Alzheimer's disease: A brief update on the influence of gut microbiota and the impact of functional food.

Alyne Mendonça Marques Ton*, Clarisse M Arpini, Bianca P Campagnaro, Thiago Melo C Pereira, Elisardo C Vasquez

Laboratory of Translational Physiology and Pharmacology, Pharmaceutical Sciences Graduate Program, Vila Velha University, Brazil

Abstract

Alzheimer's disease (AD) is a degenerative, progressive and disabling disease that affects the central nervous system (CNS), being the mainly cause of dementia worldwide. The symptoms of the AD are due to progressive loss of cholinergic function due to neuronal cell death mainly in the hippocampus cerebral cortex and other different regions of the brain leading to reduction of cholinergic function and clinical deregulation of thought process and memory. It is now known that the development of the disease is the result of these complex environmental and genetic interactions in which gut microbiota plays a special role. Apparently, the inputs from the CNS can modify gut functions, while inputs from the gut to the CNS can modulate specific symptoms. According current evidences, the disturbance of gut microbiome may lead to incremented intestinal and blood-brain barrier permeabilities causing CNS and systemic inflammation, resulting in the occurrence of neurological disorders. Therefore, it has been suggested that diet and specific nutrients can affect the composition of the gut microbiome and may influence the aggregation or production of amyloid proteins. These findings indicate that the modulation of the gut microbiome through specific nutritional interventions as by using prebiotics and probiotics might represent an effective and safe strategy to reduce the level of chronic inflammation and β-amyloid aggregation associated with AD pathology, preventing or improving the clinical symptoms.

Keywords: Alzheimer's disease, microbiota, functional food.

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Introduction

Alzheimer's disease (AD) is a degenerative, progressive and disabling disease that affects the central nervous system (CNS), being the leading cause of dementia in the world [1-8]. The symptoms of AD are due to progressive loss of cholinergic function due to neuronal cell death mainly in the hippocampus cerebral cortex and other different regions of the brain which regulate thought process and memory [3,5,9-11].

The neuropathological changes associated with AD are similar in sporadic and familial forms of the disease and are characterized by extracellular deposition of β-amyloid protein (β-A) and intracellular entanglements of hyper-phosphorylated tau protein [1,3,8,12,13]. β-A is a transmembrane protein which is, during cell metabolic functions, cleaved into peptides. However, in situations of excessive production or impaired clearance, β-A aggregates into extraneuronal space. Another hallmark of AD is related to Tau, which is an intracellular protein which performs the function of stabilizing microtubules. When hyper-phosphorylated, tau protein fails the axonal transport compromising synaptic and neuronal functions [3].

The contribution of inflammatory cytokines

There is evidence of an inflammatory response in brain areas related with the AD. Astrocytes, a sub-type of microglia, are recruited to sites of inflammation and once activated, become hypertrophic and contribute to the inflammatory processes by releasing cytokines that play a proinflammatory role, such as tumor necrosis factor and interleukin-1. Activated astrocytes also produce apolipoprotein E (ApoE) which may be involved in β-A fibrillization. Over a period of months or years, the cycle of continued release of proinflammatory cytokines and amyloidosis exacerbates neuronal damage [1].

Following studies that approaches genome-wide in AD patients, there is evidence that some genomic regions may be associated with AD. According to Shoemark, some susceptibility genes of Alzheimer's disease had been identified, mostly involving in the inflammation, immune reaction, lipids transport pathways and cell migration. ApoE is one of the most common susceptible genes, with three allele polymorphism (ApoE2, ApoE3 and ApoE4), in which ApoE2 is a protective factor, ApoE3 is a neutral allele and ApoE4 is an AD high-risk allele [1,12].

Evidence of the contribution of gut dysbiosis

Now, it is known that the development of the AD is the result of complex genetic and environmental interactions in which gut microbiome plays a significant role [1,8,14-18]. The gut microbiome can be defined as all the microorganisms that live harmoniously within the human gastrointestinal ecosystem. Table 1 shows the main microbes found in the microbiological analysis of kefir in previous and ongoing studies in our laboratory. They are considered the major reservoir of microbes in the

Table 1. *Main microorganisms found in samples of the probiotic kefir, being tested in experimental and clinical studies in our laboratory.*

Acetobacter aceti	*Lactobacillus delbruecki delbruecki*
Acetobacter	*Lactobacillus fermentum*
Acetobacter sp.	*Lactobacillus frutivorans*
Candida famata	*Lactobacillus kefir*
Candida kefir	*Lactobacillus kefiranofaciens*
Candida krusei	*Lactococcus lactis lactis*
Enterococcus faecium	*Leuconostoc mesenteroides cremonis*
Geotrichum klebahnii	*Sacharomyces cerevisiae*
Lactococcus brevis	*Streptococcus salivarius thermophilus*

human body, containing approximately 1014 units [2,3,17-19]. Apparently, the inputs from the CNS can modify gut functions, while inputs coming from the gut to the CNS can modulate specific symptoms [20]. Alterations of these communications may contribute to neuroinflammation and the pathogenesis of CNS diseases [21]. Human gut microbiota can contribute to brain function, not only via neural, humoral, immune pathways, but also via the cumulative effects of microbial metabolites [3]. In healthy individuals, gut microbiome is fairly stable to form a host-bacterial mutualism, which when disrupted seems to increase the dysfunction of brain, digestive system and metabolism [16].

