severe colonic inflammation [63].

Blood-brain barrier disruption

Even in the early stages of AD, disruption of the BBB has been preset. This disruption is linked to increased amyloid pathology because it impairs the clearance of Aβ, as well as the loss of pericytes and endothelial tight junctions [64]. Aβ and tau aggregation or neuronal death may be preceded by BBB changes, according to animal studies [65].

On the other hand, gut dysbiosis is associated with increased BBB permeability in animal studies which improves after restoring gut microbial homeostasis [66].

Oxidative stress

Under stressful conditions, reactive oxygen species formation increases within mitochondria and increases the risk of developing AD. Oxidative stress increases tau hyperphosphorylation and Aβ accumulation in AD, which leads to the eventual loss of synapses and neurons [67].

Because gut dysbiosis affects the CNS's levels of oxidative stress, it may play a role in the development of AD. For example, NO conversion from nitrate and nitrite by Lactobacillus, E. coli, and Bifidobacterium increases the permeability of the BBB and contributes to neurotoxicity in AD [68]. Pathogenic enteric bacteria, such as Salmonella and E. coli, may cause the stomach to produce hydrogen sulfide, which lowers mitochondrial oxygen consumption and increases the expression of pro-inflammatory cytokines [69]. The primary source of hydrogen, a highly diffusible bioactive gas, is anaerobic cocci which are members of the Enterobacteriaceae family. Reduced hydrogen synthesis and restricted gas availability to CNS neurons may result from gut dysbiosis [70].

Leaky gut

The condition known as inflammation is linked to the breakdown of the intestinal epithelial barrier, which makes it easier for endotoxins, inflammatory cells, and germs to enter the bloodstream [71]. While certain gut species such as Lactobacillus plantarum, Escherichia coli Nissle, and Bifidobacterium infantis enhance the expression of tight junction proteins, others such as the Bacteroides fragilis toxin disrupt the intestinal barrier [72]. Serum samples from individuals with dementia have increased markers of gut permeability, such as serum diamine oxidase levels, and increased inflammatory mediators including the soluble cluster of differentiation 14 levels compared to controls [73].

The cross-talk between AD and sex- differences

SEX DIFFERENCES IN THE INCIDENCE OF AD

Two-thirds of AD patients are women, and women have a greater lifetime risk of developing AD (1 in 5) compared with men (1 in 10) [74]. Sex-specific differences in genetics, race, brain structure, and function, sex hormones, traumatic brain injury, infection and inflammations, and lifestyle factors (e.g., education, occupation, exercise, and sleep) may contribute to AD development. Females have a higher frequency of AD due to their greater longevity than males [75].

Genetic factor (The APO E gene)

The gene of APOE is present on chromosome 19 and there are three alleles (ε2=8 %, ε3=77 %, and ε4=15 %). APOE ε4 is associated with AD [76]. The effect of the APOE ε4 genotype is more pronounced in women than in men [77]. AD risk increases nearly 4- and 10-fold in women with one and two APOE ε4, whereas men exhibit essentially no increased risk with one APOE and a four-fold increased risk with two APOE ε4 [78].

Race

In general, older Hispanics and African Americans are more likely to get AD than older whites [79]. Differences in health, lifestyle, and socioeconomic status are believed to contribute to their increased risk of AD. These include a higher prevalence of CVD, T2DM, hypertension, and early childhood adversity, as well as low education and physical activity [80].

Brain structure and functions

Head size and cerebral brain volume are 10 % larger in men than in women [81]. Also, women have a higher percentage of grey matter and hippocampus, whereas men have a higher percentage of white matter, amygdala, and thalamus. These sex differences contribute to performance differences. In particular, men perform better on visually oriented tasks, while women perform better on verbal memory [82].

Hormonal factor

Estrogen is protective against AD pathology. It reduces levels of Aβ by stimulating the generation of amyloid precursor protein (APP)-containing vesicles from the Golgi network, thereby promoting APP delivery to cell surfaces [83].

It has been shown to play a role in emotions, memory, and cognitive functions. Several studies have shown a higher incidence of AD in females after menopause [84]. Females who started hormone replacement treatment within 5 years after menopause had a 30 % reduced incidence of AD than women who did not utilize hormone replacement therapy [85].

In addition to estrogen and testosterone, other hormones, including oxytocin, prolactin, and follicle-stimulating hormone (FSH), have been implicated in processes related to AD. Oxytocin and prolactin may be involved in neuroprotection and the regulation of inflammation [86]. Elevated FSH levels are associated with lipid metabolism, obesity, and cognitive deterioration in menopausal women. The blockade of FSH improved cognition in mice with AD [87].

