60 ANOS ARQUIVOS DE GASTROENTEROLOGIA

REVIEW

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Alzheimer's disease and its relationship with the microbiota-gut-brain axis

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ABSTRACT – Background – Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease, characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain. Several pathways enable bidirectional communication between the central nervous system (CNS), the intestine and its microbiota, constituting the microbiota-gut-brain axis. **Objective –** Review the pathophysiology of AD, relate it to the microbiota-gut-brain axis and discuss the possibility of using probiotics in the treatment and/or prevention of this disease. **Methods –** Search of articles from the PubMed database published in the last 5 years (2017 to 2022) structure the narrative review. **Results –** The composition of the gut microbiota influences the CNS, resulting in changes in host behavior and may be related to the development of neurodegenerative diseases. Some metabolites produced by the intestinal microbiota, such as trimethylamine N-oxide (TMAO), may be involved in the pathogenesis of AD, while other compounds produced by the microbiota during the fermentation of food in the intestine, such as D-glutamate and fatty acids short chain, are beneficial in cognitive function. The consumption of live microorganisms beneficial to health, known as probiotics, has been tested in laboratory animals and humans to evaluate the effect on AD. **Conclusion –** Although there are few clinical trials evaluating the effect of probiotic consumption in humans with AD, the results to date indicate a beneficial contribution of the use of probiotics in this disease.

Keywords – Alzheimer; brain; gut microbiota; dysbiosis; probiotic.

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INTRODUCTION

Dementia, characterized by the deterioration of cognitive function, affects 47 million people worldwide and it is estimated that by 2050 the number of patients with this condition will increase to 131 million[1], which could cause major social and economic impact.

Alzheimer's disease (AD) is the most common form of dementia. Clinical manifestations presented by AD patients include amnesic cognitive impairment, spatial cognition, working memory and language impairment[2]. These and other manifestations make the patient dependent on help to perform their daily tasks, which causes physical and emotional stress for family members and overload for caregivers[3].

AD was described by the German neurologist Alois Alzheimer in 1907, who followed the case of a 51-year-old woman with memory-related problems. After the patient's death, Alzheimer microscopically analyzed her brain and noted the presence of neuritic plaques, neurofibrillary tangles and amyloid angiopathy[4]. In 1963, Robert Terry and Michael Kidd, using electron microscopy, aroused scientific interest by showing neurofibrillary tangles in brain biopsies of patients with advanced AD. Since then, the pathophysiological mechanisms of AD have been studied, as well as new forms of diagnosis and treatment[5].

Recent studies have demonstrated a relevant role of microorganisms residing in the intestine, collectively known as the gut microbiota, in the development or progression of AD. The gut microbiota and the central nervous system (CNS) interact in several ways, establishing a two-way communication, called the microbiota-gut-brain axis. It has already been found that AD patients have less microbiota diversity than healthy patients[6].

Another point to be considered is that so far there are no drugs that cure AD. Existing drugs only treat the symptoms of the disease. This reinforces the need for new therapeutic approaches to provide a cure or at least an effective interruption in the progression of the disease. In this sense, interventions that change the composition of the intestinal microbiota, such as the use of probiotics, have been proposed as a promising option for the prevention and treatment of AD[7]. Probiotics are live microorganisms that, when ingested in adequate amounts, provide health benefits[8]. Studies related to the use of probiotics to restore intestinal microbial balance, maintain, promote or restore health have been increasing in recent years[9].

Therefore, the objective of this narrative literature review is to describe AD and its relationship with the microbiota-gut-brain axis, as well as to discuss the use of probiotics as an opportunity for the treatment or even prevention of AD.

METHODS

This narrative review of the literature was writing from PubMed database articles published in the last 5 years, covering the years 2017 to 2022. The keywords (Alzheimer, disease, history, tau, amiloid beta, diagnosis, treatment, microbiota, microbiome, gut, brain, axis, mucus, probiotic, diarrhea, dysbiosis) were used combined in different ways for the articles search.

