Introduction

The brain-gut axis reflects the bidirectional, constant communication between the central nervous system (CNS) and the gastrointestinal tract. There is also a growing body of evidence that the intestinal microbiota influences the brain-gut interactions in different points of time (from early life to neurodegeneration), as well as at different levels (from the gut lumen to the CNS). The importance of microbiota impact on the brain led to broadening the term to “brain-gut-microbiota axis.” The mechanisms of this communication include neural, immune, endocrine, and metabolic signaling. The neural network controlling gastrointestinal function—the enteric nervous system (ENS)—has the ability either to work independently or to be influenced by the CNS via sympathetic (prevertebral ganglia) and parasympathetic (the vagus nerve) signaling. The results of animal studies using germ-free mice point to the key role of gut microbiota in early brain development and adult neurogenesis.

In the elderly, hyperstimulation of the immune system results in chronic, low-grade state of inflammation (“inflammaging”). It may be associated with persistent inflammatory state of the gut mucosa evoked by age-related alterations in the gut microbiota composition characterized by its decreased diversity and stability. This leads to
the gut barrier breakdown, further increase of proinflammatory cytokines and bacteria-derived products in the circulation, the blood-brain barrier impairment and neuroinflammation. Apart from protecting against infection, the immune system influences neural function and development. The results of studies in germ-free mice confirm microbiota impact on microglia maturation. This could be mediated by short chain fatty acids (SCFAs) which are products of bacterial metabolism. Similarly, specific products of microbial tryptophan metabolism modulate astrocyte activity via aryl hydrocarbon receptors. Microbiota influences peripheral immune cell activation and cytokine profile, which affect systemic and CNS inflammation and injury, but also neurodevelopment. A recently identified network of lymphatic vessels in the meningeal spaces connects peripheral lymphatic tissues to the CNS.

In addition, the gut microbiota may affect the CNS function via direct synthesis of various neurotransmitters and neuromodulators like serotonin, dopamine, or SCFAs. Importantly, the gut microbiota signaling may modulate the function of intestinal enterochromaffin cells, which produce different hormones and neurotransmitters including serotonin. Disturbances along the brain-gut-microbiota axis may significantly contribute to the pathogenesis of neurodegenerative disorders such as Alzheimer’s disease (AD).

AD is the most frequent cause of dementia characterized by a progressive decline in cognitive function. The key feature of the disease is deposition of amyloid beta (Aβ) followed by formation of plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. Those deposits trigger neuroinflammation leading to synapse loss and neuronal death. It is still not well-known what triggers amyloid plaque formation, but the gut microbiota plays certainly an important role in the process. Regarding tau, it is a highly soluble protein modulating the stability of axonal microtubules. According to the tau hypothesis, altered and aggregated forms of this protein appear to act as toxic stimuli contributing to neurodegeneration.

AD is classified based on the age of onset into early-onset (EOAD) starting before the age of 65 and late-onset (LOAD) beginning above that age. The EOAD accounting for 1-5% of all cases is in majority associated with the mutations in APP, PSEN1, and PSEN2 genes with autosomal dominant inheritance. Depending on the mutations, the consequences are: an increase in total Aβ production, an increase in more amyloidogenic and prone to aggregation Aβ42 production or a change in amino acid sequence resulting in increased aggregation properties. The increased amount or aggregation propensity of Aβ is sufficient to cause AD, while Aβ aggregation is critical for the pathogenesis of the disease. The majority of AD cases are its LOAD type, where different genes contribute to susceptibility for the disease. Those genes code proteins which are involved in amyloid precursor protein (APP) metabolism, immune response, inflammation, intracellular trafficking, or lipid metabolism, indicating the potential pathogenetic factors. Other, non-genetic, risk factors for LOAD encompass cerebrovascular disease, brain injury, hypertension, type 2 diabetes, and obesity.

