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REVIEW ARTICLE

# Microbiota Alterations in Alzheimer's Disease: Involvement of the Kynurenine Pathway and Inflammation

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## Abstract

Alzheimer's disease (AD) is a neurodegenerative disease considered the major cause of dementia in the elderly. The main pathophysiological features of the disease are neuronal loss (mainly cholinergic neurons), glutamatergic excitotoxicity, extracellular accumulation of amyloid beta, and intracellular neurofibrillary tangles. However, other pathophysiological features of the disease have emerged including neuroinflammation and dysregulation of the kynurenine pathway (KP). The intestinal microbiota is a large and diverse collection of microorganisms that play a crucial role in regulating host health. Recently, studies have highlighted that changes in intestinal microbiota contribute to brain dysfunction in various neurological diseases including AD. Studies suggest that microbiota compositions are altered in AD patients and animal models and that these changes may increase intestinal permeability and induce inflammation. Considering that microbiota can modulate the kynurenine pathway and in turn neuroinflammation, the gut microbiome may be a valuable target for the development of new disease-modifying therapies. The present review aims to link the interactions between AD, microbiota, and the KP.

**Keywords** Alzheimer's disease · Microbiota · Probiotics · Inflammation · Kynurenine pathway

## Alzheimer's Disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease that causes progressive loss of brain functions resulting in memory, spatial orientation, language, and behavioral deficits that leave patients dependent on caregivers (Howard et al. 2015; Prischmann 2016; Vickers et al. 2016).

### Alzheimer's Disease Etiology

The etiology of AD has not been fully elucidated, but multiple environmental and genetic factors appear to be involved. Several gene mutations have been implicated in the development of familial AD including amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) (Lanoiselee et al. 2017). However, in sporadic late-onset AD (LOAD), which accounts for over 90% of AD cases, apolipoprotein E (*APOE*) gene polymorphisms are the only known genetic risk factor consistently identified (Yu et al. 2014). Several other genes have been identified following genome-wide association studies including genes involved in the inflammatory response such as complement receptor 1 (CR1), CD33, membrane-spanning 4A (MS4A), clusterin (CLU), ATP-binding cassette sub-family A member 7 (ABCA7), and ephrin receptor A1 (Lambert et al. 2013). Genes related to microglia function such as inositol polyphosphate-5-phosphatase D (INPP5D) and genes related to endocytosis including phosphatidylinositol-binding clathrin assembly protein (PICALM), triggering receptor expressed on myeloid cells 1 and 2 (TREM1, TREM2), and sortilin related receptor 1 (SORL1) have also been reported (Lambert et al. 2013; Ridge et al. 2016).

Environmental factors related to the development of AD include gender, low levels of education, depression, diabetes, and low cognitive activity (Durazzo et al. 2014; Schipper 2011). However, aging is the main risk factor, with prevalence doubling every 5 years from the age of 65 (Savva et al. 2009). The prevalence of the disease is estimated as 0.7% in individuals among 60–64-year-olds and increases to 5.6% among

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70–79-year-olds, reaching approximately 38.6% in people aged 90 years or older (Dubois et al. 2016).

## Pathological Features of Alzheimer's Disease

Neuronal loss, amyloid beta (Aβ) accumulation, and neurofibrillary tangles (NFTs) are the histopathological hallmarks of the AD (Sery et al. 2013). Hyperphosphorylated tau protein is the major component of NFTs and accumulates in the somatodendritic compartment of neurons leading to a loss of stability and function of the neuronal cytoskeleton (Avila et al. 2010; Hernandez et al. 2013; Iqbal et al. 2009). Aβ peptide with 40 or 42 amino acids (Aβ40 and Aβ42) accumulates and form extracellular senile plaques following abnormal processing of the amyloid precursor protein (APP) (Buoso et al. 2010; Serrano-Pozo et al. 2011). These hallmarks are commonly observed in brain regions responsible for cognitive function such as the cerebral cortex, hippocampus, entorhinal cortex, and ventral striatum (Selkoe 2008).

Glutamatergic dysfunction occurs early in AD progression and is evident before the decline in cognitive abilities (Rudy et al. 2015; Scott et al. 2011). Glutamate is a key central nervous system (CNS) neurotransmitter and contributes to learning and memory formation through long-term potentiation (LTP) (Bliss and Collingridge 1993). However, at high concentrations extracellular glutamate can lead to cell death through the excessive activation of the N-methyl-D-aspartate (NMDA) receptor, a process known as glutamatergic excitotoxicity (Wang and Qin 2010). Abnormal activation of these signaling pathways may lead to synaptic dysfunction, activation of pro-apoptotic caspases, and activation of the calcium-dependent pathway of calpain causing neuronal loss (Crews and Masliah 2010; Morales-Cruz et al. 2014).