Literature review

Pathophysiology of Alzheimer's disease

Dementia can have many causes, such as: cerebrovascular disease, presence of Lewy bodies, frontotemporal lobe degeneration, Parkinson's disease, hippocampal sclerosis and Alzheimer's disease (AD). AD is the most common cause of dementia, accounting for 60 to 80% of cases[10].

AD is a progressive and irreversible neurodegenerative disease in which there is an extracellular accumulation of amyloid-beta (Aβ) peptide and intracellular hyperphosphorylated tau protein (p-tau) in nerve cells, forming amyloid plaques and neurofibrillary tangles, respectively[11].

The Aβ peptide results from the cleavage of the amyloid precursor protein (APP), an integral membrane protein expressed in various tissues and which has different isoforms, ranging in size from 695 to 770 amino acids. Cleavage of APP by β-secretases and γ-secretases produces the Aβ peptide, with 37 to 49 amino acid residues. Aβ monomers aggregate to form oligomers, protofibrils and amyloid fibrils. The latter are insoluble and can form amyloid plaques, also called senile plaques, constituting the main component of the brain neocortex of patients with Alzheimer's disease[12]. Aβ peptides with 40

(Aβ40) and 42 amino acids (Aβ42) stand out in the formation of amyloid plaques and induction of neurotoxicity. Comparing these two, the Aβ42 peptide is less abundant, more neurotoxic and more prone to aggregation[13].

Microglia are CNS immune cells that phagocytose pathogens, apoptotic neurons, cell debris and Aβ. In this way, microglia have a protective and homeostasis function in nervous tissue, preventing the development of AD. However, it is proposed that the chronic activation of microglia leads to a pro-inflammatory state inducing the secretion of neurotoxic cytokines that damage neurons and stimulate the development of AD[14].

Tau is a phosphoprotein that regulates microtubule stability, mainly in CNS neurons. However, the hyperphosphorylation of tau decreases its capacity to bind to tubulin, compromising the microtubule structure. P-tau accumulates in somatodendritic compartments forming neurofibrillary tangles that alter axoplasmic flow and lead to neuronal dysfunction and death[15]. Many kinases can phosphorylate tau, but the main one is a protein involved in the regulation of glucose metabolism, glycogen synthase kinase 3β (GSK3β)[16].

AD can be divided into 4 phases: preclinical, mild, moderate and severe[17]. The first can last for decades and there are no symptoms, although there is already brain accumulation of Aβ peptide and phosphorylation of tau protein with release into the cerebrospinal fluid[18]. In the mild phase, there is loss of concentration and memory, disorientation of place and time, mood swings and depression[17], and even memory distortions may occur[19]. In the moderate phase, there is difficulty in communicating and performing routine activities, as well as behavioral changes. In the severe phase, patients need full-time follow-up, as they are usually bedridden and have difficulty swallowing. They become malnourished, with an increased risk of pneumonia and death[20].

For the diagnosis of AD, neuroimaging techniques such as magnetic resonance imaging and positron emission tomography (PET) can be used to measure amyloid and tau deposition, metabolism and brain volume. Pathological deposition of amyloid plaques can be detected by PET 15 to 20 years before the first symptom occurs. By magnetic resonance imaging or computed tomography, it is possible to identify hippocampal and cortical atrophy in the temporal and parietal regions, which is related to a neurodegenerative pattern of AD, however, the absence of this pattern does not exclude AD[21]. Additionally, neuropathological studies have shown that hippocampal subfields, such as the subiculum, CA1-4 and dentate gyrus, are differentially vulnerable to AD. In this way, the volumetry of hippocampal subfields may be more accurate than the volumetry of the total hippocampus to detect AD[22].