The review presents recent data on the role of brain-gut-microbiota axis dysregulation in the pathogenesis of AD based on the results from animal studies and available clinical observations. Potential therapeutic implications of the gut microbiota modulation in AD are also briefly discussed.

**Amyloid Plaque Formation**

**Central Nervous System**

The amyloid plaques are composed mainly of Aβ which is a cleavage product of APP. This transmembrane protein is involved in various biological processes such as neuronal development, signaling, or intracellular transport. APP is processed by secretases in the non-amyloidogenic pathway (α- and γ-secretase) or amyloidogenic pathway (β- and γ-secretase). The amyloidogenic pathway creates Aβ peptides of different lengths, among which most frequent are Aβ40, and less abundant, but more neurotoxic Aβ42 peptides that form the core of the plaque. Those peptides can aggregate to form oligomers, protofibrils, and fibrils that deposit into senile plaques, the intermediate forms being the most neurotoxic (Fig. 1). Monomeric and oligomeric structures are bonded to the ends of the initial seed, which finally breaks generating in this way new amyloid seeds that makes the process self-propagating. The process of seed formation (nucleation phase) is the most time-consuming step, thermodynamically unfavorable and may not occur in physiological conditions. In vitro, the time that precedes protein aggregation can be greatly shortened by the addition of exogenous seeds.

Interestingly, Aβ has recently been recognized as antimicrobial peptide (AMP), a part of the innate immune system. In addition, while monomeric Aβ shows little antimicrobial activity, its capability of aggregation allows to form antimicrobial pore-forming structures. The process of amyloid formation includes myeloid differentiation primary response 88 (MyD88) pathway activated by toll-like receptor 2 (TLR2). MyD88 is a universal adaptor protein used by almost all TLRs, except for TLR3, to activate transcrip-
tion factors such as nuclear factor kappa B (NF-κB). It has been shown that MyD88 deficiency ameliorates β-amyloidosis in an animal model of AD. The generated TNF-α in conjugation with TNF-α converting enzyme becomes α-secretase, splitting APP. Then, NF-κB produced in this process together with Aβ converting enzyme activates β- and γ-secretases forming Aβ. The normally protective Aβ function and harmful properties in dysregulated state is consistent with observations concerning other human AMPs.

Enteric Nervous System

The ENS is the intrinsic nervous system of the gastrointestinal tract. Its neurons are organized in microcircuits allowing for modulation of gastrointestinal function independently of the CNS, although the systems are interconnected and influence one another. This connection also allows for the disease spreading. In Parkinson’s disease (PD) gastrointestinal dysfunction is present in almost 80% of the patients, preceding motor dysfunction. In fact, α-synucleinopathy of the ENS has been suggested to be an early indicator of PD pathology. The regular APP expression in the ENS supports the theory of the ENS involvement also in AD. The APP transgenic mice develop accumulation of Aβ in the enteric neurons leading to a decrease in enteric neuron abundance, dysmotility, and increased vulnerability to inflammation. Preliminary data confirm that changes in the ENS in APP overexpressing transgenic mice correlate with the disease expression.

The Role of Gut Microbiota in the Development of Alzheimer’s Disease

Bacterial Amyloids

The gut microbiota is a source of a significant amount of amyloids. The best studied bacterial amyloid is curli produced by Escherichia coli. The production of amyloid proteins helps bacterial cells to bind to each other forming biofilms and to resist destruction by physical or immune factors. Although bacterial amyloids differ from the CNS amyloids in their primary structure, they share similarities in their tertiary structure. The exposure to bacterial amyloid proteins in the gut may cause priming of the immune system, consequently enhancing immune response to endogenous production of neuronal amyloid in the brain. In the pioneer study by Chen et al. rats exposed to curli-producing E. coli displayed increased neuronal alpha-synuclein (α-syn) deposition in both the gut and brain, and enhanced microgliosis and astrogliosis compared to rats exposed to bacteria without the ability to produce curli. Moreover, in the brain of animals exposed to curli-producing bacteria an increased expression of TLR2, II-6, and TNF was found. Friedland and Chapman have even proposed a new term “mapranosis” to describe the process (“-osis”) of microbiota-associated proteopathy and neuroinflammation. Through molecular mimicry bacterial amyloids may act as prion proteins, eliciting cross-seeding, in which one amyloidogenic protein (curli, tau, Aβ, α-syn, and prion) causes...
another (eg, host proteins with a different primary structure) to adopt pathogenic β-sheet structure. Cross-seeding of amyloidogenic proteins by bacterial amyloids has been documented both in vivo and in vitro.26,29