Traumatic Brain Injury

There is a link between traumatic brain injury (TBI) and an increased AD risk [88]. Compared to their male counterparts, females are far more likely to experience worse outcomes, more severe symptoms, and a slower pace of recovery after moderate traumatic brain injury and concussions [89]. Estrogen administration pre- and post-TBI is associated with increased neuronal survival, significant reductions in apoptosis, and improvements in functional outcomes [90].

Infection and Inflammation

It has been shown that there are sex differences in the way that infections and inflammation are responded to and experienced; in particular, when there is a decrease in estradiol levels, females tend to have more severe illness and poorer prognoses than males [91]. For example, especially after menopause, women are more likely to develop chronic inflammatory diseases such as multiple sclerosis, lupus, and rheumatoid arthritis [92].

Lifestyle Factors

A sedentary life is associated with a higher risk of dementia and greater cognitive decline among older adults [93]. Women tend to engage in less physical activities than men. It has been demonstrated that increased physical activity increases the synthesis of brain-derived neurotrophic factor (BDNF), which is crucial for the development, growth, and plasticity of neurons, as well as the creation, survival, and synaptic plasticity of new neurons in the hippocampus [94].

A higher risk of AD is linked to low levels of occupational and educational performance. More education and mentally demanding jobs increase one's cognitive reserve. Women in low-income nations are less likely than males to have access to schooling, which may have negatively impacted their ability to accumulate cognitive reserve [95]. When compared to men, women are generally at a greater risk for sleep deprivation and insomnia, especially after menopause. Sleep deprivation leads to an increase in Aβ plaque accumulation [96].

SEX DIFFERENCES IN SYMPTOMS

Female patients were more frequently to show cognitive and functional decline, depression, delusion, and memory impairment including verbal learning, delayed recall, and visual memory [97]. While males were more likely to exhibit indifference, anxiousness, and hostility [98].

A meta-analysis of 15 studies revealed a consistently better performance in males over females on verbal, visuospatial, episodic, and semantic memory independent of age, education level, and disease severity [99]. However, it has been reported that premorbid depressive symptoms, significantly increased the risk for dementia, particularly AD in men but not in women [100]. Women seem to be more susceptible to pathological lesions while men have greater cognitive reserve [101].

SEX DIFFERENCES IN DIAGNOSIS

A study examined Aβ and tau levels in the brain by positron emission tomography scanning in 298 cognitively normal-aged men and women found that women had higher levels of AD pathology, despite not having symptoms. This shows that while women may be more susceptible to the development of AD pathology and symptoms, there may be sex-specific characteristics that compensate for the early stages of the illness [102]. In example, cognitive impairment in women is linked with bigger reductions in fluency capability, whereas in males it is associated with considerable declines in visual-spatial ability. In women, the intensity of delirium was connected with dementia [103].

In women, delirium severity was related to dementia severity. For men, unlike for women, delirium severity was greater in those with lower educational levels. Differences were noted based on gender and race. African American women reported greater difficulty with all Basic activities of Daily Living (BADLs) and Instrumental Activities of Daily Living (IADLs) except dressing and using the telephone. In comparison to males, non-Hispanic White women reported considerably more difficulty with transfers, indicating a gender gap in this mobility-related daily activity. African American men and non-Hispanic White men demonstrated an equivalent prevalence of difficulty for all BADL tasks. However, for all IADLs African American men reported greater difficulty compared to non-Hispanic White men [104].

Studies using magnetic resonance imaging (MRI) showed greater loss of gray matter in brain regions, including the bilateral precuneus, caudate nucleus, entorhinal gyrus, thalamus, middle temporal gyrus, insula, and amygdala in women with AD compared to men [105]. Furthermore, neuroimaging studies showed that the rate of hippocampal atrophy affects the progression of AD in females more than in males. A neuroimaging study showed that post-menopausal women exhibited higher tau and global Aβ deposition than men in the inferior parietal, rostral middle frontal, and lateral-occipital regions compared to age-matched men [106].

Potential Therapeutic Strategies for AD Targeting the Microbiota-Gut-Brain Axis

Dietary modification

Mediterranean diet is associated with a high input of fruits, vegetables, cereals, and legumes; and a low input of meat, high-fat dairy, and sweets [107]. It's characterized by bettered cognition, reduced brain atrophy in regions vulnerable to announcement pathology, advanced tube carotenoid situations and paraoxonase exertion, advanced SCFA situations, increased gut microbial diversity, and lower supplemental labels of inflammation (e.g., C- reactive protein) [108].