For laboratory diagnosis, reduction of Aβ42, increase in total tau and phosphorylated tau in threonine (p-tau-181) in cerebrospinal fluid can be analyzed. A decline in cerebrospinal fluid Aβ42 can be detected up to 20 years before the onset of symptoms[23]. In fact, the ratio between Aβ42 and Aβ40 (Aβ42/40) in cerebrospinal fluid has been suggested as a more accurate diagnostic method than the isolated analysis of Aβ42 to identify patients with AD[24].

Among the drugs used in the treatment of AD are three acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) and an N-methyl-D-aspartate receptor antagonist (memantine). The first three improve the patient's cognition and are effective in mild and moderate AD. Memantine, on the other hand, reduces excitotoxicity caused by excess glutamatergic transmission in AD and is used in moderate and severe stages of the disease[25]. Recently, the Food and Drug Administration (FDA) approved a new therapeutic approach, Aducanumab[26]. This is a human monoclonal IgG1 antibody with affinity for the Aβ peptide and promises to eliminate extracellular amyloid beta plaques, reversing the pathological process and clinical decline of AD[27].

Approximately 5 to 10% of AD cases are early-onset, occurring before age 65 years[28]. The others are of late onset, after 65 years. The AD incidence increases with age and shows an exponential growth pattern starting at age 65 The population over 65 years of age has increased in the world and consequently, the number of individuals with AD will also increase[10].

Besides age, there is a wide range of risk factors associated with the development of AD, such as: gender, demographic factors (education, race, social class and marital status), genetic and epigenetic

factors, lifestyle (alcohol consumption, smoking, nutritional deficiency, inadequate sleep, physical and mental inactivity), comorbidities (obesity, metabolic syndrome, diabetes, hypertension, dyslipidemia, cancer, cardiovascular disease, traumatic brain injury and mitochondrial dysfunction), environmental factors (air, metals, occupation), psychiatric factors (depression and stress) and infections[29, 30].

Several microorganisms and bacterial DNA have already been detected in the brain tissue of patients with AD[31, 32]. Bacterial, viral, fungal, and parasitic infections that target the CNS are associated with an increased risk of AD because they likely promote chronic inflammatory responses in the CNS that can contribute to neurodegeneration, such as synaptic degeneration and amyloidosis[33]. Furthermore, the role of microorganisms that inhabit the human body, mainly in the intestine, in the development of AD has been studied[34].

Microbiota-intestine-brain axis

Microbiota is the set of microorganisms that inhabit the host, consisting of bacteria, archaea, fungi, protozoa, viruses and bacteriophages[35]. There are approximately 10^{14} microorganisms in the human gastrointestinal tract, an amount 10 times greater than that of human cells. The term microbiome refers to the set of genomes of all microorganisms that inhabit an environment. Gut microbiome exceeds human genomic content by 100 times[36].

Microbial colonization of the gut is initiated when the fetus is in the uterus. A transition occurs after birth and lactation, resulting in an intestinal microbiota predominantly composed of *Bifidobacterium*. Later, with the introduction of solid foods, a second transition takes place, resulting in a microbiota consisting mainly of *Bacteroidetes* and *Firmicutes*. By age three, the gut microbiota is established. The modulation of the microbiota is influenced by the type of delivery, type of milk ingested (breast or formula) and foods consumed daily in childhood[37]. Finally, 90% of the adult human intestinal microbiota consists mainly of bacteria from the phyla *Bacteroidetes* and *Firmicutes*; the other bacteria belong to the *Actinobacteria*, *Proteobacteria*, *Fusobacteria* and *Verrucomicrobia* phyla[38]. However, with aging, the composition and diversity of the intestinal microbiota are affected, which may be related to the decline of the beneficial functions of the microbiota and the increase of diseases in the host[39].

The state of equilibrium between the microbiota and the host is called eubiosis. When there are changes in the proportion of phyla that make up the human microbiota or an increase in other bacterial groups, an imbalance called dysbiosis occurs[40]. Several studies are aimed at understanding the diversity of the human microbiota as well as the interaction between the microbiome and the host[41-43]. Nowadays, it is known that the intestinal microbiota plays several roles in the host, such as: enzyme production[44], immune system development[45], influence on circadian rhythm[46], vitamin production[47], nutrient metabolism[48], reduced insulin resistance[49] and protection against pathogens[50].

