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REVIEW ARTICLE

The link between gut health and neurodegenerative disorders: the importance of the microbiota

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Abstract

The gut microbiota, a complex ecosystem of microorganisms, plays an essential role in human health by influencing metabolism, immune function, and the gut-brain axis. Emerging evidence links gut dysbiosis (imbalance) to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Mechanistic pathways include the propagation of amyloidogenic proteins, production of neurotoxic metabolites such as trimethylamine N-oxide, and intestinal permeability disruption. This review highlights key mechanisms and explores therapies such as fecal microbiota therapy, probiotics, and lifestyle changes to modulate the microbiota and slow neurodegeneration. Despite significant advances, further research is essential to fully understand the microbiota's role in neurodegeneration and to develop microbiota-targeted therapies for clinical application.

Keywords: *Gut microbiota. Neurodegenerative diseases. Gut-brain axis. Bacterial amyloid. N-óxido de trimetilamina. Microbiota-targeted therapies.*

El vínculo entre la salud intestinal y los trastornos neurodegenerativos: la importancia de la microbiota

Resumen

La microbiota intestinal, un ecosistema complejo de microorganismos, desempeña un papel esencial en la salud humana al influir en el metabolismo, la función inmunológica y el eje intestino-cerebro. Evidencia reciente vincula la disbiosis intestinal (desequilibrio) con enfermedades neurodegenerativas como la enfermedad de Alzheimer (EA), la enfermedad de Parkinson (EP), la esclerosis lateral amiotrófica (ELA) y la enfermedad de Huntington (EH). Entre los mecanismos propuestos se incluyen la propagación de proteínas amiloidogénicas, la producción de metabolitos neurotóxicos como el N-óxido de trimetilamina (TMAO) y la alteración de la permeabilidad intestinal. Esta revisión destaca los mecanismos clave y explora terapias como el trasplante de microbiota fecal (TMF), los probióticos y los cambios en el estilo de vida para modular la microbiota y retrasar la neurodegeneración. A pesar de los avances significativos, es esencial continuar con la investigación para comprender plenamente el papel de la microbiota en la neurodegeneración y desarrollar terapias dirigidas a la microbiota para su aplicación clínica.

Palabras clave: *Microbiota intestinal. Enfermedades neurodegenerativas. Eje intestino-cerebro. Amiloide bacteriana. TMAO. Terapias dirigidas a la microbiota.*

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Introduction

The gastrointestinal tract hosts a large community of microorganisms, including bacteria, fungi, yeast, archaea, and viruses. Symbiosis among humans and communities of microorganisms is highly relevant due to the benefits it provides to our health. These microbes are fundamental for the proper functioning of our gut by metabolizing macronutrients such as carbohydrates and proteins, primarily in the cecum and distal colon, where microbial populations are most abundant. This type of microorganism is well known as gut microbiota. The gut microbiota thrives on undigested food and mucus shed from the intestine, promoting tissue growth and intestinal immune development. This community is capable of producing metabolites that can promote or inhibit the progress of different pathologies such as diabetes, obesity, colitis, Crohn's disease, and even neurodegenerative diseases[1].

The gut-brain axis, primarily mediated by the vagus nerve, enables bidirectional communication between the gut microbiota and the central nervous system. Metabolites such as short-chain fatty acids, endotoxins, and key neurotransmitters (e.g., dopamine and gamma-aminobutyric acid) influence neuronal function[2].

Gut microbiota metabolites can also reach the brain through systemic circulation, although two barriers, the intestinal barrier and the blood–brain barrier, limit their access. The intestinal barrier has a mucus layer, a glycoprotein biofilm that protects the intestinal epithelium. A low fiber diet or the presence of inflammatory mediators can weaken this barrier. The blood–brain barrier, composed of tightly packed endothelial cells, regulates the entry of substances into the brain and has specific transporters that limit the passage of harmful molecules.

