

# Role of Gut-Microbiome-Brain-Axis in Neurodegenerative Diseases: A Review on Mechanisms and Potential Therapeutics

Fernanda Susy Bessa Menezes Cavalcante <sup>1</sup>, Laís Lobato de Araújo <sup>2</sup>, Gabriel Felipe Gomes <sup>3</sup>, Stéfani Lara Galvão <sup>3</sup>, Talitta costa Sant'ana Esteves Hipólito <sup>4</sup>, Milene de Campos Piagentini <sup>5</sup>, Júlio César Claudino dos Santos <sup>6,\*</sup>

<sup>1</sup> INTA University Center, UNINTA, Sobral, Ceará, Brazil.

<sup>2</sup> Belo Horizonte University Center, UniBH, Belo Horizonte, Minas Gerais, Brazil.

<sup>3</sup> Barão de Mauá University Center, CBM, Ribeirão Preto, São Paulo, Brazil.

<sup>4</sup> Universidade Paulista – UNIP, São Paulo, SP, Brazil.

<sup>5</sup> Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP, São Paulo, SP, Brazil.

<sup>6</sup> Graduate Program in Morphofunctional Sciences, Federal University of Ceará - UFC, Fortaleza, CE, Brazil.

<sup>7</sup> Unifacvest University Center - UNIFACVEST, Lages, Santa Catarina, Brazil.

\* Correspondence: julio.santos@alu.ufc.br.

**Abstract:** Neurodegenerative diseases encompass a group of disorders with diverse etiologies characterized by the accumulation of neurotoxic substances that contribute to neuronal damage and brain degeneration. The integration of the microbiota-intestine-brain axis mechanism occurs via afferent and efferent pathways with the assistance of the vagus nerve and peripheral circulation. The gut microbiota produces pathogenic proteins and other harmful substances that can cross the blood-brain barrier and develop into even more pathogenic proteins when in contact with the bloodstream. The microbial metabolites most commonly associated with neurodegenerative diseases are butyrate and amyloid, although the precise role and mechanism of their relationship with the microbiota have yet to be fully elucidated. Additionally, in Parkinson's disease, the microbiome is directly linked to an increase in opportunistic pathogens, a decrease in beneficial anti-inflammatory species, and higher levels of carbohydrate metabolizers.

**Keywords:** Neurodegenerative Disease; Brain Gut Axis; Microbiota-Gut-Brain Axis; Nervous System Degenerative Diseases.

Citation: Cavalcante FSBM, Araújo LL, Gomes GF, Galvão SL, Hipólito TCSE, Piagentini MC, Santos JCC. Role of Gut-Microbiome-Brain-Axis in Neurodegenerative Diseases: A Review on Mechanisms and Potential Therapeutics. Brazilian Journal of Clinical Medicine and Review. 2025;Jan-Dec; 03(1):bjc-mr5.

Received: 10 June 2024

Accept: 7 July 2024

Published: 10 July 2024



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## 1. Introduction

Studies in animal models has established the microbiota-intestine-brain axis as a real phenomenon; to date, evidence for its operation in humans is limited and faces considerable logistical challenges [1]. This axis is the communicant between two systems in our body, the gastrointestinal system and the central nervous system. Through it, biological and physiological interactions occur that involve and correlate with many conditions, such as neurodegenerative diseases, anxiety, schizophrenia, and obesity [2]. Neurodegenerative diseases comprise a set of diseases, of different etiologies, characterized by accumulation of neurotoxic substances that contribute to neuronal damage due to brain degeneration. Among these diseases we can list Alzheimer's and Parkinson's which basically constitute the deposition of neurotoxic proteins in specific regions of the human brain and thus cause the characteristic clinical manifestations of neurodegenerative diseases [3]. In recent years, a causal correlation has been noted between the gut microbiota and its singularities tied to neurodegenerative diseases, the microbiota-intestinal-brain axis [4, 5].

Integration of the microbiota-intestine-brain axis mechanism occurs via afferent and efferent pathways with the aid of the vagus nerve and peripheral circulation. The gut microbiota produces pathogenic proteins and other harmful substances that cross the blood-brain barrier and in contact with the blood circulation develop even more pathogenic proteins [6]. Among the accumulated proteins are found tau protein, b-amyloid protein and alpha-synuclein (a-syn) most associated with the occurrence of neurodegenerative diseases due to overstimulate astrocytes and microglia causing a series of neuronal damage [7].

Also in this sense, the gut microbiota is dynamic and can be altered by external factors such as xenobiotics, diet composition, or antibiotics. The composition of the microbiota of the GI tract can be influenced by dietary intake of natural bioactive molecules or probiotics, such as polyphenols and prebiotics. Therefore, therapies that aim to shape the predisposing factors of microbiota metabolism can affect gut bacterial composition and, consequently, brain biochemistry [8]. Further, this dynamism of the gut microbiota provides an environment that is influential by environmental and pharmacological experiences that modulate the onset and progression of various neurological disorders associated with deficits of the microbes, which justifies the critical link the gut-brain axis has with modulating cognition [9].

