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Mini-Review

The role of Gut-Microbiome-Brain-axis in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by cognitive decline and progressive loss of memory. Recent research has unveiled a potential link between the gut microbiome and the pathogenesis of AD, giving rise to the concept of the gut-microbiome-brain axis. This narrative review synthesizes current literature to elucidate the intricate interplay between gut microbiota and the development of AD. We explore the bidirectional communication along the gut-brain axis and its impact on neuroinflammation, amyloid-beta accumulation, and tau hyperphosphorylation—key hallmarks of AD pathology. Additionally, we discuss the potential influence of gut dysbiosis on systemic inflammation and its contribution to the neuroinflammatory milieu observed in AD. The modulation of gut microbiota emerges as a promising avenue for therapeutic interventions in AD, with probiotics, prebiotics, and dietary strategies showing potential to positively impact cognitive outcomes. As we delve into the evolving landscape of the gut-microbiome-brain axis, this review provides a comprehensive overview of the current understanding and potential implications for targeting the gut microbiome to ameliorate Alzheimer's disease.

Keywords: Alzheimer disease; Gut-brain axis; Dementia.

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1. Introduction

Alzheimer's disease (AD) is the major cause of manifestation in the world, a global health problem that affects the immune system of elderly patients [1]. The prevalence of this disease tends to grow, as the world population tends to age more and more, increasing the number of elderly people exposed to risks [2]. This is because degeneration of the central nervous system (CNS) is intrinsic to aging, causing reductions, for example, in attention, sensory perception, motor coordination and greater propensity for neurodegenerative diseases. The deposition of β-amyloid (Aβ) plaques is the most important characteristic of AD, concomitant with the formation of neurofibrillary tangles composed of tau protein, triggering neuroinflammation, interruption of synapses and consequent death [3, 4]. AD can be triggered by different factors, genetic or not, as observed in amyloid precursor proteins (APP), a membrane protein whose increase results in increased production of Aβ and Aβ42, resulting in greater aggregation and influencing the pathogenesis of AD.

The brain-gut axis (GBA) is a bidirectional communication pathway between the gastrointestinal tract and the CNS that has the function of reconciling the role of both, the

intestine uses signals such as variation in intestinal permeability, enteric reflex and neuroendocrine signaling, while the brain signals bowel movements and secretions [5]. Thus, due to its important regulatory role in the CNS, the intestinal microbiota is studied as a tool for the diagnosis and treatment of neurodegenerative diseases, such as Alzheimer's disease, to offer a better prognosis [6]. Thus, in addition to age, cognitive capacity is influenced by the brain-gut axis, which can act on the CNS, through the autonomic or autonomous nervous system, through intestinal metabolites capable of crossing the blood-brain barrier [1, 7]. One of the main modulators of this axis is the intestinal microbiota, composed of several phyla of bacteria that cause pro-inflammatory or homeostatic metabolites [1].

That said, aging causes a reduction in the intestinal microbiota, giving way to pro-inflammatory bacteria [7]. Still, older age contributes both to increased permeability of the gastrointestinal tract and to increased permeability of the blood-brain barrier, which facilitates the arrival of metabolites and compounds released by bacteria into the brain through the bloodstream and the beginning of the process. neuroinflammatory responsible for AD [8, 9]. Therefore, according to the information provided in this brief introduction and, also, considering the great impact that the cerebrum-intestinal axis has in neurodegenerative diseases such as Alzheimer's, further study of the subject is necessary. Therefore, this article seeks to delve into the relationship between *GBA* and the brain, the mechanisms of neuroinflammation and how these can be used to treat patients with AD.

2. Methodology

A narrative literature review was executed in the Medline database (PubMed), from 2018 to 2023, about the role of gut-microbiome-brain-axis in Alzheimer's disease. In the Medline database (PubMed), 473 articles were found through the Mesh descriptor "(gut-brain-axis) AND (Alzheimer disease)" of which 269 were included, after the exclusion of articles following the first set of criteria - exclusion of titles that did not address the role of gut-microbiome-brain-axis in Alzheimer's disease, articles not included in the research period of 2018-2023, as well as articles that were not originally in English. After this phase, a second set of criteria was applied - exclusion of the abstracts that did not address the role of gut-microbiome-brain-axis in Alzheimer's disease, which led to the exclusion of 209 articles. After the selection, 7 new articles were manually selected and added, according to their relevance to the study. Finally, aiming to enrich the discussion, 32 articles originally in English were manually selected and added according to their relevance in the synthesis of qualitative evidence.

