REVIEW PAPER

Dysbiosis and Alzheimer's Disease: Cause or Treatment Opportunity?

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Abstract

Recent investigations have increased the interest on the connection between the microorganisms inhabiting the gut (gut microbiota) and human health. An imbalance of the intestinal bacteria representation (dysbiosis) could lead to different diseases, ranging from obesity and diabetes, to neurological disorders including Alzheimer's disease (AD). The term "gut-brain axis" refers to a crosstalk between the brain and the gut involving multiple overlapping pathways, including the autonomic, neuroendocrine, and immune systems as well as bacterial metabolites and neuromodulatory molecules. Through this pathway, microbiota can influence the onset and progression of neuropathologies such as AD. This review discusses the possible interaction between the gut microbiome and AD, focusing on the role of gut microbiota in neuroinflammation, cerebrovascular degeneration and Aβ clearance.

Introduction

In recent years, there has been an increasing interest in the possible connection between the gut colonizing bacteria (gut microbiota) and human health. The gut microbiota is composed of more than 100 trillion bacteria in adults, nearly ten times as many as cells in the body, containing more than 1000 different species of bacteria (Bermon et al. 2015). The gut microbiota differs from one individual to another, conferring each one personal identity (Qin et al. 2010). Based on the data obtained by several studies, a healthy microbiota is the one that maintains community stability and species diversity, defining a good microbiota. Specifically, most abundant species (around 70–75%) are the anaerobic bacteria from the *Firmicutes* or *Bacteroidetes* phyla (Wang and Wang 2016) followed by *Proteobacteria*, *Actinobacteria* (such as *Bifidobacterium*), and C*yanobacteria* (Qin et al. 2010). Interestingly, in the development of diseases ranging from obesity and diabetes to neurological disorders an

imbalance in gut bacterial species, known as dysbiosis, has been observed (Sherwin et al.2018).

The numerous connections between the brain and the gut are known as the "gut-brain axis". This crosstalk involves the participation of the autonomic, neuroendocrine, and immune systems together with metabolites and neuromodulatory molecules produced and released by gut bacteria (Quigley 2017). The gut microbiota has a central role in the regulation of the gut-brain axis, influencing not only gut but also central nervous system (CNS) activities. Indeed, several studies have demonstrated the direct connection between neuropsychiatric disorders and changes in the microbiome, microbiota-derived products and even exogenous antibiotics and probiotics. Data also indicate that microbiota, through the gut-brain axis, can influence brain plasticity and cognition, inducing the onset and progression of neuropathologies such as Alzheimer's disease (AD).

AD is characterized by significant cognitive deficiencies, with amyloid-beta (Aβ) peptide aggregation and hyperphosphorylated tau tangles being the most prominent histopathological signs (Hyman et al. 2012; Montine et al. 2012; Menzies et al. 2015). Other hypotheses explaining AD pathogenesis include neuroinflammation, calcium signaling and energy metabolism imbalances, and vascular degeneration, but therapies based on these theories have failed in the past. This breakdown of therapeutic approaches based

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on current hypotheses has contributed to the need for a re-examination of AD pathogenesis from a new angle.

To date, the complexity of the impact of the gut microbiota in neuropathological disorders has not been understood (Bostancioklioğlu 2018). This review discusses the multiple ways the gut microbiome and AD may interact, focusing on the role of gut microbiota in neuroinflammation, cerebrovascular degeneration and Aβ clearance. Altogether, there seems to exist convincing evidence that modulation of the cross talk between gut and CNS through intestinal commensal microbiota control may be a potential treatment for neurodegenerative disorders such as AD (Bonfili et al. 2018).

Gut-Brain Axis and AD

The increasing knowledge obtained in the past years of the impact of the gut microbiota on the CNS has suggested the "brain-gut-microbiota axis" (Kowalski and Mulak 2019). The gut-brain axis is controlled bidirectionally. On one hand, the CNS modulating the enteric nervous system controls several aspects of the gut such us secretion, permeability, motility and immunity, and the efferent autonomic nervous pathways control muscle tissue and the mucus layer of the intestine (Carabotti et al. 2015). On the other hand, afferent signaling pathways and active molecules secreted by gut microbiota can alter brain functions (Burokas et al. 2015; Petra et al. 2015). Several studies have shown that changes in diet, the existence of pathogenic microorganisms, as well as the use of antibiotics and non-steroidal anti-inflammatory medications can induce the gut dysbiosis that can impact on brain cognitive function (Gareau 2014; Jiang et al. 2017). More specifically, there is convincing evidence for the interplay between AD and impaired gut microbial diversity, which is an incentive for suggesting a hypothesis on the pathogenesis of AD.