Neuroinflammation is another critical pathophysiological feature observed in the AD. Activation of microglia and astrocytes leads to the production of inflammatory mediators such as cytokines, chemokines, and reactive oxygen species (ROS) (Tan et al. 2013). Indeed, recent studies have demonstrated that the Aβ peptide can activate microglial pattern recognition receptors (PRRs) (Bachstetter et al. 2011; Lin et al. 2013). This neuroinflammation caused by the Aβ1–42 peptide initially occurs following activation of toll-like receptors 2, 4, and 6 (TLR) (Liu et al. 2012; Udan et al. 2008) and in turn induces the activation of the immune system and the production of inflammatory mediators (Cuello et al. 2010; Lin et al. 2013). An increase in pro-inflammatory cytokines was observed in serum, brain, and cerebrospinal fluid (CSF) of AD patients (Dursun et al. 2015; Jack et al. 2013; Zhang et al. 2013). Furthermore, several studies highlight correlations between the level of pro-inflammatory cytokines and cognitive decline (Harries et al. 2012; Solfrizzi et al. 2006; Westin et al. 2012).

## Intestinal Microbiota

The gut microbiota–brain axis comprises many fundamental elements including the CNS, neuroendocrine and neuroimmune systems, autonomic nervous system, enteric nervous system (ENS), and the intestinal microbiome (Moloney et al. 2014). A triad of neural, hormonal, and immunological lines of communication combines to allow the brain to influence the motor, sensory, autonomic, and secretory functions of the gastrointestinal tract (Kennedy et al. 2014). These same connections allow the gastrointestinal tract to affect brain function (Mayer 2011; Van der Leek et al. 2017) and although the reciprocal communication between ENS and the CNS is well described, the role of the intestinal microbiota within this system remains unclear.

Bacterial cells within the human body exceed human cells 10 to 1, and their total gene count exceeds that of the host more than 100-fold (Backhed et al. 2005; Ley et al. 2006). In addition to the production of neurotransmitters such as serotonin, dopamine, noradrenaline, and GABA (Clarke et al. 2014) results in numerous biological processes that would otherwise be unavailable to the host. For example, the production of indole following the metabolism of tryptophan (Trp) by tryptophanase, an enzyme not present in eukaryotic cells (Scherzer et al. 2009). Impacts of tryptophan-derived indoles are varied and include changes to oxidative stress, intestinal inflammation, hormone secretions, and the mucosal barrier (Lee et al. 2015) as discussed in the "Microbiota and Tryptophan Metabolism" section.

During human development different intrinsic and extrinsic factors can affect intestinal microbiota and it has been hypothesized that the consolidation of "a healthy/unhealthy microbiota" occurs between birth and early childhood and may contribute to the emergence of chronic diseases later in life (Junges et al. 2018).

## Microbial Metabolites and the Immune System

Microbial colonization plays an important role in the development of the immune system. For example, it has been shown that intestinal microbiota influences maturation and microglial function. In contrast to conventionally colonized controls, germ-free mice show an increase in the number of immature microglia in the gray and white matter of the cortex, corpus callosum, hippocampus, olfactory bulb, and cerebellum (Erny et al. 2015).

Furthermore, microbe-associated molecular pattern (MAMPs; e.g., lipopolysaccharides (LPS), bacterial lipoproteins (BLP), flagellin and CpG DNA) activates several cells of the immune system including macrophages, neutrophils, and dendritic cells. Once activated these cells produce pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, which target the brain through the blood-brain barrier (BBB) (Sampson and Mazmanian 2015) and are involved in the development and progression of AD and other neurodegenerative diseases (Heneka et al. 2014).

While humans are unable to degrade fiber, anaerobic commensal bacteria in the cecum and large intestine can ferment fiber resulting in the production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate (Fig. 2b) (Levy et al. 2016). SCFAs can promote differentiation of $CD4^+$ naive T cells in the gut into Th1, Th17, and Treg cells and interact with metabolite-sensing G protein–coupled receptors (GPR41, GPR43, and GPR109A) expressed in both gut epithelium and immune cells. This leads to anti-inflammatory effects (e.g., production of IL-10), secretion of hormones (e.g., GLP-1), and regulation of adipogenesis and lipolysis (Kim et al. 2014; Sun et al. 2018). Additionally, SCFAs act on intracellular targets including histone deacetylases (HDACs) (Singh et al. 2010) impacting a number of genes and proteins which are related to neuroprotection and neuroinflammation (Castellano et al. 2014; Garcez et al. 2018; Kannan et al. 2013).

Members of the gut microbiota synthesize vitamin K and metabolize most of the water-soluble B vitamins (LeBlanc et al. 2011) which have been closely related to the immune activation and neurodegenerative diseases (Bondi et al. 2008; Cobianchi et al. 2008; Ji et al. 2014; Shen and Ji 2015; Veber et al. 2006). This includes the microbial metabolite of vitamin B2 (riboflavin), 6-hydroxymethyl-8-D-ribityllumazine, which activates mucosa-associated invariant T (MAIT) cells and 6-formyl pterin (6-FP), a metabolite of vitamin B9, which binds to MHC-like protein 1 (MR1) (Patel et al. 2013; Zelante et al. 2013).