According to a research with 178 subjects, published by Claesson, the gut microbiota composition of elderly people is ordinarily affected by dietary habit, living environment and the health status of individuals [18]. Additionally, degeneration of gastrointestinal and digestive motility, malabsorption of nutrients, drug uses and affected immunity also influences [19]. Alterations of the intestinal microbiome can activate pro-inflammatory cytokines and increase gut permeability, developing insulin resistance [22]. Furthermore, the microbiome bacteria of the gut excrete immunogenic compounds of amyloids, lipopolysaccharides (LPSs) and other microbial exudates into their circumjacent environment [23,24]. Bacterial amyloids also may activate signaling pathways that plays a role in AD pathogenesis and neurodegeneration, while the gut microbiota may enhance the inflammatory responses leading to cerebral accumulation of β-A [25].

It has been suggested that diet and specific nutrients can affect the microbiome composition and may influence the aggregation or production of amyloid proteins [25]. Harach reported an experimental study in which they observed marked variations on the composition of the gut microbiota when comparing AD's model and wild-typed healthy mice [26]. Their results strongly suggest that a diverse microbial constitution in that AD animal model play a role in the promotion of cerebral A-β amyloidosis [26]. According to data from Wu et al., on drosophila's AD model published in 2017 doing a comprehensive genetic and phenotypic analysis demonstrated that enterobacteria infection nettled the neurodegeneration via immune hemocyte recruiting to the brain [4]. Moreover, Heijtz have established on a germ-free animal study conducted in 2010, that exposure to microbial pathogens during similar developmental periods result in behavioral abnormalities, including anxiety-like behavior and impaired cognitive function [17].

The above findings suggest that modulating the intestinal microbiome through specific nutritional mediations might represent an efficient strategy to prevent or improve AD symptoms. New evidences have shown that the influence of diet habits on brain health was not only due to the inflammatory response induced by the diet compounds but caused by the disruption of the gut microbiota [8,13,21,27].

The beneficial effects of nutraceuticals

A study conducted by Trully in 2002 with 148 subjects with dementia and 45 healthy controls found that the serum docosahexaenoic acid (DHA) of AD subjects were significantly decreased [27]. The DHA is the main omega 3 polyunsaturated fatty acid (O-3 PUFA) amongst eicosapentaenoic acid (EPA). Evidences suggest that body low levels of O-3 PUFAs may be associated with the development of neurodegenerative diseases, including AD. Large scale intake of O-3 PUFAs can lower the risk of AD and slower cognitive decline related to age [28-30]. Besides that, the authors found that increasing the fish consumption could significantly reduce the risk of AD [28]. Studies on aged individuals showed that people who drank from three to five cups of coffee per day at midlife showed a 65% decreased risk of AD in comparison to people who drank less than two cups of coffee per day [31]. Apparently, coffee reduces oxidative stress and lowers the risk of developing AD since it is rich in antioxidant polyphenols.

Excessive accumulation of reactive oxygen species (ROS) and altered redox balance induced oxidative damage which is mainly involved in the pathological process of chronic cardiovascular and renal diseases, as recently reviewed by Pereira et al. and in neurodegenerative diseases, including AD [32,33]. Following the same principle, the dietary intake of other antioxidant compounds, such as vitamin C, vitamin E and flavonoids is also considered to be related to reduced risk of AD [34-37]. In one of these studies it was observed in a cohort of 1,367 subjects above 65 years of age that flavonoid intake could be associated with a lower incidence of dementia [38].

Some researchers found that the incidence of AD was superior in countries with high fat or calories intake habits and inferior in those with low fat intake diet. Epidemiological studies evidences that consumption of excessive saturated fat is a higher risk factor of AD being related to cognitive performance, mainly in domains of global cognitive function, semantic memory and psychomotor speed [8,39]. High fat diet variations of gut microbiome can lead to raised intestinal permeability, LPS absorption, and consequently increased endotoxemia, triggering systemic inflammation and disease pathogenesis [8]. Caloric restriction can promote host health by optimizing the gut microbiome composition, including the increase of bacteria positively related with health, such as *lactobacillus*, and decrease of bacteria negatively associated with health [39].

Amyloids are also associated with fungal surface-structures and the recent observation of diffuse mycoses and proteins derived from amyloidogenic fungal in the blood of AD subjects suggest chronic fungal infection and the presence of some intestinal bacteria increases AD risk [7].