**Lipopolysaccharides**

An experimental study in an animal model has shown that injection of bacterial lipopolysaccharide (LPS) into the fourth ventricle of the brain reproduces many of the inflammatory and pathological features seen in AD.30 Moreover, the injection of LPS into the peritoneal cavity of mice has led to prolonged elevation of Aβ in the hippocampal region resulting in cognitive defects.31 The results of in vitro studies confirmed that bacterial LPS promotes amyloid fibrillogenesis.32 It is also known that LPS is capable to induce a more pathogenic β-pleated sheet conformation of prion amyloids.33

Recently, LPS presence has been detected in the hippocampus and neocortex brain lysates from AD patients.34 Most of LPS is aggregated in the perinuclear region35 significantly reducing output of DNA transcription products.36 Moreover, LPS colocalizes with Aβ1-40/42 in amyloid plaques and around blood vessels.37 The plasma concentration of LPS in AD patients is also significantly higher than in healthy people.38 Other bacterial products such as E.coli pili protein39 or nucleic acids40 were also found in human brain and were more prevalent in AD patients.

LPS activates TLRs expressed in microglial cells of the innate immune system, which recognize common damage or pathogen associated molecular patterns.40 Through interactions with CD14 and MD-2 proteins, LPS activates TLR4 receptor promoting inflammatory response.41 The TLR4 activation by CD14 also mediates the inflammatory response to Aβ42 and S100A8/A9 proteins.43 The other LPS-activated receptor, TLR2, is also triggered by Aβ and bacterial amyloids.44 These interactions support the concept of molecular mimicry of those particles.

**Gut Inflammation and Gut Barrier Dysfunction**

Intestinal inflammatory process causes migration of polymorphonuclear cells from the circulation to the gut mucosa or even further to the gut lumen, in the case of mucosal architecture disturbance. The process of intestinal inflammation can be indirectly measured by assessing stool calprotectin concentration. This small calcium-binding protein which is a heterodimer of S100A8/A9 contributes to 60% of cytosol protein content of neutrophils and has antimicrobial properties.45 The S100A8 and S100A9 proteins have intrinsically amyloidogenic amino acid sequences and can form amyloid oligomers and fibrils, which closely resemble amyloid polypeptides such as Aβ and α-syn, and in vitro monomeric and dimeric S100A9 may induce Aβ fibrilization.46,47 S100A9 secreted by macrophages and microglia during amyloid plaque formation also induces its expression in neuronal cells and these may further activate microglia via TLR4 and receptor for advanced glycation end products (RAGE) pathways.48 Calprotectin levels are significantly increased in the cerebrospinal fluid and the brain of AD patients, which promotes its amyloid aggregation and co-aggregation with Aβ.49 The elevated fecal calprotectin level was found in nearly 70% of AD patients in one study, and it was assumed that it could translocate into circulation and contribute to neuroinflammation.50 Analogical changes in the intestinal epithelial barrier integrity and gut immune system activation expressed by elevated fecal calprotectin have also been reported in PD patients.51 It is possible that this intestinal source of calcium binding proteins may contribute to amyloid fibril formation in the gut or directly in the brain. Gut inflammation and dysbiosis is directly associated with gut barrier dysfunction and increased intestinal permeability ("leaky gut") may contribute to the process of neurodegeneration.52,53