There is a bidirectional communication between the CNS and the intestinal microbiota that occurs through different pathways, constituting the microbiota-gut-brain axis[51]. The vagus nerve is the tenth cranial nerve and the main component of the parasympathetic nervous system, carrying information between the digestive system and the brain. Vagal afferent fibers do not come into direct contact with the microbiota of the intestinal lumen, so communication between them occurs by the diffusion of compounds from microorganisms or by cells in the intestinal epithelium that relay the signals of the microbiota, establishing a mutual communication between the microbiota and the brain[52].

Another form of connection between the CNS and the microbiota occurs through the enteroendocrine cells, which are located dispersed in the gastrointestinal tract, forming the epithelial lining of the intestinal mucosa along with other intestinal cells. Enteroendocrine cells secrete hormones responsible for motility and gastropancreatic secretion, and it is suggested that the gut microbiota or its metabolites stimulate these cells to secrete hormones[53, 54].

The microbiota-gut-brain communication can also take place through the enteric nervous system, which coordinates intestinal motility and the movement of intestinal fluids. It is made up of two main ganglionic networks located in the gastrointestinal tract, the myenteric plexus and the submucosal. Just as the enteric nervous system can influence

the microbiota, it and its products can influence the enteric nervous system, and as the enteric nervous system is interconnected to the CNS by sympathetic and parasympathetic nerves, the CNS can also be influenced[51].

In the hypothalamic-pituitary-adrenal (HPA) axis, corticotropin-releasing hormone (CRH) is synthesized by the hypothalamus and stimulates the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary, which acts on the cortex of the adrenal gland, which synthesizes the cortisol. Cortisol inhibits ACTH and CRH secretion, providing a negative feedback. It has been shown that just as changes in the HPA axis interfere with the intestinal microbiota[55], the microbiota can interfere with the balance of the HPA axis by regulating the behavior of the host[56, 57].

The metabolism of tryptophan, branched-chain amino acids, peptidoglycans, microbial metabolites such as short-chain fatty acids (SCFAs) and neurotransmitters are also communication pathways of the microbiota-gut-brain axis[51]. There are bacteria, for example, that produce neurotransmitters in their mammalian hosts such as dopamine, noradrenaline, serotonin, gamma-aminobutyric acid (GABA), acetylcholine and histamine, which can influence the physiology of the host[58].

Tryptophan is an essential amino acid obtained from the diet. When it is metabolized by the intestinal microbiota, it generates serotonin, kynurenines, tryptamine and indole compounds, which participate in the microbiota-gut-brain communication[59]. Dietary tryptophan metabolites produced by the gut microbiota control microglial activation, production of transforming growth factor alpha (TGFα) and vascular endothelial growth factor (VEGF-B), modulating CNS inflammation[60].

SCFAs are the main signaling molecules of the gut-brain axis. In the colon microbiota there is a predominance of obligate anaerobic bacteria, which produce SCFAs of two to six carbon atoms by fermentation of undigested dietary fibers, forming mainly acetate, propionate and butyrate, among other SCFAs. Butyrate is detected by the host epithelial PPAR-γ signaling pathway, which modulates the energy metabolism of colonocytes for β-oxidation of butyrate, preserving epithelial hypoxia and maintaining healthy gut homeostasis[61]. A small amount of SCFAs reach the systemic circulation and cross the blood-brain barrier, being detectable in human cerebrospinal fluid[62]. In fact, SCFAs are associated with protecting the integrity of the blood-brain barrier and brain function[63]. SCFAs enter CNS cells, which leads to cell acidification, modification of calcium signaling, release of neurotransmitters and inhibition of gap junctions, which can modify communication and neuronal behavior[64]. It has also been shown that butyrate can attenuate the expression of pro-inflammatory cytokines in microglia in aged mice[65]. Therefore, the gut microbiota and its metabolites can influence the health and disease of the host and a correlation with neurodegenerative diseases such as AD has been pointed out[66,67].