Table 2. *Examples of non-pharmacological products that have been studied in Alzheimer and correlated diseases.*

Individuals in the study	Nutraceutical or Functional Food or Supplement	Main Results or conclusion	Author from the reference list
Rat model of Alzheimer disease.	Administration of resveratrol	Resveratrol suppressed Na_3VO_4-induced p-S396-tau levels via ERK1/2 and GSK-3β signaling cascades in hippocampus	Jhang [36]
Aged individuals	Daily vitamin consumption.	Higher vitamin D dietary intake was associated with a lower risk of developing AD among older women.	Annweiler [37]
Atherosclerotic mice	Kefir chronic administered	Attenuation of lipid deposition in blood vessels	Santanna [41]
Aged individuals	Effect of flavonoids in a cohort of 1367 individuals	Intake of antioxidant flavonoids was inversely related to the risk of incident dementia.	Commenges [38]
Hypertensive rats	Kefir chronic administration	Marked reduction of blood pressure, cardiac dysautonomia and baroreflex,	Klippel [42]
Alzheimer Disease Rat model.	Effect of chronic treatment with *Lactobacillus.*	Restores acetylcholine and attenuation of amyloid plaques; ameliorated cognition deficits.	Nimgampalle [44]
Aged men	Dietary daily intake of vitamin E and C	Consume of these supplements may protect against vascular dementia and may improve cognitive function in late life.	Masaki [34]
Alzheimer disease patients	4 months taking either omega-3 PUFAs or placebo	Findings showed an overall benefit of omega-3 PUFA supplementation for those with cognitive impairment and dementia.	Phillips [30]
Aged women	7-year follow-up of higher vitamin D dietary intake	This food supplement was associated with a decreased risk of developing AD	Annweiler [37]
Spontaneous hypertensive rats (SHR)	Chronic administration of kefir	Anti-hypertensive effects, attenuation, or reversion of the endothelial dysfunction, associated with concurrent decreases in reactive oxygen species	Friques [43]

Finally, the disturbance of gut microbiota may directly leads to increased intestinal permeability and blood-brain barrier permeability and causes both systemic and CNS inflammation, which ultimately results in the occurrence of neurological disorders. The metabolites of gut microbiome and its influence on neurochemical changes of the host might also decrease or increase the risk of AD, such as GABA, serotonin, N-methylamino-L-alanine, the expression of N-methyl-D-aspartate glutamate receptor and brain derived neurotrophic factor and the biosynthesis of vitamins [39]. In line with the proposal that chronic dysbiosis can compromise the physiological bidirectional signaling that characterizes the gut–brain axis, one can predict that the modulation of gut microbiome through individualized diet or microbiota intervention will most likely become a fresh potential treatment for AD (Table 1) [40].

Recently, our laboratory has investigated the beneficial actions of the synbiotic kefir in diverse experimental models of chronic diseases such as hypertension and atherosclerosis. One of those studies has revealed that prolonged administration of the non-bacterial fraction of kefir decreases lipid deposition in LDLr-/- mice [41]. In a model of hypertension, Klippel observed that kefir attenuated the dysautonomia observed in the cardiac control of heart rate and on baroreflex sensitivity that characterizes the spontaneously hypertensive rats [42]. In this same model of hypertension Friques, chronic administrations of the kefir ameliorate the endothelial via decreasing the high levels ROS and pro-inflammatory cytokines [43]. Others have observed in the rat model of AD the chronic treatment with microorganisms isolated from probiotics, such as the *Lactobacillus plantarum,* resulted in significant decrease of amyloid plaques and amelioration of the cognition deficits [44]. The above results could indicate that kefir could also have similar effects in patients with AD. Clinical studies are being designed by our group to test this hypothesis (Table 2).

Conclusions and New Insights

AD is a progressive, incapacitating and fatal cause of dementia with dramatic financial and social impacts worldwide because its incidence rates increases with aging. It is known that currently available treatments for AD are only symptomatic and do not attenuate or prevent the progression of the disease. The challenge of developing disease-modifying interventions has targeted the Aβ pathway compounds and that strategy is recognized as an imperative necessity. To reduce this social problem new approaches are being designed aiming to modify, slowing or stabilize, the initial pathological phases which result in progressive neuroinflammation and neurodegeneration, culminating in a subsequent phase of clinical dementia.

In the current scenario, several recently concluded or ongoing studies have already demonstrated the importance of analyzing the gut-brain axis in the development and evolution of mild cognitive impairment and dementia subjects. In these studies, it has or is being demonstrated that diet compounds can directly affect the composition of the gut microbiome and, consequently, influencing the aggregation or production of amyloid proteins.

Looking forward, our and other laboratories, are proposing to modulate the gut microbiota through specific nutritional interventions as by using prebiotics and probiotics. This may represent an effective and safe strategy to reduce the level of chronic inflammation and β-amyloid aggregation associated with AD pathology. We hope that in the near future, the efforts are being made through the design of clinical trials, can result in a positive demonstration of important neuroprotective actions of functional food (including probiotics and synbiotics) in patients suffering from dementia.

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***Correspondence to:**

Alyne Mendonça Marques Ton
Laboratory of Translational Physiology and Pharmacology
Vila Velha University (UVV)
Vila Velha, ES, Brazil.
E-mail: Lyne_MSV@hotmail.com