There are many processes that link gut microbiota function and AD. The gut microbiota has been shown to be essential for some brain processes like myelinization, neurogenesis and microglial activation and it has been closely related to behavioral, mood and cognitive modulation (Cenit et al. 2017).

Several groups have reported gut microbiome alterations in AD mouse models such as 5xFAD (Brandscheid et al. 2017) and APP/PS1 (Harach et al. 2017). In both models, gut microbiota dysbiosis has been described with an inverse correlation between the amount of *Firmicutes* and *Bacteroidetes* species, which means that when one is increased, the other is decreased. Very interestingly, it has been also demonstrated that APP/PS1 mice bred under sterile conditions show significantly lower levels of Aβ deposits compared to the same mice bred in non-sterile conditions (Harach et al. 2017). Similarly, when mice bred under sterile conditions

are transplanted with normal condition-bred mice microbiota, a significant increase in brain Aβ deposits has been observed (Harach et al. 2017).

In a similar manner, altered microbiota diversity has been described in an amyloid transgenic *Drosophila* model (Wu et al. 2017). The impairment of the gut microbiota-induced neuroinflammation and cerebrovascular degeneration in this AD model suggests a connection between microbiota and brain damage.

AD patients show gut dysbiosis with significant changes in the composition of the intestinal microbiome when compared to healthy subjects (Vogt et al. 2017; Bostancioklioğlu 2019). Specifically, AD patients have decreased levels of bacteria in *Actinobacteria* (specifically, bacteria of the genus *Bifidobacterium*) and in the phylum Firmicutes. Noteworthy, decreased levels in Firmicutes have also been reported in the microbiome of individuals with type 2 diabetes (T2DM) (Larsen et al. 2010) as well as obesity and interestingly, diabetes and insulin resistance are defined risk factors for the developing of AD (Ott et al. 1999; de la Monte and Wands 2005; Rawlings et al. 2014).

In the same study, subjects with AD showed an increase in the phylum Bacteroidetes, reflected by increased *Bacteroidaceae* family and elevated *Bacteroides* at the genus level. The phylum Bacteroidetes encompasses a diverse and abundant group of gram-negative commensal bacteria in the gut (Rajilić-Stojanović M and de Vos 2014), including the genus *Bacteroides*, which has been detected at higher levels in the gut of individuals with T2DM (Larsen et al. 2010). The major outer membrane component of gram-negative bacteria is lipopolysaccharide (LPS), which is capable of triggering systemic inflammation and the release of pro-inflammatory cytokines after translocation from the gut to systemic circulation (Cani et al. 2007).

Additionally, compared to control subjects, AD patients showed reduced Actinobacteria. These differences were mostly driven by changes in Bifidobacterium. Actinobacteria, particularly the *Bifidobacterium* genus, are an important bacterial inhabitant of the human gut, and their beneficial health effects have been extensively described (O'Callaghan and van Sinderen 2016; Arboleya et al. 2016). Specifically, certain species of *Bifidobacterium* are associated with anti-inflammatory properties and decreased intestinal permeability (Underwood et al. 2015). Moreover, *Bifidobacterium* supplement has been shown to decrease LPS levels in the intestine and improve gut mucosal barrier properties in mice (Griffiths et al. 2004; Wang et al. 2006). Interestingly, in germ-free mice colonized with human gut microbiota, increased levels of *Bifidobacterium* are associated with decreased bacterial translocation to systemic circulation, while increased levels of *Bacteroides* have been shown to increase bacterial translocation (Rommond et al. 2008). Considering all these findings, increased *Bacteroides* and

decreased *Bifidobacterium* in AD participants may represent a gut microbial phenotype with particular propensity for translocation of pro-inflammatory bacterial components.

Noteworthy, a tight correlation has been described between gut microbiome genera and AD biomarkers, i.e., $A\beta_{42}/A\beta_{40}$, p-tau and the $A\beta$/p-tau ratio in the cerebrospinal fluid (CSF) (Vogt et al. 2017). A significant association in AD subjects between CSF YKL-40 and abundance of *Bacteroides, Turicibacter*, and *SMB53* (family *Clostridiaceae*) was observed. Moreover, marked variation in the composition of bowel bacteria has been also observed in AD subjects (Zhuang et al. 2018). However, the species that changed differ compared to the study performed by Vogt et al. (2017). Many factors could be behind those differences; ethnicity, comorbidities, dietary preferences and lifestyle are some of those factors (Tasnim et al. 2017).