Reduced inflammation and oxidative stress in the brain, and high situations of fiber, vitamin C, β- carotene, and folate are the neuroprotective mechanisms of these diets. As a result, it improves brain integrity and increases the quantum of brain towel [109]. It has also been reported that impregnated and trans adipose acid insufficiency may reduce BBB dysfunction and amyloid aggregation [110].

Also, the high input of fiber, vitamins (e.g., B1, B9, and B6), and minerals (copper, manganese, magnesium, iron, and potassium), were associated with bettered cognition and reduced frailty in another study [111]. Salutary rudiments rich in Vitamin D3 (e.g., dairy and fish) promote the neural growth factor protein [112], and those rich in flavonoids (e.g., grapes, citrus, and green tea) or the polyunsaturated adipose acid, docosahexaenoic acid (e.g., fish) may reduce Aβ and tau pathology and neuroinflammation [113].

Analogous diets, similar to the Dietary Approaches to Stop Hypertension (DASH) diet, also have salutary goods on brain health when combined with exercise [114]. Diets that combine rudiments from both the Mediterranean and DASH diets, which are rich in fruits, vegetables, whole grains, low-fat dairy, and spare protein, may be more effective in delaying cognitive decline [115].

The ketogenic diet also has salutary goods in brain health. In announcement mouse models, ketones reduce oxidative stress, help intracellular uptake of Aβ, and ameliorate synaptic malleability [116]. In mice models, ketone bodies have been demonstrated to influence neurotransmission, reduce neuroinflammation and oxidative stress, as well as reduce Aβ accumulation, and ameliorate literacy and memory capacities [117]. likewise, the ketogenic diet has been shown to alter the gut microbiome, reduce announcement pathology and ameliorate cognition [118].

The combination of the Mediterranean and ketogenic diets is associated with increased SCFA product by GM, bettered CSF labels of Aβ and tau, and better cognitive performance [119].

Table 1. *Potential therapeutic strategies for ad targeting the microbiota-gut-brain axis*

Therapeutic strategies	Mechanism	Refs
1. Dietary Modification:		
Mediterranean diet	It enhances cognition and gut microbial diversity. It also reduces brain atrophy, BBB dysfunction, amyloid aggregation oxidative stress and neuroinflammation.	108, 109, 110
Ketogenic diet	It reduces neuroinflammation, Aβ accumulation and oxidative stress. It helps intracellular uptake of Aβ, and ameliorate synaptic malleability	116, 117
Intermittent fasting	It promotes hippocampal neurogenesis through activation of GSK-3β and increased BDNF, increase insulin perceptivity, reduce inflammation, and promote autophagy	120
2. Antibiotics	It reduces the intestinal microflora, microglial exertion and pro-inflammatory cytokines.	122, 123
3. Prebiotics	It enhances cognitive and memory functions, butyrate levels, production of SCFAs, restoring the balance between anti- and pro-inflammatory bacteria in the GM, insulin sensitivity and production of nerve growth factor and BDNF. It also reduces Aβ accumulation, restoration of redox homeostasis and neuroinflammation.	127, 128, 42, 130
4. Probiotics	It enhances cognitive and memory functions , immunomodulation, long-term potentiation, and intestinal epithelial barrier and BBB functions. It also reduces neuroinflammation, Aβ accumulation and oxidative stress.	134, 136
5. Fecal microbiota transplantation	It enhances cognitive and memory functions, synaptic plasticity and boosted SCFA-producing gut microbes. It reduces neurogenesis, memory impairment, inflammatory cytokines, and Aβ plaque formation.	123, 108

Intermittent fasting has also been shown to promote hippocampal neurogenesis through activation of glycogen synthase kinase (GSK)- 3β and increased BDNF, increase insulin perceptivity, reduce inflammation, and promote autophagy and protein concurrence in beast studies [120]. A 30 reduction in calories from carbohydrates averted Aβ shrine accumulation in a model of AD complaint in womanish, but not manly mice [121], which was associated with coitus-specific changes in amyloid-precursor processing enzymes.

In summary, salutary interventions are generally safer and further salutary than medicine remedies because they're affordable, easy to administer, and reduce the burden on caregivers of announcement cases.