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are major global health concerns with limited therapeutic options. Increasing evidence links gut microbiota to these diseases, suggesting that microbial alterations may influence protein aggregation, neuroinflammation, and neuronal death. This review explores the interplay between gut microbiota and neurodegenerative diseases, highlighting potential mechanisms and therapeutic interventions.

Gut microbiota development and composition

Throughout life, humans are exposed to a wide variety of microorganisms that colonize the gastrointestinal tract, promoting either health or disease. The diversity of gut microbiota is mostly influenced by factors such as mode of delivery, diet, and exposure to microorganisms from infancy to adulthood. The observation of bacteria in the placenta and amniotic fluid supports that microbial colonization begins even before delivery[3], with distinct microbial communities established based on the delivery method: vaginal delivery promotes *Lactobacillus*, *Prevotella,* and some fecal microbe colonization, while cesarean sections favor *Staphylococcus* and *Corynebacterium*[4]*.* Breastfed infants have a more diverse gut microbiota than infants fed with formula[5], primarily due to human milk oligosaccharides, which are a group of complex carbohydrates that improve the gut microbiota's development[6].

In adulthood, the gut microbiota stabilizes, with *Bacteroidetes* and *Firmicutes* predominating. However, its composition can be altered by diet, stress, and antibiotics[7].

These compositional shifts set the stage for gut-brain axis perturbations reviewed below.

Gut microbiota and neurodegenerative mechanisms

In recent decades, researchers around the globe have been striving to uncover the mechanisms underlying neurodegenerative diseases. Although the precise mechanisms remain unclear, increasing evidence suggests that gut microbiota may play a significant role in neurodegeneration. The main characteristic of these diseases is the aggregation of proteins known as amyloids, which are toxic and lead to neuronal death. Each neurodegenerative condition is associated with a specific protein, such as alpha synuclein in PD and Lewy body dementia and amyloid beta (Aβ) and tau proteins in AD, among others[8].

AD

AD is the most prevalent form of dementia, accounting for 60-70% of cases globally, with aging as the primary risk factor[9]. Its hallmark pathological features include the extracellular accumulation of Aβ plaques and the intracellular aggregation of hyperphosphorylated tau protein, forming neurofibrillary tangles. These aggregates disrupt neuronal signaling, induce synaptic loss, and ultimately lead to widespread neuronal death, manifesting as progressive cognitive decline and memory loss, a link between gut dysbiosis and AD pathogenesis[10]. Inflammatory bowel diseases, such as ulcerative

colitis and Crohn's disease, have been linked to a 2.54-fold increased risk of dementia, highlighting the gut's influence on neurodegenerative processes[11].

PD

PD is a leading neurodegenerative disorder worldwide, with its global burden increasing significantly over the past decades[12]. It is clinically characterized by motor symptoms such as bradykinesia, postural instability, rigidity, and resting tremor. These symptoms arise due to progressive loss of dopaminergic neurons in the substantia nigra and noradrenergic neurons in the locus coeruleus. Lewy bodies, observed in post-mortem evaluations, are a hallmark of PD. These are formed by the accumulation of misfolded alpha-synuclein fibrils[13].

One of the most important hypotheses regarding the origin of PD is Braak's hypothesis. In his study published in 2004, Braak observed Lewy bodies in the gastrointestinal tracts of PD patients during post-mortem analysis. This finding suggested that α-synuclein aggregation might begin in the gut before propagating to the brain. This was supported by a study carried out in 2007, where researchers observed that α-synuclein, which is mostly expressed in the brain, is also expressed in enteroendocrine cells of the intestinal epithelium[14].

As intestinal cells can produce α-synuclein, researchers propose that it may travel to the brain through the vagus nerve in a prion-like manner[15].

Experimental evidence supports this mechanism. In a mouse model, pathological α-synuclein preformed fibrils were injected into the gut. The results showed that truncal vagotomy (severing the vagus nerve) and α-synuclein knockout reduced neurodegeneration by limiting α-synuclein aggregation and propagation[16].