The findings of these experiments indicate that variations in the intestinal microbiota may affect brain functions. Published data also provide signs of the impact of the gut microbiome on amyloid pathology, and suggest the possible function of the gut microbiome as one of the AD pathogenesis factors. In addition, the gut microbiota is extremely susceptible to lifestyle and aging as a complex modifiable system. Therefore, in the following sections we will discuss the impact of contemporary lifestyle and aging on the gut microbiota and the relationship to AD pathology.

Gut Microbiota Alterations Induced by AD Risk Factors

The most important factors that impact and modulate the gut microbiome are dietary changes (Pistollato et al. 2016). In addition, many of the factors that can modulate gut microbiota composition, such as aging, stress or obesity, are also considered risk factors for AD.

As already mentioned, gut microbiota composition can vary in different pathological conditions like depression (Wang et al. 2017) or neurodegenerative diseases (Brandscheid et al. 2017; Parashar and Udayabanu 2017). However, this issue raises an important question: is it the disease per se that changes the microbiota or are the disease risk factors the ones affecting the gut microbiome? Deleterious lifestyle conditions in our actual societies have been considered the significant risk factors for the onset and development of AD (van Praag 2018). The most remarkable feature of epidemiological studies is that significant rise of AD in developing countries is associated with dietary changes (Grant 2014). Furthermore, apart from the main AD risk factor, that is aging, in modern culture there are several unhealthy lifestyle conditions that lead to the development of AD. These factors include unhealthy diets and stress, and simultaneously, the gut microbiome is highly sensitive to these factors. From this point of view, the assessment of the purported connections between aging, modern lifestyle, gut microbiota and AD is a considerable issue that requires special attention.

Aging

As advanced age is a significant risk factor for AD, age-related changes in the gut microbiota could play a central role in the development of neuropsychopathologies. In this line, several studies have shown that gut microbiota composition suffers significant variations in the aging process (Salazar et al. 2017; Nagpal et al. 2018).

Several studies show that gut composition differs between old and young people. However, it is not possible to set a specific point where the microbiome gets altered as it occurs gradually over time (O'Toole and Jeffery 2015; Zapata and Quagliarello 2015).

Colonization of the gut may start in utero from the placenta. Most of infant microbiome is acquired during birth and follows with feeding and exposure to environment (Quigley 2017). The gut microbiota evolves rapidly the first three years and at the age of 3 years old, microbiota composition becomes similar to that of adults (Zapata and Quagliarello 2015; Quigley 2017). Childhood and adolescence are two critical periods for gut microbiota composition and neuronal development (Cenit et al. 2017) which get more diverse with dietary changes.

Aging is closely related with reduced microbiota diversity and this fact has been related to frailty while healthy aging is associated with a diverse microbiome (Cenit et al. 2017). Several authors have described that in elderly people the amount of *Bifidobacterium* and *Lactobacillus* is decreased (Gavini et al. 2001; Hopkins and Macfarlane 2002). These variations in the number and composition of the gut microbiota could be due to decreased bacterial adhesion to the intestinal wall related to the alterations in the structure of the colon mucous membrane (He et al. 2001). Moreover, in the aging process it has been observed that *Bacteroides* species diversity vary (Bartosch et al. 2004; Layton et al. 2006) and proteolytic bacteria (*Fusobacteria*, *Propionibacteria*, and *Clostridia*) increase, leading to putrefactive processes. It should be noticed that the impact of aging on the microbiome is intimately associated with diet and lifestyle, so it remains uncertain if aging per se, independent of external influences, is able to alter the microbiome (Quigley 2017). For instance, while bacterial cells do not age per se, people getting older start to take antibiotics, other drugs and begin to present comorbidities affecting the gut.

Stress

CNS stress levels may affect gut physiology and alter gut composition (Pistollato et al. 2016). Stress may provoke the

release of hormones and neurotransmitters that could influence gut physiology and alter microbiome habitat, favoring the growth of certain strains (Cenit et al. 2017). Moreover, stress may cause huge changes in microbiota and intestinal physiology such us greater macromolecular permeability and increased secretory state. Stress has also been related to bacterial attachment and internalization in the epithelium: indeed, several studies have showed that the use of probiotics can reverse and normalize those stress-associated changes (Zareie et al. 2006).