The intestinal barrier is composed of the mucus layer, intestinal epithelium, and lamina propria. Interruption of this barrier leads to increased permeability causing translocation of bacteria (process known as atopobiosis) and harmful substances into the bloodstream.50-52 A very high number of bacteria localized in the colon is physically separated from the host by a thick, impenetrable mucus layer. Contrary, in the small intestine the mucus allows particles as large as bacteria to penetrate, although high concentrations of antibacterial products prevent bacteria from reaching the cell surface. The microbiota composition determines mucus layer properties influencing its permeability.53 The abundance of mucin-degrading bacteria Akkermansia muciniphila improves the gut barrier function, reduces obesity and systemic inflammation.54,55 Some probiotic strains such as Lactobacillus plantarum, E. coli Nissle, and Bifidobacterium infantis enhance intestinal barrier increasing expression of proteins forming tight junctions.56 Other bacterial products, exotoxins, disrupt epithelial cell integrity. Different pathogenic E. coli strains, Salmonella, Shigella, Helicobacter pylori, Vibrio, or Clostridium mediate changes in tight junctions.57 The exotoxin of Bacteroides fragilis disrupts adherence junctions by cleavage of cell adhesion molecule—E-cadherin.58 Damaged tight junction structures and increased intestinal permeability connected with shifted microbiota profile were also found in a mouse model of amyotrophic lateral sclerosis—another neurodegenerative disorder connected with amyloid deposition.59 In addition to alterations in the gut microbiota composition,
the increased amount of bacteria in the small intestine also influences permeability, as seen in small intestinal bacterial overgrowth (SIBO). There are some preliminary results showing the increased SIBO prevalence in AD patients.

Neuroinflammation

Neuroinflammation expressed by activation of microglia, reactive astrocytes and complement in the vicinity of amyloid plaques is a well-known feature of AD. The increased inflammatory response is also detected in blood and cerebrospinal fluid of AD patients.

The physiological clearance of Aβ is very efficient. In the early stages of AD low Aβ concentration activates microglia through CD14 and TLR promoting phagocytosis and amyloid clearance. The process of oligomerization significantly increases amyloid retention. Excessive microglial stimulation and increased neuroinflammatory signaling through NF-κB, proinflammatory cytokines and reactive oxidative and nitrosative stressors lead to neuronal and glial cell death. Another consequence of neuroinflammation is downregulation of triggering receptor expressed on myeloid cells 2 which further impairs phagocytosis leading to the accumulation of Aβ42.

An altered threshold for microglial activation seen in neurodegeneration and aging may be a consequence of repeated or chronic systemic infection. Repeated systemic exposure to LPS in mice induced microglial priming and prolonged cytokine production. Subsequent intracerebral injection of LPS in previously infected mice resulted in exaggerated inflammatory response. It is possible that microglial cells primed with bacterial amyloid may be more responsive to Aβ in the brain.

Amyloid Spreading

The Aβ seeding and propagation is well documented with experiments based on animal models. The brain infusion with Aβ extract from AD brain leads to amyloid formation and the seeding of amyloid in one brain region spreads to neuroanatomically connected regions of the brain. When a small amount of insoluble, aggregation-prone Aβ42 is seeded it acts as a template promoting otherwise soluble and abundant Aβ40 oligomerization and spreading. The amount of the soluble target peptide in the brain is the most important feature for toxic species formation. Interestingly, intraperitoneal injection of Aβ extracts also leads to amyloid deposition in the brain. The potential mechanisms of amyloid spreading include neuron-to-neuron or distal neuron spreading, direct blood-brain barrier crossing, or via other cells as astrocytes, fibroblasts, microglia and immune system cells.