3. Results and discussion

The intestinal microbiota has approximately 1000 different types of microorganisms, including bacteria, viruses, fungi, parasites, and their populations can undergo changes in various ways, for example: how the person was born, diet, age, and exposure to antibiotics. These microorganisms together can produce metabolites that influence, through the bloodstream, inflammatory processes in the brain.

The human intestinal microbiota begins to form during uterine life and continues to be formed with food [10]. In intrauterine life, the metabolites of the maternal microbiota, such as serotonin and SCFA's, short-chain fatty acids with less than 6 carbons, are already capable of influencing neurodevelopment through the placenta [11]. In the case of babies, the microbiota varies according to the form of birth. If they were born by normal delivery, the microbiota corresponds to the microbiota of the mother's vagina, and if they were born by cesarean delivery, the microbiota corresponds to the microbiota of the mother's skin [12]. Formula-fed babies had increased populations of *E. coli*, *Bacteroides*, and *C. difficile*, while breast-fed babies had increased populations of Bifidobacterium and reduced

populations of *E. coli* and *C. difficile* [13]. Furthermore, the intestinal microbiota can still be altered by lifestyle, age, and genetics [14].

In healthy individuals, the most frequent phylum of bacteria in the microbiota are Bacteroidetes and Firmicutes, and their populations may be altered in some neurodegenerative diseases [15], such as Parkinson's disease, where there are signs of worsening of the clinical picture in patients with dysbiosis [16]. On the other hand, in the microbiota of patients with AD, the dominant bacteria are Bacteroidetes, Firmicutes, Escherichia and Shigella [17]. The dominant microbiota in healthy individuals produces anti-inflammatory metabolites and the dominant microbiota in neuropathic individuals produces pro-inflammatory metabolites [18].

In patients with AD, a decrease in the microbiota and a reduction in benign phyla, such as Firmicutes, which is responsible for digesting fibers and producing SCFA, was observed [19]. One of the bacteria important to the microbiota is the genus bifidobacterium, which was reduced in patients with Alzheimer's disease. It plays an important role in intestinal homeostasis due to the generation of anti-inflammatory metabolites, reduced intestinal permeability and decreased levels of LPS [10]. When anti-inflammatory bacteria have dominant populations in the intestine, the individual tends to have the intestinal epithelial barriers and the blood-brain barrier preserved by the bacterial anti-inflammatory properties. However, when there is an increase in pro-inflammatory bacteria, such as Escherichia, which induces the release of cytokines and the consequent activation of the immune system, intestinal permeability increases and there is extravasation of molecules that fall into the bloodstream, reach the brain and cause neuroinflammation [15].

Other studies also suggest that a westernized diet, richer in fat and less fiber, may be linked to AD by reducing the number of anti-inflammatory bacteria and increasing pro-inflammatory bacteria. An example is Japan, which over time has undergone a process of Westernization, including its diet, and has had an increased number of Alzheimer's cases [20]. Similarly, in countries of the Mediterranean Basin, studies have shown that only with diet it was possible to decrease the levels of Escherichia coli and increase the levels of Bifidobacterium and acetate, an important compound for the decrease of intestinal permeability [21]. Finally, it was also recorded that in regions where people are used to consuming meat and dairy products, such as in the West, people consume less fiber and therefore have a greater predisposition to AD and worse cognitive ability [22].

Microorganisms inhabiting the gut microbiota modulate brain activity through metabolites such as acetylcholine, dopamine, noradrenaline, gamma-aminobutyric acid, histamine, serotonin, dopamine among other signaling pathways. These metabolites mediate the gut-brain connection via vague nerve stimulation or endocrine stimulation via the bloodstream. Although the blood-brain barrier is efficient in preventing the passage of extrinsic metabolites into the brain, as a person ages, it loses its efficiency and fails some of its function, allowing metabolites from the bloodstream to reach the brain and make it more vulnerable [23]. In addition to the blood-brain barrier, the process until gut metabolites reaches the brain is also regulated by the permeability of the gut epithelium, which depends on how inflamed it is [24].