Infection with *Citrobacter rodentium*, a non-invasive murine pathogen has been associated with chronic physical stress, supporting the hypothesis that stress can produce changes in microbiota. However, infection with *Citrobacter rodentium* alone was not able to produce changes in memory or cognition in wild type mice. When mice were exposed to stress, impairments in memory and cognition could be observed in infected mice but not in the uninfected. This impairment was related to lower levels of c-fos and BDNF and it was still present after clearance of the pathogen, thus indicating a long lasting effect. Furthermore, administration of probiotics one week prior to *Citrobacter rodentium* infection was able to prevent stress-associated changes (Gareau et al. 2011).

Early life stress in rodents such as that the produced by maternal separation (MS) has been related to changes in microbiota in early life including lower levels of *Lactobacillus*, *Bacteroides* and increased levels of *Clostridium* (Gareau et al. 2006, 2007; Wang and Wang 2016), and these modifications are still present even in adulthood (O'Mahony et al. 2009). These variations in the microbiota originating from stress have been related to increased severity and risk for colitis and infections with parasites like *Nippostrongylus brasiliensis* (Barreau et al. 2004, 2006). Moreover, these changes have been also observed in rhesus monkeys in which prenatal stress induced a decrease in levels of *Bifidobacterium* and *Lactobacillus* (Wang and Wang 2016).

Obesity

Obesity is a worldwide problem that has drastic long-term impacts on people's health (González-Muniesa et al. 2017). According to a large number of studies, obese people have major risk of developing neurodegenerative diseases (Profenno et al. 2010). Clinical and experimental data, for instance, suggest that high fat diets (HFD) and obesity are related to memory and learning deficiencies (Elias et al. 2005; Sabia et al. 2009), and presumably also brain atrophy (Enzinger et al. 2005). Furthermore, mounting data suggest that mid-life obesity raises the risk of suffering dementias such as AD later in life (Anstey et al. 2011).

Studies through the literature show positive associations between consuming healthy food and better cognitive performance and unhealthy food with worse performances even in short time interventions. A study performed in people in their sixties showed that an increase of unhealthy foods intake for four years was related to smaller hippocampus volumes (Jacka et al. 2015). On the other hand, another study showed that healthy food ingestion was associated with better cognitive performance (Wu et al. 2019). Vegetable and fruit ingestion has been also related to lower risk of age-related cognitive deficiencies (Wu et al. 2018). Moreover, higher intakes of fish were associated with greater cognitive performance (Okubo et al. 2017).

Some dietary patterns such as the Mediterranean diet have been related to lower cardiovascular risk and decreased age-related cognitive impairment (Samieri et al. 2013; Wu et al. 2019). However, dietary patterns characterized by higher intakes of meat, fried food and processed products and lower intakes of whole grains have been associated with greater pro-inflammatory status and decreased cognition (Shivappa et al. 2015; Leigh and Morris 2020). Diets high in saturated fats have also been related to decreased memory and cognition performances (Eskelinen et al. 2008). In this line, HFD or high in fat and sugar (HFHS) diets have been related with cognitive deficiency in adulthood and greater risk of dementia (Leigh and Morris 2020). This issue has been extensively studied in the literature showing that diet-induced obesity impairs cognition in healthy controls and worsens it in neurodegenerative models.

In view of the high number of obese subjects, there is an urgent need for a better comprehension of the pathophysiological processes involved in the process of obesity and their effects on cognitive performance. HFHS diet intake affects the composition of microbiota and may contribute to an imbalanced microbial environment in the intestine. Therefore, it has been recently suggested that the gut microbiome may be part of a mechanistic connection between consumption of HFD and other unbalanced diets and impaired cognition. The literature has showed us that short-term diet exposure is able to change microbiota composition in humans (David et al. 2014) and mice (Carmody et al. 2015) within days and that these changes may be relevant to early onset of cognitive impairment (Leigh and Morris 2020).

Indeed, several preclinical studies have demonstrated that HFD is able to induce gut microbiota alterations and induce the progression of dementia (Studzinski et al. 2009; Nam et al. 2017; Sah et al. 2017; Sanguinetti et al. 2018). Focusing specifically on AD, a study performed in 12 months old APP23 mice showed that HFD-induced gut microbiota changes were related to increased levels of Aβ (Nam et al. 2017).