The microbiota-intestine-brain axis and Alzheimer's disease

The composition of the gut microbiota influences the CNS, resulting in changes in host behavior[68,69]. By the technique of sequencing the 16S gene of the ribosomal RNA of the bacteria of the intestinal microbiota, an alteration in the composition of the microbiota in the feces of patients with AD has already been demonstrated[70-72].

Cattaneo et al.[73], using Quantitative Polymerase Chain Reaction (qPCR), compared the abundance of certain bacterial groups in the feces of healthy individuals with individuals with cognitive impairment and cerebral amyloidosis. In these, there is an increase in the abundance of pro-inflammatory bacteria *Escherichia* and *Shigella* and a reduction in the abundance of anti-inflammatory bacteria *Eubacterium rectale*, which may be associated with a peripheral inflammatory state in patients with cognitive impairment and cerebral amyloidosis.

In this sense, a research group detected the presence of lipopolysaccharides (LPS), a pro-inflammatory component of the outer plasma membrane of gram-negative bacteria, in brain lysates from the hippocampus and neocortex of the superior temporal lobe of the brain of patients with AD. One of the main sources of LPS are Gram-negative bacteria from the human gastrointestinal tract, such as *Bacteroides fragilis* and *Escherichia coli*. Thus, it is suggested that the gastrointestinal and blood-brain barriers

become more permeable with aging, facilitating the passage of LPS to the CNS[74]. Zhan, Stamova and Sharp[75] propose that LPS acts on the TLR4-CD14/TLR2 receptors of leukocytes and microglia inducing cytokine release that increase Aβ levels, damage oligodendrocytes and cause damage to the myelin sheath in the brain of a patient with AD. In addition to LPS, peptidoglycan, a cell wall component of both gram negative and gram positive bacteria, may also be involved in chronic brain inflammation[76].

LPS and peptidoglycan stimulate intestinal mucus secretion, and the composition of the gut microbiota influences mucus properties. The mucus layer is a barrier that acts as a first line of immune defense, separating intestinal epithelial cells from bacteria. Additionally, mucus provides nutrients to the microbiota, promoting its colonization[77]. Mucus contains branched glycoproteins such as mucins, with mucin-2 (MUC-2) being the main glycoprotein in intestinal mucus. Gut microorganisms produce enzymes that break down mucus and this enzymatic cleavage of mucin expands and hydrates the mucus[78]. The bacterium *Akkermansia muciniphila* is associated with intestinal health as it increases the thickness of the colonic mucus layer[79] and improves intestinal barrier function[80]. As mucus production is also influenced by the enteric nervous system, it is proposed by Herath et al.[78] that in neurological diseases there are changes in the function of the enteric nervous system and in the production of mucus, causing gastrointestinal symptoms and dysbiosis. Dysbiosis, in turn, can change the thickness of the mucus and contribute to the progression of neurological disease.

The dysregulation of the intestinal epithelial barrier can also cause changes in the composition of the intestinal microbiota and trigger an inflammatory process that favors the accumulation of brain Aβ[81]. Thevaranjan et al.[82] demonstrated that gut microbiota or age-related microbial dysbiosis can lead to increased intestinal permeability in mice and result in inflammation. Microbial products enter the bloodstream of aged mice, where they trigger systemic inflammation, with high levels of interleukin 6. As discussed by Bostanciklioğlu[83], microbiota-derived inflammatory cytokines are able to reach the CNS via the bloodstream and lymphatic system, and can cause Aβ aggregation by inducing amyloidosis or disrupting microglial maturation that leads to decreased brain clearance.

AD transgenic mice that were bred free of germs had less Aβ deposition than the same type of mice bred conventionally, indicating that the absence of microbiota slows the progression of AD[84]. Similarly, another study showed that early postnatal antibiotic therapy in AD model mice resulted in lower brain Aβ deposition over time[85]. These results reinforce the relationship between the microbiota-gut-brain axis and AD.