ALS

ALS is a progressive neurodegenerative disease primarily affecting motor neurons. It is characterized by weakness in the limbs and bulbar muscles (mouth or throat), leading to difficulties in movement, speech, and swallowing. The average life expectancy after diagnosis is 3-5 years.

Several factors contribute to ALS pathogenesis, including genetic mutations (*SOD1*, *FUS*, *C9orf72,* and *TRADBP*), as well as gender, age, and nutritional status. The disease's physiopathology is mediated by excitotoxicity, protein aggregation, mitochondrial dysfunction, and disruption of axon transport processes. ALS affects 5.20/100,000 habitants in North America[17].

Patients with ALS often experience gastrointestinal disorders, such as delayed gastric emptying, constipation, and stool incontinence.

Evidence suggests that disruption of the intestinal barrier may play a role in disease progression. For example, one study detected inflammatory markers in the majority of stool samples from ALS patients, while another reported the presence of bacterial endotoxins (lipopolysaccharides) in the blood, with higher levels observed in advanced disease stages[18].

HD

HD is an autosomal dominant neurodegenerative disorder characterized by progressive motor and cognitive impairment, along with neuropsychiatric symptoms. It is caused by an expansion of cytosine-adenine-guanine repeats in the *huntingtin* gene, resulting in a mutant protein with toxic properties that lead to neuronal dysfunction and cell death. The median survival time of patients diagnosed with HD is approximately 18 years, and the global incidence is 2.71 cases/100,000 people[19].

Similar to other neurogenerative diseases, HD patients often experience gastrointestinal symptoms, including diarrhea, disruption of the intestinal epithelium, gastritis, and nutrient deficiencies. The exact association between gastrointestinal symptoms and disease progression is unclear; however, evidence suggests that gut microbiota alterations may play a significant role in HD pathogenesis. Certain bacterial populations in the gut have been observed to influence inflammatory and metabolic pathways, potentially contributing to disease progression[20]. Further research is needed to elucidate these mechanisms and their clinical implications.

Role of the microbiota in neurodegeneration

Studies have shown that patients with neurodegenerative disorders present variation in their gut microbiota compared to healthy controls. In a study of colonic bacterial composition, an increase of proinflammatory and a reduction of anti-inflammatory bacteria were observed in American PD patients, suggesting that this dysbiosis could be related to neurodegeneration[21]. The alteration of gut microbiota, increasing the presence of pathological bacteria, can disrupt the intestinal barrier by augmenting proinflammatory cytokines, promoting the pass of bacterial metabolites to the circulation, leading to a weakening of the blood–brain barrier[22].

Amyloid-producing bacteria and cross-seeding

The presence of amyloids produced by gut bacteria may facilitate protein aggregation by cross-seeding[23]. *Escherichia coli* produces curli, a functional bacterial amyloid that interacts with host proteins (CsgA and CsgB). Those proteins form a biofilm that helps bacteria to attach to the intestinal epithelium[24]. *Salmonella* Typhimurium and *Citrobacter koseri* can also produce curli, and their interactions, along with cross-seeding, contribute to the formation of interspecies biofilm[25].

Even though curli was the first protein described as a bacterial amyloid, there are other proteins that are also linked with neurodegenerative diseases, such as FapC, a functional amyloid produced by *Pseudomonas* sp. in the formation of a biofilm called amyloid-like fimbriae[26]. Experimental studies have demonstrated that oral exposure to curli-producing bacteria enhances α-synuclein aggregation in the gut and brain, supporting Braak's hypothesis of PD pathogenesis.

Bacterial amyloids and neurodegenerative diseases

Curli

The capacity of bacterial amyloids for cross-seeding *in vivo* has triggered a series of studies with amyloids associated with neurodegeneration. It has been observed an enhance in the accumulation of α-synuclein in the intestine, hippocampus, and striatum of Wild-type rats after weekly oral administration of curli-producing bacteria compared with controls[27].