Neuronal Transport

An amyloid protein—α-syn, forming intracellular deposits constituting a hallmark of PD—was found in the myenteric neurons of the gut wall. The protein may gain access to neuronal cells from the gut lumen via epithelial microfold cells (M cells) and dendritic cells in the Peyr’s patches of the small intestine. The dorsal motor nucleus of the vagus nerve is one of the first affected brain regions containing α-syn deposits. These data suggest that misfolded proteins spread along the gut-brain axis. The accumulation of misfolded proteins in neuronal cells and subsequent cell death result in release of misfolded proteins into the intracellular space. Moreover, living cells may release the proteins via exocytosis. These proteins are then taken up by other neurons leading to local transmission of misfolded proteins. Absorbed misfolded proteins may then induce templated conformational changes in susceptible proteins of the cell. The process may spread across neuronal network via synapses. Propagation of the misfolded tau protein from the outside to the inside of the cell, subsequent intracellular protein misfolding, aggregation and transfer to other co-cultured cells were observed in vitro. In addition to extracellular Aβ deposition, the protein accumulates inside neurons. This process is observed early in the disease course, preceding neurofibrillary tangles formation and extracellular Aβ deposition. Regarding previously mentioned in vivo observations of Aβ spreading across neuronal networks, the potential role of neuronal transport in amyloid misfolding propagation can be assumed.

Compromised Blood-Brain Barrier

The blood-brain barrier formed by brain endothelial cells and pericytes separates the CNS from blood-derived molecules, pathogens, and cells. In normal conditions soluble Aβ is transported from the blood to the brain via RAGE and via low-density lipoprotein receptor-related protein 1 in the opposite direction.

In post-mortem studies in AD patients, the blood-brain barrier damage and accumulation of blood derived products in the brain were demonstrated. This process was confirmed by MRI studies of the living human brain, which showed age-dependent blood-brain barrier breakdown in the hippocampus associated with learning and memory. The breakdown was worse in mild cognitive impairment and correlated with pericyte injury shown by cerebrospinal fluid analysis. The pericyte injury is accelerated by the ε4 allele of theapolipoprotein E gene, the major genetic risk factor for LOAD.
Gut Microbiota in Animal Models of Alzheimer’s Disease

The contribution of gut microbiota to the pathogenesis of AD is well depicted in animal models of AD (Table 1). In 2016, for the first time, Minter et al reported that antibiotic-induced perturbations in the gut microbiota diversity influence neuroinflammation and amyloidosis in a murine model of AD. The results of another study, in which sequencing bacterial 16S ribosomal RNA from

| AD model             | Main findings                                                                                                                                                                                                 | Reference   |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| APP/PS1 mice         | Antibiotic-treated Tg mice display alterations in the gastrointestinal microbiome composition (expansion of Lachnospiraceae) and circulating inflammatory mediators; antibiotic-treated male Tg mice display reduced Aβ deposition but increased soluble Aβ levels, reduced reactive glosis surrounding Aβ plaques and significantly altered microglial morphology Early post-natal antibiotic treatment results in long-term alterations of gut microbial genera (expansion of Lachnospiraceae) and reduction in brain Aβ deposition in aged Tg mice; plaque-localized microglia and astrocytes reduced in antibiotic-exposed mice | Minter et al, 2016 |
| 3×Tg-AD mice         | Probiotic treatment influenced plasma concentration of inflammatory cytokines and gut hormones, and induced also a reduction in brain damage and accumulation of Aβ aggregates | Bonfili et al, 2017 |
| 5×FAD mice           | Changes in fecal microbiota composition along with age; reduced trypsin amount in fecal proteins; human APP expressed not only in the brain but also in the gut tissue | Brandscheid et al, 2017 |
| ApoE−/− mice         | Active invasion of Porphyromonas gingivalis and infection-induced complement activation in ApoE−/− mice brains | Poole et al, 2015 |
| AD mouse model (ICV injection of Aβ) | Oral administration of Bifidobacterium breve strain A1 prevented Aβ-induced cognitive dysfunction and suppressed Aβ-induced changes in gene expression in the hippocampus; B. breve A1 did not affect the gut microbiota, but significantly increased plasma acetate levels; non-viable B. breve A1 and acetate partially ameliorated behavioral deficits | Kobayashi et al, 2017 |
| AD rat model (IP injection of D-galactosea) | Lactobacillus plantarum MTCC 1325 restored acetylcholine level, attenuated Aβ plaque formation, and ameliorated cognitive function | Nimgampalle et al, 2017 |
| AD rat model (intrahippocampal injection of Aβ) | Lactobacillus and Bifidobacterium ameliorated memory and learning deficits and oxidative stress | Athari et al, 2018 |
| Transgenic flies: Drosophila | Enterobacteria infection exacerbates progression of AD by promoting immune hemocyte recruitment to the brain; genetic depletion of hemocytes attenuates neuroinflammation and alleviates neurodegeneration | Wu et al, 2017 |