The permeabilization of the intestinal wall is regulated by a few factors, including its bacteria, such as Lactobacillus plantarum, Escherichia coli, Nissle and Bifidobacterium infantis, which promote the expression of tight junction proteins, also such as Bacteroides fragilis, which weakens the intestinal barrier [24]. The weakened intestinal barrier allows bacterial enterotoxins, such as LPS, to enter the systemic circulation and trigger an immune response, which in turn will cause the release of cytokines. Finally, through the circulation, these cytokines are able to cross the blood-brain barrier and cause neuroinflammation.

This axis is greatly influenced by the microbiome it harbors and can trigger Alzheimer's pathogenesis, since in patients with inflammatory bowel disease, a pathogen that increases the permeability of the intestinal epithelium, the manifestation of Alzhei-

mer's disease occurs 7 years earlier than in people without inflammatory bowel disease [5]. It is worth noting that just as there are metabolites that negatively influence brain integrity and function, there are metabolites that protect the CNS. Among these metabolites are sodium acetate and sodium butyrate, which have been shown to be effective in protecting the CNS [15]. While acetate acts by reducing the permeability of the blood-brain barrier and prevents the entry of extrinsic compounds into the CNS, sodium butyrate acts by reducing the permeability of the intestinal epithelium and reducing inflammation by inhibiting the secretion of pro-inflammatory cytokines and reducing oxidative stress [5, 25].

Evidence points out that GBA is responsible for mediating inflammation from the gut to the brain via the vagus nerve, as introducing AB oligomers into the gastrointestinal tract for one year caused AB deposition in the vagus nerve and brain, ultimately Alzheimer's disease [5]. Since Hardy and Higgins proposed the pathogenesis of AD in 1992, AD was treated as a problem intrinsic to the brain by the deposition of β-amyloid plaques. With the advent of new discoveries from research, the pathology has been studied as a multifactorial problem [3]. AD is a disease that, due to chemical marker studies, can be traced decades before the first clinical signs by the detection of Aβ plaques, neurofibrillary tangles of hyperphosphorylated tau protein, and hippocampal atrophy [26].

The mechanisms that increase the risk of AD progression, such as alterations in the microbiota and the production of metabolites by bacteria and changes in the brain, somehow have a link to neuroinflammation. CNS immune cells, the mycroglia, of the monocyte lineage, can assume two active forms, M1 and M2, which have pro-inflammatory or anti-inflammatory function, respectively [25]. Invasion of the CNS by external substances can trigger activation of the mycroglia to the M1 form through activation of Toll-like receptors (TLR) via cytokines such as INF-γ and TNF-α [25].

Also, neuroinflammation occurs through immune reactions. Pro-inflammatory bacteria, such as Escherichia coli, release curli amyloid peptide. This peptide contains amyloid precursor proteins that is recognized by macrophages via TLR2. This recognition activates the macrophage and triggers the release of pro-inflammatory markers that will reach the brain, causing inflammation (Tarawneh R, Penhos E, 2022). Middle-aged people who have these increased markers, such as IL-10, IL-6, and TNF-B, may show cognitive decline when elderly [5].

Aβ-secretase originates from the cleavage of APP, a transmembrane protein that is cleaved by two enzymes, β-secretase, and γ-secretase [8]. While β-secretase cuts APP from the extracellular side, γ-secretase cuts APP from the intracellular side. The products of this cleavage are Aβ precursors, which, when folded incorrectly, accelerate Aβ formation. The spread of amyloids happens neuron-to-neuron, direct crossing of the blood-brain barrier through the bloodstream or through cells of the immune system [4].

There are recent studies in mice about the APOE gene, a gene that establishes how the gut flora influences the immune response and the aggregation of misfolded proteins in the brain. In these studies, researchers Lao et al defined 4 types of APOE, APOE 1, 2, 3 and 4, and the higher their number, the higher the risk of developing Alzheimer's [27-28]. Evidence from other studies points out that sterile-bred mice had lower AB deposition when compared to non-sterile-bred mice [10, 29]. Similarly, mice carrying APOE were also found to have the same benefit when given antibiotics that decrease gut flora [27].