Some metabolites produced by the intestinal microbiota may also be involved in the pathogenesis of AD. Trimethylamine N-oxide (TMAO), for example, is a metabolite of the gut microbiota whose high levels have been associated with impaired cognitive function in mice[86]. It was observed that TMAO can induce neuron senescence and destroy mitochondria in the CA3 region of the mouse hippocampus, leading to an aggravation of brain aging in mice[87].

However, other compounds produced by the microbiota may have a beneficial effect on cognitive function. Several bacterial strains can produce glutamate during fermentation of food in the gut. D-glutamate is a non-essential amino acid and an excitatory neurotransmitter in the CNS, which regulates neuronal plasticity and communication between neurons. In this way, the composition of the intestinal microbiota is associated with the fecal and plasma concentration of D-glutamate and with the speed of processing and mental flexibility[88]. Low serum D-glutamate levels have been associated with decreased comprehension, difficulty following commands and naming objects in AD patients[89]. Another protective effect on the pathogenesis of AD was observed in relation to SCFAs. In vitro tests showed that SCFAs produced by the microbiota, such as valeric acid and butyric acid, interfere with the conversion of monomeric Aβ1-40 and Aβ1-42 into Aβ fibrils[90].

Considering that dysbiosis is related to the development of neurodegenerative diseases, the restoration of altered intestinal microbiota can be of great contribution to AD therapy. Eubiosis can be achieved by dietary intervention, the use of probiotics or fecal microbiota transplantation. This last mentioned procedure can be performed by transferring fecal material from a healthy donor to a re-

cipient by colonoscopy, nasoenteral tube or capsule ingestion[91].

Effect of probiotic supplementation in Alzheimer's disease

Probiotics, live microorganisms that benefit the health of the host when administered in adequate amounts, are marketed as yogurts or as capsules, tablets, sachets, liquids or other presentations[8]. The effect of probiotics depends on the strain and dose consumed. Human probiotics consist of bacteria belonging to the genera *Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus, Enterococcus* and *Bacillus* and yeasts of the genus *Saccharomyces*[92].

There are studies that demonstrate the benefits of probiotics in gastrointestinal diseases, such as the improvement of symptoms in patients with irritable bowel syndrome[93,94] and prevention of diarrhea caused by *Clostridium difficile* in patients on antibiotic therapy[95]. It is also suggested that probiotics may aid in glycemic control, increasing insulin sensitivity in gestational diabetes[96].

There is increasing evidence of bidirectional communication between the nervous system and the gut through multiple pathways that involve the gut microbiota. As reviewed by Frausto et al.[97], diet influences the gut microbiota and this can influence cognitive function and the development of AD. Administration of probiotics for four weeks to volunteers was associated with changes in brain activation patterns in response to emotional memory and emotional decision-making tasks, analyzed by functional magnetic resonance imaging[98]. In view of this, microbiota regulation with the use of probiotics may be a promising therapy for AD. The systematic review by Naomi et al.[99] shows that the most tested probiotics in animal models with AD are single or multiple strain preparations of *Bifidobacteria infantis*, *Bifidobacteria longum*, *Lactobacilli acidophilus, Lactobacilli plantarum* and *Lactobacilli casei*.

A formulation of lactic acid bacteria and bifidobacteria (SLAB51) was administered for 4 months to a triple transgenic mouse model of Alzheimer's disease (3xTg-AD) in the early stage of the disease. The researchers demonstrated that after the period of administration of the probiotic mixture, there was a reduction in the amount of brain Aβ, a change in the composition of the intestinal microbiota and its metabolites and an improvement in the cognitive function of the mice. Treated mice showed partial restoration of two impaired neuronal proteolytic pathways in AD, such as the ubiquitin proteasome system and autophagy[100]. Subsequently, the authors also pointed out that SLAB51 reduced oxidative stress in the brain of AD rodents by activating sirtuin-1-dependent mechanisms (SIRT1)[101].