\(^a\)D-galactose administration induces brain aging.

AD, Alzheimer’s disease; APP, amyloid precursor protein; PS1, presenilin-1; APP/PS1 mice, double transgenic mice harboring mutations in APP and PS1 genes; Tg, transgenic; Aβ, amyloid beta; WT, wild type; 3×Tg-AD mice, triple transgenic mice displaying both plaque and tangle pathologies; 5×FAD mice, mice carrying 5 familial AD mutations in APP and PS1 transgenes; ApoE−/− mice, apolipoprotein E-deficient mice; ICV, intracerebroventricular; IP, intraperitoneal.
fecal samples of APP transgenic mice was performed, revealed significant differences in the gut microbiota composition compared to that of control wild type mice.7 These changes included an increase in Rikenellaceae and a decrease in Allobaculum and Akkermansia.79 The reduced abundance of Akkermansia has previously been associated with obesity and type 2 diabetes,57 which are known risk factors for developing dementia.89 Moreover, its relative abundance negatively correlated with the amount of Aβ42 in the brain.79 In germ-free APP transgenic mice cerebral Aβ was significantly reduced. In addition, reduced microgliosis and changes in cytokine profile were observed. Recolonization of the germ-free mice with conventionally raised APP transgenic mice microbiota increased cerebral Aβ pathology, and this increase was less effective when wild type mice microbiota was used.79 Similarly, germ-free mice overexpressing α-syn, used as a model of PD, developed reduced α-syn inclusions and microglial activation compared to the controls.88 These features were restored by reintroduction of microbiota (especially those derived from PD patient donors) or by addition of SCFAs—products of bacterial metabolism. Interestingly, recolonization with bacteria derived from PD patients enhanced physical impairments, which was connected with different SCFA profile produced by this bacterial strains.91

Clinical Data on the Gut Dysbiosis in Alzheimer’s Disease

Many human studies implicated microbiota presence in the brain in the etiology of AD,57 although most of the studies were conducted post-mortem, diminishing the evidence for their causative role in AD pathology (Table 2).14,49,60,90-102 These pathogens include Chlamydia pneumoniae,95 Borrelia burgdorferi, and other spirochetes88 or herpes simplex virus type 1.103 Also H. pylori infection was linked with AD.96 AD patients with H. pylori infection had lower Mini-Mental State Examination scores corresponding with more serious cognitive impairment.97 A recently published study has revealed an increase in the abundance of Helicobacter and Odoribacter and a decreased level of Prevotella in APP transgenic mice.40 Also, in PD patients H. pylori infection was linked with disease severity and progression.98 The significantly increased levels of H. pylori-specific IgG antibody in the cerebrospinal fluid and serum of AD patients were found.97 Moreover, the titer of this antibody correlated with the degree of severity of AD.97 However, in a recent population-based cohort including 4215 participants, the association between H. pylori serology and dementia risk was not confirmed.104 A potential mechanism of bacterial translocation to the brain is transmigration of infected monocytes and T cells through the compromised blood-brain barrier.105 Another possibility is that the entry point for pathogens might be the olfactory nerves, as their plasma membrane is the only barrier between the nasal cavity and the brain.26 Moreover, poor dental hygiene has been linked to AD.97 Although the data are limited, some studies demonstrated elevated serum antibodies to bacteria associated to periodontitis in AD patients.100,101