FapC

In a study using FapC obtained from *Pseudomonas aeruginosa*, researchers found that FapC promotes Aβ aggregation through a series of complementary experiments. *In silico:* Discrete molecular dynamics simulations demonstrated the molecular interactions between FapC and Aβ. *In vitro:* Thioflavin T assays were used to analyze amyloid kinetics, while stimulated emission depletion microscopy provided insights into the interaction between Aβ and FapC. *In vivo*: A zebrafish model of AD was used to assess the effects of FapC on Aβ aggregation through immunohistochemistry and behavioral tests[28].

In addition, *E. coli* is particularly relevant due to its natural presence in the healthy human gut microbiota, unlike other amyloid-producing bacteria[29]. Studies have shown that *E. coli* is more prevalent in the gut microbiota of patients with neurodegenerative diseases such as PD and AD, suggesting a potential role in disease pathogenesis[21,30].

Trimethylamine N-oxide (TMAO)

TMAO is a gut microbial metabolite associated with several pathologies, including neurodegenerative diseases like AD[31]. Choline and L-carnitine are obtained by the consumption of red meat, eggs, dairy, and saltwater fish metabolized by the gut microbiota obtaining trimethylamine (TMA). This compound can pass through the intestinal barrier to circulation and be converted to TMAO by the enzyme flavin-containing monooxygenase 3 in the liver[32]. TMA is mostly absorbed in the small intestine due to bacteria that use choline and L-carnitine as substrates and is more present than in the large intestine[33]. There is a large diversity of bacteria capable of producing TMA, and *E. coli* is the most common TMA-producing bacteria[34]. It has been observed in studies that TMAO is elevated through age progression and it is related to neuronal plasticity deficits by inducing endoplasmic reticulum stress through PERK- EIF2α-ER. This was identified in the hippocampus tissue of mice models[35]. In other study using Alzheimer's models (APP/PS1) fed with choline and probiotics (*Lactobacillus plantarum*), researchers observed that there was a decrease in beta-amyloid levels in the hippocampus as well as in plasmatic TMAO in the group fed with probiotics, suggesting that TMAO is involved in disease progression[36].

Recently, TMAO plasma levels were correlated with PD progression and the need for an increment in medication (levodopa). Moreover, it was observed that PD patients present lower TMAO plasma concentration compared with healthy controls, a need for dose increment, and a higher risk of dementia conversion was observed in the patients with lower levels of TMAO[37]. It was also observed that PD patients present lower levels of TMA and TMAO than healthy controls in fecal samples[38].

Therapeutic approaches targeting gut microbiota

Several strategies have been proposed to modulate gut microbiota and potentially mitigate neurodegenerative disease progression. These include:

Inhibition of bacterial amyloid aggregation

Epigallocatechin gallate (EGCG), a small molecule with reported neuroprotective properties, has been

Table 1. Gut microbiota alterations and therapeutic strategies in neurodegenerative disorders

Disease	Microbiota changes	Key mechanisms	Evidence	Interventions
AD	↓*Firmicutes/Bacteroidetes* ↑*Escherichia coli*	FapC cross-seeds Aβ/tau TMAO induces ER stress	28,30,31,35	Mediterranean diet[46] *Lactobacillus plantarum*[36]
PD	↓*Roseburia* ↑*Proteobacteria*	*Curli* enhances α-synuclein Vagus propagation	16,21,40	EGCG[39] FMT[44]
ALS	↑Pathobionts ↓Barrier integrity	LPS neuroinflammation Cytokine surge	17,18	High-fiber diet[48] Butyrate (preclinical)
HD	↓Diversity ↓*Bacteroides*	Metabolic dysfunction	19,20	Aerobic exercise[50] Personalized probiotics

↑: indicates increase.
↓: indicates decrease in microbial abundance or function.
AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease; FMT: fecal microbiota transplantation; TMAO: trimethylamine N-oxide; ER: endoplasmic reticulum; LPS: lipopolysaccharide.

shown to reduce the toxicity of alpha-synuclein and amyloid-beta fibrils. *In vitro* studies have demonstrated that EGCG inhibits the formation of CsgA, a key component of bacterial amyloids, by interfering with the assembly of curli subunits on the bacterial outer membrane[39].