In this line, a study performed in the 3xTg-AD AD mouse model showed that HFD and genetic predisposition to neurodegenerative diseases share similar abnormalities in the gut microbiome (Sanguinetti et al. 2018). The analysis of serum

and fecal metabolites of those mice revealed a decrease in choline and unsaturated fatty acids, and elevated levels of lactate, amino acids, ketone bodies, trimethylamine (TMA), and trimethylamine N-oxide (TMAO) in HFD fed 3xTg-AD mice, which analogously are associated with impaired cognition (Janeiro et al. 2018).

In the same way, some studies have shown the benefits of using probiotics in combination with HFD, even in healthy subjects. Most of these studies have used *Bifidobacteria* or *Lactobacillus* strains for their research reporting restored cognition impairment (induced by HFD) and improvements in some cognitive tests like MWM or fear conditioning (Savignac et al. 2015; Chunchai et al. 2018; Ishikawa et al. 2019; Romo-Araiza et al. 2018).

Exercise and Sedentary Lifestyle

Intimately related to unhealthy nutrition, sedentary lifestyle is another important condition in obese individuals. Because of being associated with a variety of chronic health problems, sedentary lifestyle is emerging as an important public health issue in many countries (Owen et al. 2010). Mounting evidence shows that sedentary habits may be a risk factor for cognitive impairment (Wheeler et al. 2017), while regular exercise can be an useful method for dementia prevention (Fenesi et al. 2017).

Increasing data indicate that the gut microbiome can be influenced by exercise (Fernandez et al. 2018), and this effect is particularly noticeable in sedentary subjects and obese people (Bressa et al. 2017; Allen et al. 2018). Moreover, in a study performed in APP/PS1 mice (Abraham et al. 2019), the authors showed that physical activity induced an increase in butyrate-producing bacteria, and a reduction in pro-inflammatory and H_2O_2-generating bacteria. These changes in microbiota were accompanied by a reduction of Aβ levels in brain and a slowdown of progression of AD symptoms.

How Dysbiosis Could Contribute to AD?

As mentioned before, AD is characterized by significant deficiencies in cognition, with Aβ peptide aggregation and hyperphosphorylated tau tangles being the most prominent histopathological signs. Several mechanisms triggered by dysbiosis may affect the gut-brain axis and could be involved in AD onset and progression, with inflammation, gut permeability and Aβ accumulation being the ones gaining major interest (Fig. 1).

Gut Permeability

Gut microbiota dysbiosis induces a reduction in the expression of tight junction proteins in epithelial colon cells, inducing intestinal inflammation. The alteration of gut barrier function causes the release of microbial metabolites to the circulatory system, which promotes inflammation. Consequently, elevated amounts of circulating pro-inflammatory

Fig. 1 Dysbiosis as a possible link between AD risk factors and neurodegeneration. Aging, stress and obesity can contribute per se to gut disruption, that in a situation with a pathological blood-brain barrier (BBB) leaking, could lead to neuroinflammation. Moreover, these factors can lead to a dysbiosis that could further cause a major neuroinflammation due to increased pro-inflammatory cytokine production and secretion of inflammatory gut metabolites like TMAO or LPS. Finally, a link between gut dysbiosis and brain Aβ accumulation has also been suggested
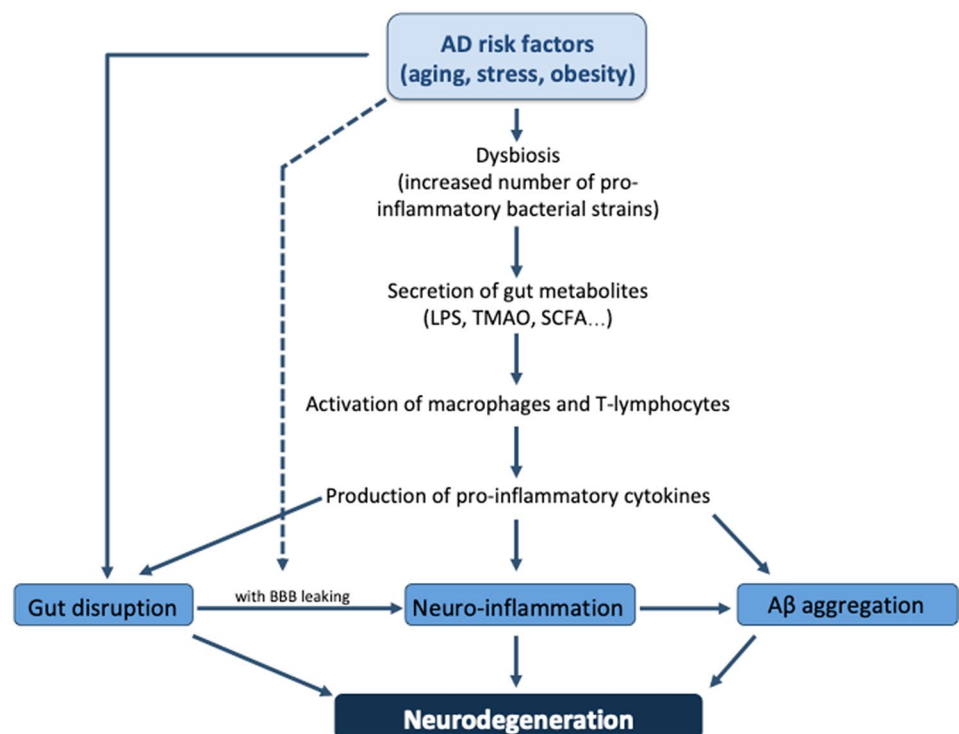
cytokines could enter the CNS in BBB leaking situations and induce neuroinflammation through activation of microglia (Erny et al. 2015) and astrocytes (Rothhammer et al. 2016).