Bacteria-produced indoles activate the aryl hydrocarbon receptor (AhR; Fig. 2b) (Perdew and Babbs 1991). The AhR is essential for immune activation as shown by immunological deficits (including reduced resistance to bacteria and fungus infection) in *AhR-/-* mice (Shi et al. 2007). AhR is a ligand-activated transcription factor critical for maintaining intraepithelial lymphocytes (IELs) and innate lymphoid cells (ILCs) populations (Stockinger et al. 2014). AhR activation promotes the maintenance of type 3 innate lymphoid (ILC3) cells which strengthens the integrity of the intestinal mucosa following the secretion of IL-22 (Kiss et al. 2011; Lee et al. 2011) and has been shown to promote differentiation of T cells into Tregs (Mezrich et al. 2010). Finally, AhR activation inhibits NLRP3 expression, caspase-1 activation, and subsequent IL-1β secretion in mouse peritoneal macrophages (Huai et al. 2014). This has implications in AD as when the NLRP3 inflammasome is activated by Aβ peptide, this complex binds to the ASC adapter molecule which in turn activates caspase-1. The inflammasome cleaves the inactive forms of pro-IL-1β and pro-IL-18 forming mature cytokines and in turn activating neutrophils and macrophages amplifying the inflammatory response in AD (Heneka et al. 2015).

### Microbiota and Oxidative Stress

Oxidative stress plays an important role in AD pathology as pro-inflammatory cytokines and some kynurenine pathway (KP; see the "The Kynurenine Pathway and Alzheimer's Disease" section) metabolites trigger potent ROS bursts that damage neurons and glial cells (Castellano-Gonzalez et al. 2019; Li et al. 2016; Song et al. 2011).

It has been postulated that gut microbiota–host interactions may also influence the oxidative state of the CNS by interfering with the level of ROS and the antioxidant defense system (Dumitrescu et al. 2018). However, mechanisms are still unclear. For example, bacteria oxidize ammonia back to nitrites and nitrates, while *Lactobacteria*, *Bifidobacteria*, and *Escherichia coli* can convert nitrate and nitrite into nitric oxide (NO) (Oleskin et al. 2016). Elevated NO levels have been shown to increase the permeability of the BBB and react with superoxide forming peroxynitrite, a potent oxidizing agent, which contributes to neurotoxicity in AD (Heneka et al. 2014; Tse 2017). When NO and hydrogen peroxide ($H_2O_2$) are elevated and *L*-Trp levels are low (e.g., following the activation of IDO during inflammation) the heme peroxidase activity of IDO increases resulting in self-inactivation. This may highlight a mechanism by which T cell-mediated inflammation is enhanced following oxidative stress (Freewan et al. 2013).

Hydrogen ($H_2$) is highly diffusible bioactive gas produced by bacteria that has antiapoptotic, anti-inflammatory, and antioxidant properties (Ohta 2014). Reduced availability of $H_2$ has been observed to neurodegenerative disorders such as Parkinson's disease (Ostojic 2018). As microbiota (*Enterobacteriaceae* family and certain strains of the *Clostridium*) generate approximately 1 L of $H_2$ per day (Hung et al. 2011), it is probable that gut dysbiosis may result in lower $H_2$ production limiting the availability of the gas to CNS neurons. In contrast, the build-up of $H_2$ in the intestine has an inhibitory effect on fermentation of polysaccharides resulting in a reduction of its products including SCFAs (Bauchop and Mountfort 1981). Thus, the symbiosis between $H_2$-producing bacteria and hydrogenotrophic microbes, such as *Methanobrevibacter smithii*, is important for homeostasis and redox state.

Similarly to $H_2$, methane ($CH_4$) acts as an anti-inflammatory, antioxidant, and antiapoptotic gas (Zhang et al. 2016). Methane protects against oxidative stress by increasing the level of superoxide dismutase (SOD) and decreasing malonaldehyde (MDA) and 3-nitrotyrosine (3-NT) (Jia et al. 2018; Wang et al. 2017). *Methanobrevibacter smithii* is responsible for almost all $CH_4$ production in the intestine, reducing $CO_2$ to $CH_4$ in the presence of $H_2$ (Ghavami et al. 2018).