A recent study utilizing a PD mouse model (Thy1-aSyn), which overexpresses alpha-synuclein, evaluated the effects of EGCG on pathological alpha-synuclein aggregation and cognitive impairment. Mice administered curli-producing bacteria exhibited increased alpha-synuclein aggregation and cognitive deficits. However, treatment with EGCG significantly reduced both alpha-synuclein aggregates and cognitive impairment compared to the control group, without altering *Escherichia coli* composition in the gut microbiota[40].

Fecal microbiota transplantation (FMT)

FMT has shown promise in restoring microbial balance and improving clinical outcomes[41-43]. In PD patients, FMT significantly alleviated motor symptoms and gastrointestinal dysfunction in randomized trials[44], with minimal adverse effects (e.g., transient diarrhea). Animal studies further demonstrate that FMT from young donors reduces neuroinflammation and extends lifespan[42], suggesting its potential as a disease-modifying therapy.

Lifestyle interventions: diet and exercise

Lifestyle modifications, including diet and exercise, synergistically modulate gut microbiota composition and function[45]. Adherence to a Mediterranean diet, rich in polyphenols, fiber, and unsaturated fats, reduces neuroinflammation and amyloid aggregation, with meta-analyses showing a 13% lower incidence of PD and AD[46]. Fermented foods (e.g., kefir and kombucha) provide probiotics that, combined with high-fiber diets (prebiotics), enhance microbial diversity and short-chain fatty acid production[47,48].

Moderate exercise stabilizes gut microbiota and improves barrier integrity, though excessive intensity may exacerbate intestinal permeability[49,50]. These interventions collectively mitigate neuroinflammation and oxidative stress, critical pathways in neurodegeneration.

Discussion

The interplay between the gut microbiota and neurodegeneration is complex and multifaceted. While evidence strongly suggests a role for microbiota in disease progression, the exact mechanisms remain to be fully elucidated. As summarized in table 1, disease-specific microbial alterations, key pathological mechanisms, and candidate interventions highlight the potential for microbiota-targeted therapies in neurodegeneration.

These findings underscore the need for personalized approaches, as microbiota composition varies significantly between individuals. For example, while FMT shows promise in PD[44], its efficacy may depend on donor-recipient compatibility. Similarly, the Mediterranean diet's benefits in AD[46] could be mediated by individual differences in microbial metabolite processing.

The current limitations include the lack of large-scale longitudinal studies in humans and the challenge of establishing causality between dysbiosis and neurodegeneration. Most evidence derives from animal models or cross-sectional human studies, which cannot fully capture the temporal dynamics of microbiota-brain interactions. Future research should prioritize microbiota-based biomarkers for early disease detection and randomized controlled trials testing interventions like FMT or targeted probiotics.