The influence of gut microbiota on brain function is being constantly investigated, and the mechanisms of the brain-gut-microbiota axis contribution to pathogenesis of stress-related conditions or brain disorders is being discovered.106 In irritable bowel syndrome, where altered microbiota is one of key pathophysiological factors of the disease,106 some preliminary results indicate that there is also increased risk for either AD or non-AD dementia development.107 Other conditions, where the gut microbiota influence has been implicated, include autism, schizophrenia or multiple sclerosis.1,2,48,105

A recently conducted study revealed that the increased abundance of proinflammatory Escherichia/Shigella and decreased abundance of anti-inflammatory Eubacterium rectale were possibly associated with peripheral inflammation in patients with cognitive impairment and brain amyloidosis.60 In another study fecal microbiota compositions of AD and non-AD patients were compared.95 Fecal microbiota profile in AD patients was characterized by the reduced microbial diversity, decreased abundance of Firmicutes and Bifidobacterium and increased abundance of Bacteroidetes. The relative bacterial abundance correlated with the increase of cerebrospinal fluid markers of AD pathology.95 Neurodegenerative disorders usually reveal in advanced age, when the gut microbiota composition is influenced by variety of factors. Poor diet is associated with reduced microbial diversity, contributing to the increased local and systemic inflammation in the elderly. As mentioned in the introduction, the phenomenon is adequately named as “inflammaging”.2,3 Multiple comorbidities influence microbiota composition directly or by used medications such as antibiotics, metformin or proton pump inhibitors.2

Microbiota Modulation as a Therapeutic Target in Alzheimer’s Disease

A better understanding of the role of gut microbiota in the pathogenesis of AD and the close association between gut dysbiosis, increased intestinal permeability, and neurological dysfunction creates opportunity for potential therapeutic interventions.108 The results of numerous studies confirm the beneficial effect of probiotics
Table 2. Recent Clinical Data on the Role of Microbiota in the Pathogenesis of Alzheimer’s Disease