## Alterations in Intestinal Microbiota in Alzheimer's Disease

Recent studies show that intestinal microbiota contribute to brain dysfunction in various neurological diseases (Fung et al. 2017). For example, Cattaneo et al. (2017) analyzed the fecal gut microbiota of 40 cognitively impaired amyloid-positive patients

and 33 cognitively impaired amyloid-negative patients and controls. An increase in *Escherichia* and *Shigella* and a decrease in *Eubacterium rectale* and *Bacteroides fragilis* were found in the cognitively impaired amyloid-positive group compared to both controls. In addition, a positive correlation was observed between the pro-inflammatory cytokines (IL-1β, NLRP3, and CXCL2) and the abundance of the inflammatory bacteria taxon *Escherichia*/*Shigella*. In contrast, a decrease in abundance of the anti-inflammatory bacterial species *E. rectale* correlated with increases in these pro-inflammatory markers.

Gut microbiota composition and diversity were also altered in AD patients compared with cognitively normal controls. As summarized in Fig. 1, at the family level, decreased *Lachnospiraceae*, *Bacteroidaceae*, and *Veillonellaceae* and increased *Ruminococcaceae* and *Lactobacillaceae* were reported in the AD group compared to controls. In addition, the authors found that the relative abundance of *Actinobacteria* and *Bacilli* increased, while that of *Negativicutes* and *Bacteroidia* significantly decreased. The authors speculated that these changes in gut microbiota may facilitate the leak of gut bacteria and their components into the body (Zhuang et al. 2018). This was further supported by DNA sequencing analysis of 16S ribosomal genes which identified signatures of the intestinal microbiome in postmortem AD brain. Furthermore, the AD patients were shown to present with significantly larger bacterial loads compared to controls (Emery et al. 2017).

In the APP/PS1 mouse model of AD cerebral amyloid pathology was reduced in mice raised under germ-free conditions (Harach et al. 2017). In a separate study, increases in the genera *Odoribacter* and *Helicobacter* and decreases in *Prevotella* were reported in APP/PS1 fecal samples (Shen et al. 2017). In fecal samples of 5xFAD mice, Brandscheid et al. reported increased *Firmicutes* phylum, increased *Clostridium leptum*, and decreased *Bacteroidetes* phylum (Brandscheid et al. 2017). Therefore, studies suggest that microbiota compositions are altered in AD patients and AD animal models. These changes in the composition of the gut microbiota could increase intestinal permeability and induce inflammation.

A major limitation of most studies investigating the microbiome in AD is that they are cross-sectional studies. This makes it difficult to establish a causal relationship between the alteration of gut microbiota and the development of AD.

In addition, potential confounders include co-morbidities and the use of polypharmacy which can affect the absorption of micro-nutrients (e.g., water-soluble vitamins (B vitamins), fat-soluble vitamins (A, D, E, K), and minerals) and composition of the gut microbiota. For example, an increased risk of pneumonia and other infections in AD results in the use of antibiotics (Biesalski 2016; Blaser 2016).

The composition of the microbiota may also be altered following changes to diet. This includes eating disturbances which are common in both early and late stage AD and result from changes in the appetite, food preference, and swallowing disturbances (Kai et al. 2015). A cross-sectional study of 98 healthy volunteers showed that a high-protein and animal fat diet was associated with an enterotype composed of increased *Bacteroides*, whereas *Prevotella* increased in individuals on high-carbohydrate diets (Wu et al. 2011). Similarly, alterations in gut microbiota related to the diet were reported in a study comparing European and rural African children. African children (diet low in fat and animal protein and rich in starch, fiber, and plant polysaccharides) showed a significant enrichment in Bacteroidetes (*Prevotella* and *Xylanibacter*) and reductions in Firmicutes and Proteobacteria (*Shigella*,