Since the gut microbiota is composed of a diverse and changeable ecosystem, several studies are aiming at therapeutic targets that may emerge as new therapies for the disorders proven to be related to intestinal dysbiosis, including neurodegenerative diseases. Understanding the mechanisms present in these associations may allow new studies to modulate preventive and therapeutic actions on several neurodegenerative diseases. Thus, in this review, we elucidate the mechanisms that permeate the gut-brain axis linked to recent therapeutic proposals that aim to minimize such influence.

## 2. Material and Methods

A narrative literature review was executed in the Medline database (PubMed), from 2020 to 2023, about Microbiota-Gut-Brain Axis in semantic neurodegenerative disease. In the Medline database (PubMed), 80 articles were found through the Mesh descriptor “(Neurodegenerative Disease) AND (Brain Gut Axis) AND (Microbiota-Gut-Brain Axis) AND (Nervous System Degenerative Diseases)” of which 77 were included, after the exclusion of articles following the first set of criteria - exclusion of titles that did not the mesh terms, articles not included in the research period of 2021-2023, as well as articles that were not originally in English. After this phase, a second set of criteria was applied - exclusion of the abstracts of titles that did not address Microbiota-Gut-Brain Axis or semantic Neurodegenerative Disease, which led to the exclusion of 58 articles, remaining 19 articles.

After the selection, utilizing the BIREME database (BVsalud), from 2018 to 2023, 117 articles were found through the Mesh descriptor “(Neurodegenerative Disease) AND (Brain Gut Axis) AND (Microbiota-Gut-Brain Axis) AND (Nervous System Degenerative Diseases)” using the same exclusion criteria, 117 articles remained within the time criterion (2018 to 2023), but 110 articles remained as original writing in English and only 8 articles were selected after the criterion of articles in the format of observational study, systematic review and controlled clinical trial. Finally, to enrich the discussion, 2 articles originally in English were excluded by excluding titles other than mesh terms, remaining 6 articles. Furthermore, utilizing the Scielo database, 1 article was found through the Mas descriptor “(Brain Gut Axis) AND (Microbiota-Gut-Brain Axis)”, then, no exclusion qualification was used because of the single article found. Other research that did not provide original or unpublished results were excluded.

Finally, aiming to enrich the discussion, 19 articles originally in English were manually selected and added according to their relevance in the synthesis of qualitative evidence.

### 3. Review

#### 3.1 Microbiome in Health and Disease

Most microbiota in the human body are anaerobic bacteria, and the most numerous types are Firmicutes and Bacteroidetes, which constitute 80% of the microorganisms living in the gastrointestinal tract. This microbiota keeps the number of other microorganisms under constant control, and thus has an important impact on the health of the individual [10]. The microbiota in the human body is made up of a dynamic system of changes and at the same time specific to each person. These processes of change can occur without major impact on the host organism but can also lead to serious systemic damage and metabolic changes, also affecting the permeability of the blood-brain barrier and thus affecting brain functionality [11].

The influence of this microbiota is through modulating the bioavailability of chemicals such as tryptophans, short chain fatty acids, serotonin, quinurenine, as well as blood-brain barrier permeability and the activation of peripheral immune cells and brain glial cells. This barrier breakdown in the gastrointestinal mucosa allows certain substances to penetrate and alter some physiological functions, leading to an activation of the innate immune response with a consequent increase in the levels of inflammatory mediators that will be directly related to the process of development of certain diseases, such as neuropsychiatric [12].

#### 3.2 Brain-Intestine Axis in Neurodegeneration

The gastrointestinal tract barrier is lined by an organized epithelial layer with various cell types, derived from various self-sustaining stem cells that interact with this gut microbiota being highly sensitive to external lifestyle, diet, sleep disturbances, and diet [2]. Thus, as a result of these numerous factors and with a consequent dysbiosis linked to the promotion of a permeable gut, inflammation and modification in the function of the enteric glia and, consequently, neurodegeneration ensues [13].

According to recent studies, the brain-intestine axis establishes a causal relationship between the gut microbiota and the brain, forming a bidirectional neuroendocrine pathway that plays an important role in the development and progression of neurodegenerative diseases [10]. Inside the gut is a small group of specialized intestinal cells called enteroendocrine cells (EEC) that monitor the contents of the lumen and secrete signaling mediators and hormones that bind to the vagal afferents, thus delivering signals directly to the brain via the vagus nerve. This mechanism propagates information to the brain about diet and gut ecosystem function [14].

The microbial metabolites most associated with neurodegenerative diseases are butyrate and amyloid, however the precise role and mechanism of relationship with the microbiota has not been fully elucidated. Furthermore, a reduced number of gram-negative bacteria and increased intestinal permeability have been identified in Alzheimer's disease, as well as production and accumulation of pathological amyloid proteins by some potentially pathogenic intestinal residents, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. In Parkinson's disease, on the other hand, the microbiome would be directly related to the increase of a group of opportunistic pathogens, reduction of beneficial anti-inflammatory species, and increased levels of carbohydrate metabolizers [14].