It has been hypothesized that gut leaking could be the underlying mechanism linking obesity and AD. According to this hypothesis, in a study performed in mice under a HFD, a profound gut microbiota alteration was observed (Cani et al. 2008). Moreover the group treated with HFD showed elevated gut permeability, presumably due to the decreased expression of tight junction proteins, i.e. zonulin (ZO-1) and occluding (OCL), increasing the circulating levels of the bacterial LPS and inflammatory markers like TNF-α and IL-1. Interestingly, the administration of oral antibiotics normalized gut microbiota diversity and gut permeability by increasing the expression of both ZO-1 and OCL (Cani et al. 2008). In line with this idea, another study found that subjects with neurodegeneration had increased circulating LPS and monocyte activation levels compared to controls (Zhang et al. 2009). Since it is recognized that the BBB is disrupted in AD and this can result in anomalous microglial activation and brain inflammation, the combination of impaired gut permeability could also initiate pathogenic signals between the gut microbiota and the CNS. Indeed, microbial dysbiosis that alters the permeability of the gut can cause a systemic inflammatory state that can strengthen the usual neuro-inflammatory reactions observed in AD (Calsolaro and Edison 2016; Zhao et al. 2017a, b; Spielman et al. 2018).

Apart from the impact on gut permeability, it has been suggested that the intestinal microbiome could have a direct effect on AD biomarkers too (Spielman et al. 2018). Indeed, a recent study found a positive association between a pattern of around 50 microbial metabolites and the onset of AD and cognitive impairment (Xu and Wang 2016). Noteworthy, TMAO was among the most elevated microbial metabolites; TMAO is a molecule which has been linked to the consumption of animal fats, therefore supporting the idea that HFD can be considered as a risk factor for AD so they can induce gut microbial dysbiosis, which subsequently exerts several pro-inflammatory and pathogenetic functions.

Inflammation

According to a recent hypothesis, the composition of the gut microbiota is able to influence AD neuroinflammation. Specifically, it has been suggested that in AD pathology, the alteration of gut microbiota, altering the intestinal permeability, can induce an inflammatory condition not only in the gut, but also in the CNS, since the pro-inflammatory cytokines can get into the bloodstream and impact the brain (Kelly et al. 2015; Luca et al. 2015).

A recent study conducted in APP/PS1 mice found that the amount of circulating inflammatory cytokines released by gut bacteria was modified by a high-dose antibiotic cocktail (Minter et al. 2016). Furthermore, the authors assessed some of those cytokine levels in lymphocyte and splenic cells and concluded that there was no change in their levels, which reinforces the idea that the signal molecules generated by the gut microbiota influence brain homeostasis.