Kobayashi et al.[102] injected Aβ 25-35 or Aβ 1-42 protein into the intracerebroventricular region of ddY mice (Deutschland Denken Yoken) to be used as AD models. The researchers isolated *Bifidobacterium breve* A1 bacteria from the feces of human infants, which, killed by heat and sonication, were administered orally to the mice. As a positive treatment control for AD, another group of animals received donepezil hydrochloride orally. Probiotics were administered orally every day starting 2 days before Aβ protein injection. After 6 days of protein injection, cognitive function was assessed by the Y-maze test and then the mice were subjected to the passive avoidance test. It was evidenced that the oral administration of *B.* breve A1 to AD model mice prevented cognitive decline in the animals, with a reduction in the immune response and neuronal inflammation. *B.* breve A1 did not affect the intestinal microbiota, but increased the levels of acetate in the plasma of the mice.

Improvement in short-term working memory was observed in mice 8 prone to senescence acceleration (SAMP8), memory deficit models, which were orally supplemented for 12 weeks with a probiotic composed of *Bifidobacterium lactis*, *Lactobacillus casei, Bifidobacterium bifidum* and *Lactobacillus acidophilus*. In addition to improving memory deficits, probiotic treatment improved neuronal damage and modified gut and brain microbiota composition in aged SAMP8 mice[103]. In another study, researchers performed successive intraperitoneal injections of D-galactose in Wistar rats to be used as a model of AD. A group of these AD model animals received *Lactobaillus plantarum* MTCC 1325 orally for 60 days, showing significant improvement and recovery of AD[104].

In humans, there are few studies evaluating the effect of probiotics on AD. A randomized, dou-

ble-blind clinical trial, in which AD patients were given probiotics or placebo for 12 weeks, no improvement in cognition was observed. The probiotic was administered orally through two types of capsules. One of them contained *Lactobacillus fermentum, Lactobacillus plantarum* and *Bifidobacterium lacti* and the other contained *Lactobacillus acidophilus, Bifidobacterium bifidum* and *Bifidobacterium longum*. The probiotic group received one capsule each, every other day. However, most patients were already in a severe stage of AD, which could justify the ineffectiveness of the use of probiotics in cognitive improvement[105]. In contrast, in another double-blind, placebo-controlled, randomized clinical trial, AD patients who received capsules with *Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum*, and selenium for 12 weeks had an improvement on the mini-mental status exam[106].

Other researchers have focused on evaluating the effect of probiotics on the cognition of healthy humans or those with mild cognitive impairment. A randomized, double-blind, multicenter clinical trial examined the effects of probiotic consumption on gut and brain health in healthy older adults over the age of 65. The placebo group and the probiotic group ingested soybean oil capsules and *Bifidobacterium bifidum* BGN4/*Bifidobacterium longum* BORI capsules, respectively, twice daily for 12 consecutive weeks. The probiotic group had an improvement in cognitive function, a change in the composition of the gut microbiota and an increase in the serum level of BDNF (Brain-Derived Neurotrophic Factor), a molecule related to learning and memory[107]. XIAO et al.[108] performed a double-blind, randomized, placebo-controlled study in which healthy elderly people with mild cognitive impairment ingested two capsules of Bifidobacterium breve A1 lyophilisate daily for 16 weeks. After the intervention, the elderly showed significant improvement in memory.

According to the review by Arora, Green and Prakash[109], although probiotics have anti-inflammatory and anti-oxidant effects in humans, risks are not absent. Side effects such as sepsis, immunoreactivity and antibiotic resistance due to gene transfer should be considered, especially in debilitated individuals.

DISCUSSION

AD is a multifactorial disease that causes loss of memory and cognition, among other abilities. Due to the increase in life expectancy, the human population is heading towards an increase in the number of elderly people, which will result in an increase in aging-related neurodegenerative diseases, such as AD. Added to the alarming projections for the number of elderly people with AD for the next decades, no therapeutic strategy has been successful to prevent or treat this disease to date.