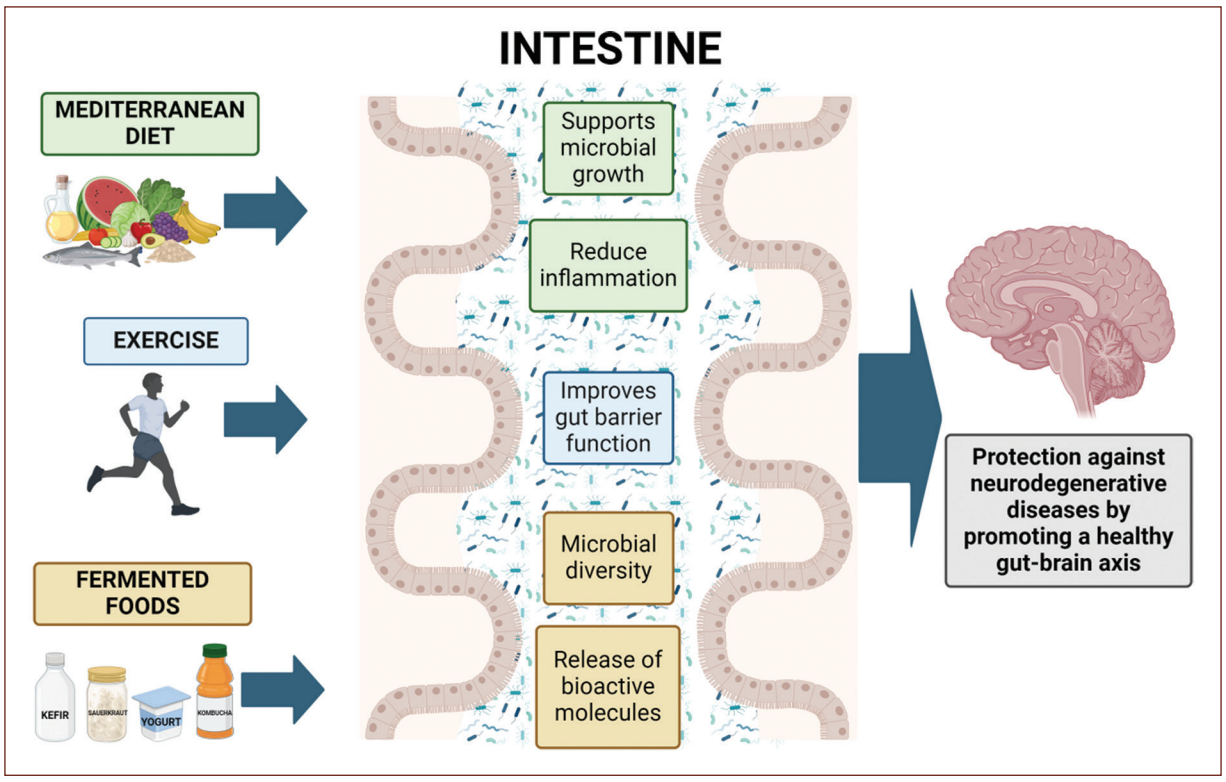

Figure 1. Impact of Mediterranean diet, fermented foods, and exercise on the gut. A Mediterranean diet, regular exercise, and the consumption of fermented foods contribute to gut microbiota diversity and stability. These interventions support microbial growth, reduce inflammation, improve gut barrier function, and promote the release of bioactive molecules. Collectively, these changes help maintain a healthy gut-brain axis, which may offer protection against neurodegenerative diseases.

The gut-brain axis offers a unique therapeutic window. Lifestyle modifications, such as combining a Mediterranean diet with aerobic exercise, may synergistically enhance microbial diversity and reduce neuroinflammation[48,50]. Pharmacological strategies (e.g., EGCG and TMAO inhibitors) could complement these approaches by targeting specific pathological cascades[39,35]. However, optimizing dosing, timing, and patient stratification will be critical for clinical translation.

To translate these findings into clinical practice, future work must address:

– Standardization of microbiota-targeted therapies (e.g., optimal probiotic strains and FMT protocols).
– Patient stratification based on microbial profiles and genetic risk factors.
– Long-term safety and efficacy of interventions, particularly in early-stage patients.

By integrating mechanistic insights (Table 1) with actionable lifestyle strategies (Fig. 1), this review highlights the gut microbiota as a modifiable frontier in neurodegenerative disease management.

Conclusion

The gut microbiota is increasingly recognized as a critical modulator of neurodegenerative diseases. Dysbiosis, bacterial amyloid production, and microbial metabolites such as TMAO may contribute to neurodegenerative pathogenesis via mechanisms involving inflammation and protein aggregation. Targeted interventions, including dietary modifications, FMT, and probiotics, offer promising therapeutic strategies. However, further longitudinal and clinical studies are necessary to elucidate causal relationships and develop effective microbiota-based therapies.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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