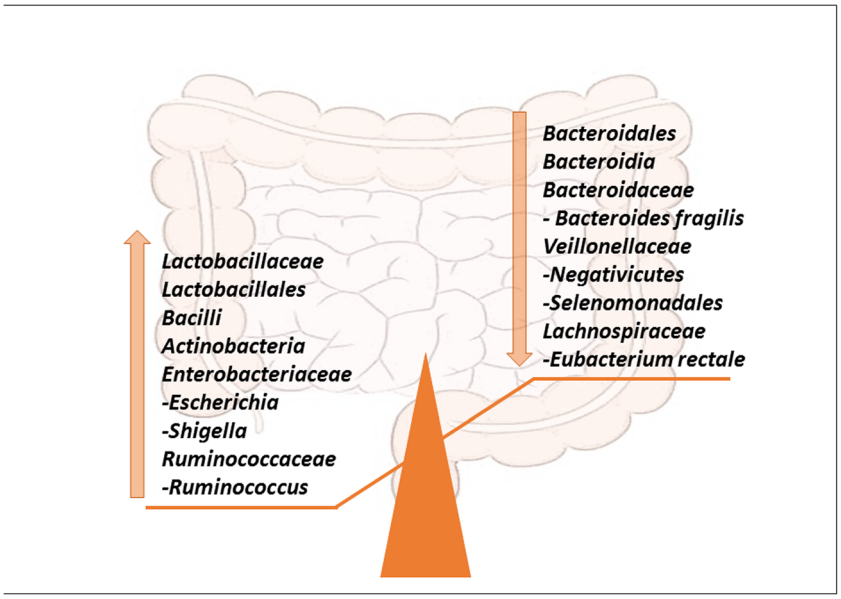


**Fig. 1** Dysbiosis in Alzheimer's disease. Anti-inflammatory bacteria such as *Bacteroides fragilis* are decreased in AD patients. Bacteria such as *Eubacterium rectale* strengthen the intestinal barrier and reverse gut leakiness. Increased abundance of the inflammatory bacteria taxon *Escherichia*/*Shigella* were also reported and further shown to correlate with increases in pro-inflammatory markers. The increase observed in the family *Lactobacillaceae*, which includes the genus *Lactobacillus*, is more complex as *Lactobacillus* was shown to be beneficial in AD patients

*Escherichia*) compared with European children (typical western diet, high in animal protein, sugar, starch, and fat and low in fiber) (De Filippo et al. 2010). Interestingly, similar alterations were found in AD patients, including increases in inflammatory bacteria taxon *Escherichia*/*Shigella* and decreases in *Bacteroides fragilis*, *Bacteroidia*, and *Bacteroidales* (phylum *Bacteroidetes*) (Cattaneo et al. 2017; Zhuang et al. 2018). Similar results were also reported in transgenic AD mouse models including decreases in the *Bacteroidetes* phylum and Prevotella and increases in Firmicutes (Brandscheid et al. 2017; Shen et al. 2017). Furthermore, negative correlations between cognitive function and the intake of saturated fatty acids and simple sugars were reported. In contrast, increased fish consumption, intake of monounsaturated fatty acids, polyunsaturated fatty acids (PUFA), and fiber were protective against cognitive decline (Solfrizzi et al. 2017). Thus, it could be speculated that alteration in gut microbiota following changes in diet may delay or exacerbate the development of AD.

## Microbiota and Tryptophan Metabolism

Humans lack the biochemical pathways to synthesize Trp which must be acquired from high-protein foods such as meat, fish, soy, nuts, seeds, and chocolate. Microbiota modulate circulating concentrations of Trp which has a number of implications for its metabolism in the periphery and CNS (Kennedy et al. 2017). In addition to upregulating the synthesis of serotonin in host enterochromaffin cells (EC) (Yano et al. 2015) gut microbiota can directly metabolize Trp and in turn limit its availability to the host. Indeed elevated plasma Trp concentrations were reported in germ-free animals and were normalized following colonization (Clarke et al. 2013).

Trp is metabolized to several intermediates which play key roles in gut homeostasis including a range of indoles (e.g., indole 3-aldehyde) which appear to be involved in immune physiology at mucosal surfaces by recruitment of host cells for IL-22 transcription. The IL-22-regulated mucosal response allows for survival of mixed microbial communities and provides colonization resistance to *Candida albicans* and mucosal protection from inflammation. In addition, transfer of microbiota from *Card9*$^{-/-}$ mice (which have an increased susceptibility for colitis) to germ-free wild-type mice resulted in decreased metabolism of Trp to AhR ligand indole 3-acetic acid (IAA) compared to controls (Lamas et al. 2016). Notably, inflammation was attenuated following inoculation with three strains of *Lactobacillus* known to metabolize Trp into indole derivatives or treatment with an AhR agonist. This demonstrates that decreased AhR ligand production can be rescued following supplementation with AhR ligand–producing *Lactobacillus* strains (Zelante et al. 2013). Therefore, microbiota significantly impact the host's immune response by regulating Trp.

Trp may also be metabolized in host cells by indoleamine 2,3-dioxygenase (IDO) and tryptophan dioxygenase (TDO) which catalyze the initial metabolic step of the KP (see the "The Kynurenine Pathway and Alzheimer's Disease" section). Notably, germ-free mice showed significantly less IDO expression in the intestinal epithelial cells compared to mice with native gut microbiota (Rhee et al. 2005). The administration of *Lactobacillus johnsonii* to rats resulted in a 17% reduction in serum kynurenine (KYN) and a 1.4-fold increase in serotonin (Valladares et al. 2013). A separate study reported an increase in plasma concentrations of Trp and kynurenic acid (KYNA) and reduced pro-inflammatory cytokine release in *Bifidobacteria infantis*–treated rats when compared to controls (Desbonnet et al. 2008).

These alterations in KP metabolite concentrations and their restoration following the re-introduction of gut microbes indicate a key role for the gut microbiota in the KP.