| Type of study | Number of subjects (M/F) | Main findings | Reference |
|---------------|---------------------------|---------------|-----------|
| Post-mortem brain samples | 10 AD (sex not specified) | LPS from periodontopathic *Porphyromonas gingivalis* present in AD brains | Poole et al, 2013 |
| | 10 C | Bacterial LPS present in AD brain lysates; mean LPS levels varied from 2-fold increase in the neocortex to 3-fold increase in the hippocampus in AD over age-matched controls | Zhao et al, 2017 |
| | 8 C (all F) | > 75% of all LPS signals associated with brain cell nuclei in AD (random association of LPS with Aβ deposits in the controls); LPS abundance greater than 7-fold in AD neocortex and > 21-fold in AD hippocampus | Zhao et al, 2017 |
| | 7 AD (all F) | LPS accumulates in neocortical neurons of AD brain and impairs transcription in human neuronal-glial primary co-cultures | Zhao et al, 2017 |
| | 7 C (all F) | LPS accumulates in neocortical neurons of AD brain and impairs transcription in human neuronal-glial primary co-cultures | Zhao et al, 2017 |
| | 15 AD (all F) | | |
| | 12 C (all F) | | |
| | 24 AD (9/15) | *Escherichia coli* K99 and LPS levels greater in AD brains; LPS colocalized with Aβ1-40/42 in amyloid plaques and around vessels in AD brain | Zhan et al, 2016 |
| | 18 C (10/8) | | |
| | 14 AD (3/11) | Increased bacterial populations in AD brain tissue showed by 16S rRNA sequencing | Emery et al, 2017 |
| | 12 C (10/2) | | |
| 5 AD | 5 C (sex-matched) | Typical intracellular and atypical extracellular *Chlamydia pneumoniae* antigens present in the frontal and temporal cortices of AD brain; C. pneumoniae, amyloid deposits, and neurofibrillary tangles present in the same regions of AD brain | Hammond et al, 2010 |
| | 10 AD | *Borrelia burgdorferi* specific DNA found in senile plaques | Miklossy et al, 2016 |
| | 4 C (sex not specified) | | |
| Living subjects | 25 AD (8/17) | Gut microbiota alterations characterized by reduced microbial diversity, decreased abundance of *Firmicutes* and *Bifidobacterium*, and increased abundance of *Bacteroidetes* | Vogt et al, 2017 |
| | 25 C (7/18) | | |
| | 18 AD (7/11) | Significantly higher levels of LPS in sALS and AD plasma specimens; a significant positive correlation between LPS plasma levels and degree of blood monocyte/macrophage activation in the disease groups | Zhang et al, 2009 |
| | 23 sALS (16/7) | | |
| | 18 healthy (12/6) | | |
| | 40 Amy (+) (20/20) | Increased abundance of proinflammatory gut microbiota taxon—*Escherichia/Shigella*, and a reduction in anti-inflammatory taxon—*Eubacterium rectale* possibly associated with a peripheral inflammatory state in Amy (+); a positive correlation between proinflammatory IL-1β, inflammasome complex (NLRP3), and CXCL2 with the abundance of *Escherichia/Shigella* and a negative correlation with the abundance of *E. rectale* | Cattaneo et al, 2017 |
| | 33 Amy (−) (15/18) | | |
| | 10 C (4/6) | | |
| | 50 AD (sex not specified) | The prevalence of *Helicobacter pylori* infection amounted to 85% in AD and 47% in C | Kountouras et al, 2006 |
| | 30 C | *H. pylori*-specific IgG antibody levels significantly increased in cerebrospinal fluid and serum of AD; Antibody titer correlated with the degree of AD severity | Kountouras et al, 2009 |
| | 27 AD (sex not specified) | | |
| | 27 C | | |
| | 53 AD (sex not specified) | Infection of *H. pylori* associated with a greater cognitive impairment in AD | Roubaud-Baudron et al, 2012 |
| | 38 cognitively normal healthy subjects (12/26) | Association between periodontal disease and brain Aβ load showed using 11C-PIB PET imaging | Kamer et al, 2015 |
FAECIUM and LACTOBACILLUS RHAMNOSUS reduce TNF-
with PD, multiple sclerosis and autisms, but not AD so far.
Its therapeutic potential has been reported in single cases of patients
exploring pathogenetic mechanisms of neurodegenerative disorders.

Reduced oxidative stress markers and induced antioxidant enzymes
and supplementation of these probiotic strains in animal studies
therapeutic potential of LACTOBACILLI and BIFIDOBACTION.

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The gut microbiota as the source of a large amount of amyloid, LPS, and other toxins, may contribute to systemic inflammation and disruption of physiological barriers. Bacteria or their products can move from the gastrointestinal tract and the oronasal cavity to the CNS, especially in the elderly. Bacterial amyloids may act as prion protein cross-seeding misfold-
ing and enhancing native amyloid aggregation. Moreover, gut microbiota products may prime microglia, enhancing inflammatory response in the CNS, which in turn results in pathologic microglial function, increased neurotoxicity and impaired amyloid clearance. Taking into account Aβ role as the antimicrobial peptide, infectious or sterile inflammatory factors may enhance Aβ formation through TLRs. The modulation of the gut microbiota composition can be used as a potential therapeutic target in AD.

Up to now, the data on the role of gut microbiota in AD and other neurodegenerative disorders are based on preclinical or cross-
The gut microbiota has been suggested to a variety of biological, social and environmental factors including the multi-dimensional nature of AD pathology, a potential reevaluation that may eventually result in a strategic breakthrough in the treatment and, more importantly, in the prevention of AD.

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