Although short-chain fatty acids are known to mitigate the effects of neurodegeneration and neuroinflammation, it was noted that in mice carrying germ-free APOE4, the variant at highest risk for developing AD, ingestion of short-chain fatty acids increased neurodegeneration and neuroinflammation [28]. In other studies, it has been reported that short-chain fatty acids can bind on aryl hydrocarbon receptors and trigger homeostasis of the blood-brain and intestinal barriers by decreasing inflammation, blocking microglia, and activating astrocytes [13].

Diet is an important factor in determining the homeostasis of the microbiota. The increase in cases of Alzheimer's disease is related to dietary changes in developing countries. Also, in the long term, healthy diets imply better cognitive performance, while unhealthy diets imply smaller hippocampal volumes [10]. Other studies found improvement in cognition, attention, mood improvement, and anxiety reduction in patients when performed microbiota modulation by psychobiotics [16]. Prebiotics are studied as a tool for microbiota homeostasis. They are non-digestible substances capable of stimulating the growth of certain bacteria, making it possible to direct the microbiome towards a pro-inflammatory or anti-inflammatory state [6]. An example of this is mice fed mannan oligosaccharides for eight weeks resulted in less AB plaque deposition in the brain, increased butyrate levels, and less LPS leakage across the intestinal barrier [6].

Studies that relate the administration of probiotics as an alternative route for the treatment of Alzheimer's disease occur all the time and are crucial to the advancement of research on the subject. Although the studies are mostly done in mice, they reveal that ingesting probiotics may be an important way to slow the progression of the disease and improve cognitive ability [21]. Among these studies are those showing that administration of bacteria from the Lactobacillus and Bifidobacterium family reduced levels of pro-inflammatory cytokines, the amount of Aβ and consequently improved behavioral performance and memory. These probiotics balance the local immune system and ultimately inhibit brain inflammation [21].

Aiming to better understand how the brain-intestinal axis can influence the brain, including mood changes, the study by Kim et al. [1] studied 63 elderly patients, the main targets of AD, in a randomized clinical trial study that divided them into a placebo group and a group that took probiotics such as Bifidobacterium bifidum BGN4 and Bifidobacterium logum BORI [1]. Starting at week 12 of probiotic intake, a cognitive test battery showed that the probiotic group had improved mental flexibility and decreased stress, as the diet with prebiotics was able to reduce pro-inflammatory microbiota species [1].

BNDF is a neurotrophic factor, related to good learning, memory function, and stress, which was increased in the patients in the probiotic group. Also, bacteria such as *Eubacterium*, *Allisonellae*, *Prevotellaceae*, stimulating inflammation were reduced in the probiotic group at the end of the study, supporting the idea that probiotics help improve cognitive function [1]. In another study, Liu et al. [3] showed in mice that probiotic treatment can increase the expression of claudins and occludins, cell junction proteins crucial for maintaining intestinal permeability and the blood-brain barrier [3].

Also, in addition to probiotic supplementation there are other interventions that rely on treating the microbiota to treat cognitive declines, such as fecal microbiota transplantation [6, 30]. The procedure consists of implanting into a patient the microbiota of a donor to balance it. In mice these procedures resulted in memory impairment, increased pro-inflammatory cytokines, and greater AB plaque deposition when transplanting feces from a mouse with AD to a healthy one. Also, beneficial effects were observed when feces from healthy mice were transplanted into mice with AD [6, 30].

5. Conclusion

It is evident from this brief review that the gut-cerebral axis is constantly influenced by gut dysbiosis, which plays an important role in neuroinflammation. It was discussed how the changing gut microbiota throughout life can impact on the pathogenesis of AD, as well as the mechanisms that can curb the pathogenesis, such as lifestyle changes, diet, pro-biotics, pre-biotics, and stool transplantation. That said, the influence of the gut microbiota is studied with the goal of using it as a means to facilitate diagnosis and treatment. Therefore, this study will aid in research on the role of the gut-microbiota-brain axis and how it influences the pathogenesis of AD.

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