### The Kynurenine Pathway and Alzheimer's Disease

Up to 95% of Trp is metabolized through the KP (Fig. 2a) resulting in the production of neurotoxic metabolites 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN) and neuroprotective KYNA and picolinic acid (PIC) (Schwarz et al. 2013; Smoller et al. 2013). In humans TDO in the liver metabolizes a large proportion of Trp to produce the essential cellular cofactor nicotinamide adenine dinucleotide ($NAD^+$) (Van der Leek et al. 2017). In the brain Trp is oxidized by the action of the IDO to N-formyl-L-kynurenine which is subsequently hydrolyzed to the first stable metabolite of the KP, KYN. KYN sits at a branch point of the KP and may be metabolized to anthranilic acid (AA), KYNA or 3-HK by kynureninase (KYNU), kynurenine aminotransferase (KAT), and kynurenine 3-monooxygenase (KMO) respectively.

Inflammatory mediators tightly regulate the activity of multiple enzymes in the KP (Campbell et al. 2014) especially IDO-1 which is induced by IFN-γ, LPS, and CpG in antigen-presenting cells (APC) (Hill et al. 2007; Mellor and Munn 2004). An increase in IDO-1 activity results in reduced of Trp levels, limiting the growth of microorganisms, inhibiting T cell proliferation, and resulting in the accumulation of downstream KP metabolites, KYN, which can activate AhR in lymphoid tissues promoting Treg cell development (Mezrich et al. 2010).

The activation of the KP results in increased production of $NAD^+$ in turn increasing energy production, DNA repair, genomic signaling, playing a key role in antioxidant defense mechanisms (Massudi et al. 2012). $NAD^+$ has been shown to extend the lifespan of *Caenorhabditis elegans* following protection against ROS (Mouchiroud et al. 2013). The sirtuins (SIRT 1–7), a class of $NAD^+$-dependent deacetylase enzymes