Antibiotics

Antibiotics can affect AD by changing the intestinal microflora. DNA analysis of the cecum and feces of mice treated with antibiotics showed that Aβ shrine deposit was significantly reduced and could restore intestinal microflora analogous to that of the control group. Likewise, intestinal permeability was also restored, and glial cell reactivity in the original area of the shrine was weakened [122]. It also reduced microglial exertion and proinflammatory cytokines similar as IL- 1β and IL- 17A in manly, but not womanish [123].

Ceftriaxone use can reduce the increase of glutamate by perfecting glutamate transport, which is generally present in the area of Aβ shrine deposit, thereby perfecting neuronal activity in mice [124].

Still, some antibiotics (similar to streptozotocin and ampicillin) can disrupt the intestinal bacteria balance [125]. The use of these antibiotics is conducive to or worsens the course of disease. Such as, rats taking ampicillin have elevated glucocorticoids, increased anxiety and worse spatial memory. The increase in glucocorticoids is related to memory impairment and dropped hippocampal BDNF, common features of AD pathology. Ampicillin treatment also significantly depresses the action of NMDA receptors in the hippocampus of rats [126].

Prebiotics

Prebiotics are short-chain carbohydrate substances able to widely stimulate the growth and/ or activity of one or more beneficial gut bacteria [127]. They have also decreased Aβ accumulation, restoration of redox homeostasis, and increased butyrate levels [42].

Yeast beta-glucan has elevated the production of SCFAs, restoring the balance between anti — and proinflammatory bacteria in the GM and reduced neuroinflammation [128].

Mannan oligosaccharides have improved cognitive and memory functions, enhanced synthesis of SCFAs, reduced accumulation of Aβ in the cerebral cortex, hippocampus, and amygdala, as well as reduced neuroinflammation [42].

Lactulose has been shown to reduce neuroinflammation, promote insulin sensitivity, and improve short-term memory and learning [129].

Ferulic acid has anti-inflammatory and anti-oxidant effects and increases the production of nerve growth factor and BDNF [130].

The effect of prebiotics was also different between the sexes. The administration of oligofructose increased the abundance of Bacteroidetes in female rats though the butyrate levels were increased, but not in males, [131].

Still, other authors suggest that further substantiation for the use of prebiotics in clinical practice is still demanded for concluding the normalization of several factors such as age, gender, race, and diet [132].

Probiotics

It is the live microorganisms that change microbiota toward a beneficial state **[133].** Probiotic supplementation causes improvement of immunomodulation, long-term potentiation, and intestinal epithelial barrier and BBB functions [134]. Mice treated with probiotics showed increased memory and significantly lower quantities of plaques and neuroinflammation [135].

Probiotics have anti-inflammatory, anti-stress, and anti-oxidant effects in humans [136].

The effect of probiotics was also different between the sexes, they lowered the colonic mucosal mast cell count and decreased the levels of inflammatory cytokines only in females but not in males [137].

A mixture of a probiotic plus a prebiotic, and synbiotic supplement improved memory, visual-spatial, executive, and linguistic abilities in test subjects and decreased the formation of proinflammatory cytokines (IL-8, IL-12, and TNF-α) [138].

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is the technique of introducing prescreened feces into patients' GI tracts to restore function and boost the total variety of GM [139]. Fecal material is expected to come from a well-organized stool bank and be administered via colonoscopy, enema, or capsule [140].

Dodiya et al. [123] found that FMT enhanced cognition, lowered Aβ buildup and tau expression, improved synaptic plasticity, and boosted SCFA-producing gut microbes. Transplanting feces from AD model donor mice into healthy mice led to decreased of neurogenesis, memory impairment, inflammatory cytokines, and Aβ plaque formation [108].

Conclusion

AD is a global health crisis. The gut-brain axis controls several aspects of brain and gut physiology. Through a number of pathways, gut dysbiosis contributes to the pathophysiology of AD and cognitive decline. It results in the aggregation of Tau and Aβ proteins,

immunological dysregulation, neuroinflammation, disruption of the blood-brain barrier, oxidative stress, and leaky gut. Sex differences may have a major impact on GM. Women make up two thirds of AD patients, and they are more likely than males to have AD during their lifetime. AD treatment strategies that target the gut-brain-microbiota axis include dietary changes. These strategies may be more effective when combined with a high-fiber, vitamin- and mineral-rich diet. Intermittent fasting combined with a ketogenic diet activates GSK-3β and increases BDNF to support hippocampal neurogenesis. Probiotics, prebiotics, and fecal microbiota transplantation might all be important.

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