Similarly, Cattaneo et al. investigated the connection between gut bacteria and AD, demonstrating a connection between cognitive deficiencies, brain amyloid levels and the presence of inflammatory markers in the circulation (Cattaneo et al. 2017). According to this study, AD patients with cognitive impairment had greater circulating levels of pro-inflammatory cytokines, i.e., CXCL2, IL-6, IL-1β and NLRP3 and decreased levels of the anti-inflammatory cytokine IL-10. Interestingly, these cytokine level alterations correlated positively with *Escherichia/Shigella* amount. In consequence, they concluded that gut dysbiosis, with higher levels of pro-inflammatory (*Escherichia/Shigella*) and lower levels of anti-inflammatory (*Eubacterium rectale*) bacteria, may play a crucial role in AD cognitive alterations (Cattaneo et al. 2017).

An important issue is that many gut bacteria secrete LPS. LPS is the key component of gram-negative bacteria's outer cell membrane, which may induce neuro-inflammatory reactions in the case of penetration from the intestinal cavity into the bloodstream. Although in healthy conditions LPS is unable to access the brain, in situations in which BBB permeability is increased, such as neurodegenerative diseases, LPS could reach the CNS. In this line, post-mortem studies performed in AD patients have shown that LPS levels in the hippocampus and cortex are two to three times greater than in elderly people of the same age without cognitive alterations (Zhao et al. 2017a, b). Moreover, intraventricular administration of LPS in mice over 4 weeks may cause nerve cell death, chronic neuroinflammation and synaptic plasticity impairment of the neurons of the hippocampus (Hauss-Wegrzyniak and Wenk 2002).

Microglia, cells that are considered the brain resident macrophages, play a crucial role on brain inflammation. LPS released by bacteria can activate NFκB in human primary microglial cells (Zhao and Lukiw 2018), a pro-inflammatory transcription factor involved in the onset and development of AD. NFκB is able to induce transcription of pro-inflammatory miRNAs like miRNA-155, miRNA-146a, miRNA-125b, miRNA-34a and miRNA-9, inducing neuro-inflammatory factors and inhibiting phagocytosis (Zhao and Lukiw 2018). Indeed, it has been shown that micro-RNA-34a inhibits TREM2 expression, disrupting microglia phagocytic potential and increasing Aβ$_{42}$ accumulation (Bhattacharjee et al. 2016).

Inflammatory mediators enter the CNS via the circulatory system as well as the lymphatic system linking the CNS and the digestive system (Louveau et al. 2015; Saksida et al. 2017). It has been shown that in the 5xFAD AD mouse model the number of T helper (Th) $CD4^+$ cells is significantly increased in gut-associated lymphoid tissues (GALT) (Saksida et al. 2017). Besides this phenotypic characterization, the authors observed that the concentration of IL-17 per cell in transgenic mice was substantially lower. IL-17-expressing Th cells migrate to the CNS throughout the GALT; and this is essential for neurodegeneration because of their interactions with microglia that can contribute to the clearance of Aβ molecules and tau aggregation (Koutrolos et al. 2014; Wekerle 2016).

Having demonstrated the interaction between the gut microbiota and the inflammatory profile, it has been questioned whether the restoration of gut microbiota by the administration of probiotics could be an efficient strategy for AD treatment. This issue has been studied in different AD experimental models. For example, the administration of SLAB51, a probiotic formulation, to the 3xTg-AD mouse model over 16 weeks decreased pro-inflammatory (IL1a, IL1b, IL2, IL12, IFNγ and TNFα) and elevated anti-inflammatory cytokine (IL4, IL6….) plasma levels (Bonfili et al. 2017). Other studies have also linked probiotics to a decrease in levels of pro-inflammatory cytokines such as IL-6, IL-1b and TNF-α (Rincón et al. 2014; Wang et al. 2015). They were also associated with increased levels of natural killer cells, activated lymphocytes, and phagocytosis (Pistollato et al. 2016). In addition, another study evaluated the effects of Fructooligosaccharide (FOS) on inflammation, Aβ accumulation and behavioral disorders, energy metabolism and the antioxidative system in Sprague-Dawley AD models (Chen et al. 2017). This work found that elevated rates of pro-inflammatory cytokines were restored with FOS therapy, promoting the development of *Bifidobacteria* and *Lactobacilli*, whose metabolites may increase plasma levels of anti-inflammatory cytokines (Bonfili et al. 2017). Moreover, the use of probiotics containing *Lactobacillus* has been shown to ameliorate anxiety and decrease memory defects related to Western diets (Gareau 2014).