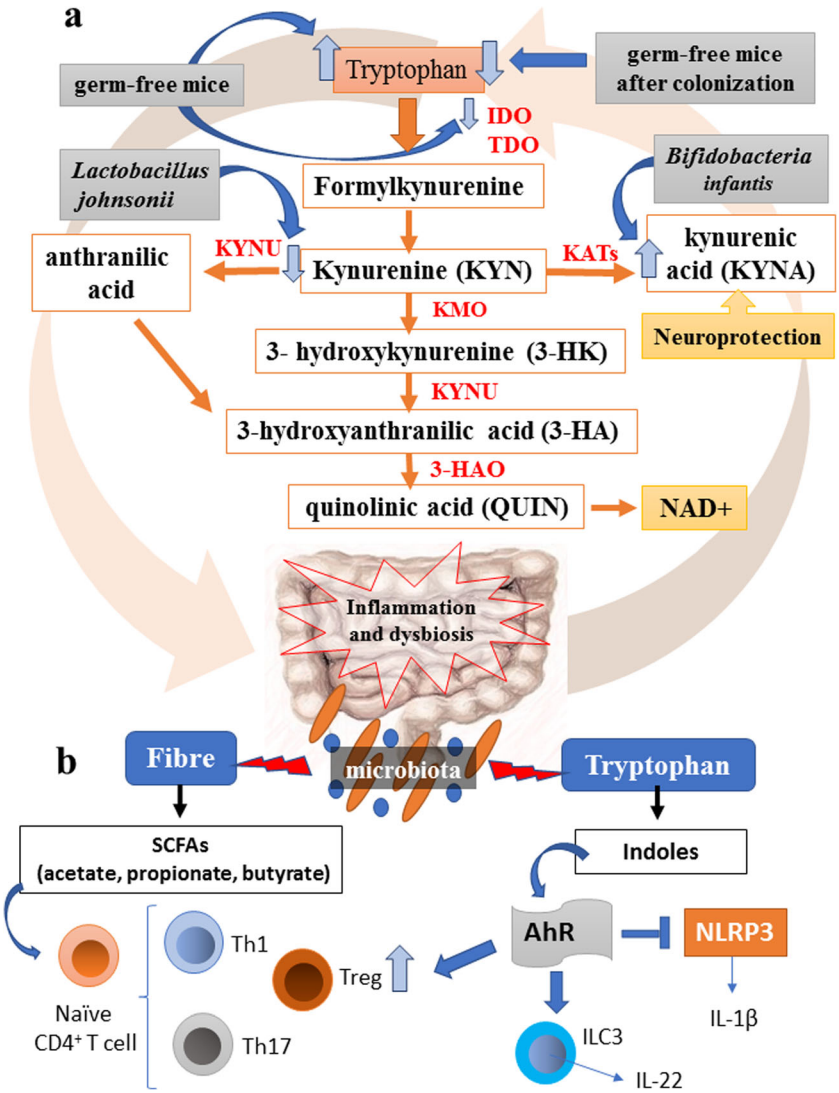


**Fig. 2** Microbiota and the kynurenine pathway. (**a**) Tryptophan is oxidized to N-formylkynurenine by the action of the indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) and is subsequently hydrolyzed to kynurenine (KYN). Downstream metabolites of KYN include redox active 3-hydroxykynurenine (3-HK) and 3-hydroxyanthranilic acid (3-HAA), neurotoxic quinolinic acid (QUIN), and neuroprotective kynurenic acid (KYNA). Gut inflammation and dysbiosis alter tryptophan metabolism changing the balance of neuroprotective/neurotoxic KP metabolites. (**b**) Gut bacteria produce metabolites from the host diet. SCFAs promote differentiation of the $CD4^+$ naive T cells necessary for intestinal homeostasis. Th1 cells are known to produce pro-inflammatory IFN-γ and TNF-α which upregulate key KP enzymes with implications in AD. Th17 cells produce pro-inflammatory IL-17 and IL-22 which aid in the survival of good bacteria in the gut and enhances epithelial barrier function. AhR activation by bacteria-produced indoles and host-produced KYN has been showed induces T cell differentiation into Treg, promote maintenance of ILC3 cells and inhibit NLRP3 expression, caspase-1 activation and subsequent IL-1β secretion in macrophages. Key enzymes are indicated in red. Abbreviations: KYNU, kynureninase; KATs, kynurenine aminotransferases; KMO, kynurenine 3-monooxygenase; 3HAO, 3-hydroxyanthranilic acid oxygenase; SCFAs, short-chain fatty acids; Treg, regulatory T cells; AhR, aryl hydrocarbon receptor; ILC3, type 3 innate lymphoid cell

are involved in mediating cellular adaptations such as improvement of mitochondrial function and maintenance of genomic stability which in part explain how calorie restriction extends life span. The decline in $NAD^+$ may be related to a decline in activity of these proteins with age (Oberdoerffer et al. 2008; Wu and Sinclair 2016).

Several studies have assessed different $NAD^+$ precursors as a potential treatment for AD. In 3xTg AD mice, treatment with nicotinamide (NAM) increased $NAD^+$ levels and proteins (e.g., ERK42 and CREB) involved in cell survival and plasticity, enhanced cognitive function, and reduced Aβ and tau pathologies in both the cortex and hippocampus of these mice (Liu et al. 2013a). Similarly, nicotinamide riboside (NR) improved cognitive function and synaptic plasticity in Tg2576 mice by promoting BACE1 degradation and preventing Aβ production in the brain (Gong et al. 2013). Nicotinamide mononucleotide (NMN) restored memory, increased neuron survival, and reduced ROS accumulation in an AD rat model

induced by intracerebroventricular Aβ oligomer injection (Wang et al. 2016). Finally, NMN restored mitochondrial function in APP/PS1 mice (Long et al. 2015).

However, chronic activation of KP may be particularly relevant to the pathogenesis of neurodegenerative diseases including AD. For example, activated microglia, one of the primary sources of neurotoxic QUIN in the CNS, can be found surrounding Aβ plaques (Heyes and Morrison 1997; Marlatt et al. 2014) and IDO-1 was shown to colocalize with NFT and Aβ plaques (Bonda et al. 2010).

QUIN is produced downstream of KMO (Fig. 2) and is an NMDA receptor agonist which in excess causes glutamatergic excitotoxicity, increases the release of glutamate by neurons, inhibits glutamate reuptake by astrocytes, and ultimately results in elevated concentrations of glutamate in the microenvironment (Ting et al. 2009). Furthermore, QUIN has been shown to induce tau hyperphosphorylation in human cortical neurons (Rahman et al. 2009).

Additional observations linking the KP and AD include increased 3-HK in AD patient serum (Schwarz et al. 2013), increased KYN/Trp ratio in AD serum compared to elderly controls (Widner et al. 2000), decreased Trp, 3-HAA, and xanthurenic acid (XA) in histopathological confirmed AD plasma (Giil et al. 2017), accumulation of QUIN in the hippocampus of AD patients (Guillemin et al. 2003), and increased expression of IDO-1 and TDO immunoreactivity in the cortex and hippocampus of AD patient brain (Bonda et al. 2010; Wu et al. 2013). In addition, in pre-clinical AD (characterized by high neocortical amyloid-β load) increased serum KYN and AA were reported in female participants compared to age-matched and gender-matched controls who were at no apparent risk of AD (Chatterjee et al. 2018).

### Impact of Diet and Exercise on KP Metabolism

Changes in diet significantly impact Trp availability in both the periphery and CNS. Despite increased plasma Trp levels in healthy middle-aged subjects with a high-protein intake, $NAD^+$ was significantly reduced and was related to inflammation and aging processes (Seyedsadjadi et al. 2018). A high-protein intake limits cerebral availability of Trp as other large neutral amino acids (LNAA) such as leucine, valine, and isoleucine, compete with Trp for transport across the BBB (Dingerkus et al. 2012). In contrast, a carbohydrate-rich diet increases the plasma Trp–LNAA ratio by an insulin-induced reduction of LNAAs available (following peripheral uptake into the skeletal muscles for conversion into protein) in turn increasing availability of TRP and serotonin in the brain (Markus 2008).