The proper functioning of the blood-brain and gastrointestinal barriers, as well as the composition of the intestinal microbiota seem to be key elements in neuroprotection. The CNS and gut microbiota communicate via the vagus nerve, enteroendocrine cells, enteric nervous system, HPA axis, and by products derived from the gut microbiota. There is evidence of altered microbiota composition in feces from AD patients and the abundance of pro-inflammatory bacteria may be associated with a peripheral inflammatory state in patients with cognitive impairment and cerebral amyloidosis. On the other hand, some metabolic compounds produced by the microbiota may have a beneficial effect on cognitive function. In this way, the relationship between AD and the intestinal microbiota is clear, which therefore led some researchers to investigate whether microbial modulation through the ingestion of probiotics would provide some benefit in patients with this disease.

In fact, probiotics are shown to be able to maintain or restore intestinal microbiota homeostasis, which can slow the progression of neurodegenerative diseases. However, as can be seen in this review, there are few clinical trials that analyze the effect of probiotic consumption in humans with AD. Most of the studies are carried out with rodents and among these studies there are differences in the animal models used, in the tests used for cognitive assessment and in the supplementation protocols. All these differences in the parameters of the studies make a more consistent analysis of the results difficult, showing that more research in this area should be conducted to fill some gaps in knowledge. It is essential that clinical trials in this area standardize the time of ingestion, concentration and microbial

composition of probiotics. In addition, possible side effects with the use of probiotic compounds should also be evaluated.

CONCLUSION

To date, the preponderance of results indicates that manipulating the composition of the gut microbiota by the use of probiotics can be an interesting approach for the development of therapies and preventive strategies for AD.

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Authors' contribution

Faulin TES contributed to the search and review of articles and writing of the manuscript. Estadella D contributed to the analysis and critical review of the manuscript. Faulin TES and Estadella D conceived of the presented idea.

Faulin TES, Estadella D. A doença de Alzheimer e sua relação com o eixo microbiota-intestino-cérebro. Arq Gastroenterol. 2023;60(1):144-54.

RESUMO – Contexto – A doença de Alzheimer (DA) é uma doença neurodegenerativa progressiva e irreversível, caracterizada pelo acúmulo de placas amiloides e emaranhados neurofibrilares no cérebro. Diversas vias possibilitam uma comunicação bidirecional entre o sistema nervoso central (SNC), o intestino e sua microbiota, constituindo o eixo microbiota-intestino-cérebro. **Objetivo** – Revisar a fisiopatogenia da DA, relacioná-la com o eixo microbiota-intestino-cérebro e discutir sobre a possibilidade do uso de probióticos no tratamento e/ou prevenção desta doença. **Métodos –** Busca de artigos da base de dados PubMed publicados nos últimos 5 anos (2017 a 2022) para estruturar a revisão narrativa. **Resultados** – A composição da microbiota intestinal influencia o SNC, resultando em modificações no comportamento do hospedeiro e pode estar relacionada com o desenvolvimento de doenças neurodegenerativas. Alguns metabólitos produzidos pela microbiota intestinal, como o N-óxido de trimetilamina (TMAO), podem estar envolvidos na patogênese da DA, enquanto, outros compostos produzidos pela microbiota durante a fermentação de alimentos no intestino, como o D-glutamato e os ácidos graxos de cadeia curta, são profícuos na função cognitiva. O consumo de microrganismos vivos benéficos à saúde, os probióticos, tem sido testado em animais de laboratório e humanos para avaliação do efeito na DA. **Conclusão** – Embora haja poucos ensaios clínicos que avaliem o efeito do consumo de probióticos em humanos com DA, os resultados até o momento indicam uma contribuição benéfica do uso de probióticos nesta doença.

Palavras-chave – Alzheimer; cérebro; microbiota intestinal; disbiose; probiótico.

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