Abeta Acumulation

The most important hallmarks of AD pathogenesis are tau aggregations and Aβ. Several studies have suggested a plausible link between gut microbiota and brain Aβ accumulation.

In a previously mentioned study performed by Minter et al. (2016) (see Sect. 4.1.), the authors evaluated the effects of the altered gut microbiome on Aβ accumulation and found that APP/PS1 mice treated with an antibiotics cocktail exhibit reduced Aβ load and plaque size, while the soluble Aβ peptide appeared elevated, which suggest insoluble Aβ plaque degradation increased.

The gut microbiome, which is mainly located in the colon and the ileum, is able to produce short-chain fatty acids (SCFAs) which are biologically active and may cross the BBB, by fermenting fibrous foods. Several SCFAs have been studied and it has been observed that they trigger the pathogenesis of AD by altering the aggregations of tau and Aβ (Cummings et al. 1987; Macfarlane and Macfarlane 2012). In an in vitro study (Ho et al. 2018) the authors found that butyric acid, propionic acid and valeric acid were able to inhibit $Aβ_{40}$ oligomerization, valeric acid showing the strongest inhibitory effect. In addition, the study determined that only valeric acid administration completely inhibited $Aβ_{42}$ oligomer formation; afterwards, the authors discovered that both butyric acid and valeric acid were able to inhibit the conversion of $Aβ_{40}$ monomers to Aβ fibrils. In conclusion, this study demonstrated that reduction of the amount of the anti-inflammatory bacteria and the subsequent decrease in the levels of secreted beneficial metabolites might enhance Aβ accumulation in the brain. Apart from the *in vitro* study, an *in vivo* study (Kobayashi et al. 2017) found that behavioral and working memory deficits in an AD model induced by intracerebral $Aβ_{25\text{-}35}$ injection were ameliorated by acetate. SCFA-induced changes in Aβ accumulation could be due to the fact that valeric acid and isovaleric acid, isobutyric acid and butyric acid, propionic acid, acetic acid and formic acid have been found to disturb the activation of microglia. The gut microbiota can control microglial maturation and activation and thus in cases having impaired gut microbiota, microglia maturation and phagocytosis capacity for tau and Aβ decreases (Erny et al. 2015). Martins and Binosha Fernando (2014) have claimed that butyric acid can normalize the excessive histone acetylation by inhibiting histone deacetylase in microglia; butyric acid thereby may increase the number of microglia, which leads to a decrease in aberrant levels of inflammation and could increase Aβ phagocytosis.

Moreover, $Aβ_{42}$ levels in mice increase with the intraperitoneal administration of LPS (Kahn et al. 2012), that could be due to the disruption of Aβ transport through the BBB, raising its influx and reducing efflux (Jaeger et al. 2009). Furthermore, in vitro studies showed that endotoxins secreted by *Escherichia coli* strains accelerate fibril formation and Aβ aggregation (Asti and Gioglio 2014). Finally, it has also been shown that intraventricular administration of LPS in combination with ascorbic acid increases the intraneuronal Aβ (Hauss-Wegrzyniak and Wenk 2002).

Although these studies show compelling evidence, further studies are necessary to demonstrate the gut microbiota metabolites' effects on Aβ accumulation, brain inflammation and vascular degeneration, so that the multiple ways intestinal metabolites and AD interact can be fully understood.

Conclusion

The present review highlights the hypothesis wherein the gut microbiome may affect the pathogenesis of AD. Emerging evidence shows that there is a relationship between the biology of AD risk factors, such as aging or obesity, and the pathophysiology of AD. Risk factors can induce microbiota dysbiosis and raise pro-inflammatory bacteria levels over anti-inflammatory bacteria levels. At that point, bacterial metabolites promote gut leaking, inducing systemic and CSN inflammation, which results in Aβ accumulation and subsequent neurodegeneration (Fig. 1). There is emerging evidence in the literature showing the effect that global microbiome composition or targeted strains can exert on cognition. Based in this idea, it is tempting to speculate that restoring gut microbiota with probiotics or by fecal microbiota transplantation could be a promising therapeutic strategy for neurodegenerative diseases. Indeed, numerous studies suggest that a healthy microbiota helps to maintain brain homeostasis by lowering inflammation in the CNS, vascular pathology and the aggregations of misfolded proteins. Nevertheless, more human studies are required to check if the benefits observed in animals are also applicable in humans and demonstrate if these beneficial effects are due to changes in the microbiome or the action that probiotics exert as dietary supplements.

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