In addition, exercise is known to impact Trp metabolism (Cervenka et al. 2017). In mice, swimming prevented memory impairment induced by Aβ1–42, reduced IDO1 activity, restored Trp and KYN, and increased the KYN:Trp ratio in the prefrontal cortex and hippocampus (Souza et al. 2017). A similar result was reported by Liu et al. (2013b) in which swimming reduced the levels of pro-inflammatory cytokines and IDO in the prefrontal cortex of rats. Exercise has also been shown to activate the transcriptional coactivator peroxisome proliferator–activated receptor (PPAR) gamma coactivator-1α1 (PGC-1α1) pathway in skeletal muscle in mice and human. This leads to increased expression of KAT enhancing the conversion of KYN into neuroprotective KYNA and reducing the conversion of KYN to toxic metabolites including 3-HK and QUIN in the CNS (Agudelo et al. 2014). This may represent a key neuroprotective mechanism with direct relevance for neurodegenerative diseases.

Several studies have shown physical activity protects against cognitive decline in the elderly (Angevaren et al. 2008; Sofi et al. 2011), individuals with mild cognitive impairment (Öhman et al. 2014) and dementia (Groot et al. 2016). However, in AD patients, this result is debated as some studies report that the physical activity interventions positively impact cognitive function (Farina et al. 2014; Hess et al. 2014) but others do not (Forbes et al. 2015; Henskens et al. 2018).

## Alzheimer's Disease Treatment and Use of Probiotics

To date, the only drugs approved for the treatment of AD by the Food and Drug Administration (FDA) are three acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and an NMDA receptor antagonist memantine which increase the concentration of acetylcholine and reduce glutamatergic excitotoxicity respectively. However, these drugs do little to improve cognitive function, are unable to prevent disease progression, and have several adverse side-effects (Hampel et al. 2018; Ramirez-Bermudez 2012).

Medicinal foods, particularly probiotics, have recently emerged as a tool for physicians to manage many gastrointestinal disorders but may also prove beneficial in a range of other conditions including AD. A 12-week clinical study in AD patients supplemented with probiotic milk containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* showed improved cognition as evaluated by the Mini-Mental State Examination (MMSE). In addition, improvements in biochemical markers such as plasma malondialdehyde, serum high-sensitivity C-reactive protein (hs-CRP), insulin metabolism markers, serum triglyceride levels, and VLDL were reported (Akbari et al. 2016). In contrast, another study using the same study group evaluated treatment with *Lactobacillus fermentum*, *Lactobacillus plantarum*, and *Bifidobacterium lactis* or *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*. They concluded that the cognitive function and biochemical markers (oxidant/antioxidant and inflammatory/anti-inflammatory

biomarkers) in patients with severe AD were insensitive to the probiotic supplementation. The authors cited the formulation, dosage of probiotic bacteria, the time of administration (12 weeks), and the severity of the disease as significant limitations (Agahi et al. 2018). Another study investigated 18 AD patients before and after probiotic supplementation for 4 weeks. The results showed an increase in *Faecalibacterium prausnitzii* compared to baseline observations and increased concentrations of serum KYN (Leblhuber et al. 2018).

Studies using mice intrahippocampally injected with Aβ1–42 show the beneficial effect of probiotics in AD. In this model, treatment with *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *Bifidobacterium lactis*, and *Bifidobacterium longum* for 8 weeks improved spatial memory and reduced markers of oxidative stress in the hippocampus of treated mice relative to controls (Athari Nik Azm et al. 2018). Another study induced AD-like characteristics in rats using D-galactose injections. These animals were treated with *Lactobacillus plantarum* MTCC1325 for 60 days resulting in improved cognition and restoration of acetylcholine levels (Nimgampalle and Kuna 2017). In addition, 3xTg-AD transgenic mice treated with SLAB51, a probiotic formulation containing *Streptococcus thermophilus*, *bifidobacteria* (*B. longum*, *B. breve*, *B. infantis)* and *lactobacilli* (*L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii subsp. Bulgaricus*, *L. brevis*) resulted in a change in the intestinal microbiota composition and its metabolites including acetic, propionic, and butyric acids. Furthermore, the treatment positively modulated inflammatory cytokines, gut hormones concentration and proteolysis, reduced Aβ load and improved cognitive function as assessed by the novel object recognition test (Bonfili et al. 2017). Thus, recent studies support the idea of intestinal microbiota modulation as a possible intervention for the AD.

## Conclusion

The pharmacological treatments currently available for AD are largely palliative and unable to prevent disease or its progression. It has been reported that the microbiota can modulate neuroinflammation and KP metabolism, disease mechanisms strongly related to AD pathophysiology. Although these pathways are closely related the interactions are multifaceted and further studies are necessary to elucidate the interactions between microbiota, the KP, and impact on AD pathology. This work may also highlight possible interventions to prevent or delay the onset of AD.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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