#### 3.3 The role of enteric glia in neurodegenerative diseases

Enteric glial cells are part of the enteric nervous system (ENS), also known as the "second brain", which innervate the entire gastrointestinal tract (GIT) coordinating aspects of functions, including permeability, motility, secretion, mucus production and immunity [15]. The ENS is part of a bi-directional communication with the brain via the

vagus nerve, playing a key role in the composition of the gut microbiome and may also contribute to neurodegenerative diseases [16].

Therefore, glial cells are located in all layers of the intestinal wall, being essential for the structural and nutritional support of enteric neurons, in addition to also having other functions, such as, for example, neuromediation, neurotransmission and neuroprotection [16, 17], including inflammatory processes [10]. They, in turn, are divided into 6 types and are based on the local subpopulations of glia based on morphology, anatomical location and location inside or outside the enteric ganglia [17].

As previously mentioned, enteric glia, because they are similar to astrocytes, both in structure and function [16], can lead to inflammatory processes resulting in increased intestinal permeability and blood-brain barrier [10, 16], thus enhancing the entry of substances produced by the microbiota into the CNS [16], that is, it ends up playing a critical role in the pathophysiology of gastrointestinal and neurodegenerative diseases [16]. In this inflammation, usually caused by dysbiosis, there is the expression of pro-inflammatory cytokines such as, for example, TNF-alpha, IL-6 and IL-1beta, mainly in neurodegenerative diseases such as Parkinson's disease (PD) [10]. Furthermore, the release of other inflammatory cytokines is associated with increased activity of Toll-Like receptors (TLR), especially TLR4 as it is prone to bacterial interaction, which are expressed in the ENS [10].

Thus, enteric inflammation, mainly caused by dysbiosis, can lead to neurodegenerative diseases such as, for example, PD, directing alpha-synuclein aggregation and influencing its pathology [10]. This is due to the fact that alterations in the intestinal microbiome can lead to an incorrect unfolding and abnormal aggregation of alpha synuclein in the intestine and ends up not being eliminated by physiological mechanisms, being then transported to the CNS through the vagus nerve [16]. Therefore, dysbiosis is a potential PD trigger in a genetically susceptible patient [16].

### **3.4 Therapeutic Strategies in Neurodegenerative Diseases with a Focus on the Brain-Gut Axis**

As exposed, data suggest that intestinal microbiota dysbiosis is a contributing factor in neurodegenerative diseases that are manifested through the microbiota-intestine-brain axis, such as Parkinson's disease and Alzheimer's disease. Therapeutic modulation of dysbiotic gut microbiota shares important areas of therapeutic opportunity, including dietary treatment such as probiotics, synbiotics, and prebiotics that can enhance neuro-immune activation [14].

There are properties in prebiotic substances that have been documented as beneficial to the organism because they are part of the diet and are natural substrates selectively used by host microorganisms divided into categories according to the type of food, for example, fructooligosaccharides (banana, garlic, onion), resistant starch (pea and lentil), inulin (beet and leek), soluble fiber (fruits, vegetables and oats) and galactooligosaccharide (beans and cashew nuts) [12]. These, being dietary carbohydrates selectively fermented by the microbiota, conferring benefits for the modulation of their composition and producing butyrate as a product of this fermentation, responsible for improving the function of the intestinal barrier, inducing regulatory cells and functioning as a signaling molecule in the intestine-brain axis [12].

Prebiotic supplementation causes changes in receptors essential for synaptic plasticity and memory function, being directly related to the reduction of the response to stress, anxiety and depressive behavior, as well as to the increase in brain-derived neurotrophic factor (BDNF) and the improvement of cognition. In addition, with its use, they showed improvement in social behavior and sleep patterns in patients with autism spectrum disorder (ASD) and improvement in anxiety in patients with irritable bowel syndrome [12, 14].

On the other hand, probiotics are defined as live microorganisms that, when used in adequate amounts, provide a beneficial effect to the individual. Among them, the com-

bination of *Lactobacillus rhamnosus* with *Bifidobacterium longum* has been shown to improve cognitive function and the metabolic state of neurodegenerative diseases (for example, Alzheimer's and Parkinson's) by influencing the composition of intestinal bacteria with lower intestinal permeability, improved cognitive function, reduction of c-reactive protein, decrease of oxidative damage and increase of enzymatic defense. In view of this, the chronic use of probiotics has been shown to be beneficial for the relief of neuropsychiatric suffering and, therefore, as one of the modulating agents of the microbiota-gut-brain axis [12].

#### 4. Conclusion

Inflammatory alterations related to enteric glia can cause harmful results to the blood-brain barrier and, consequently, to the human brain, however, diet, probiotics, symbiotics and prebiotics can provide a neuroimmune factor. In this review, our objective is to demonstrate the performance of the microbiota-intestinal-brain axis in the pathological construction of neurodegenerative diseases, as well as to elucidate associations with external and intrinsic intestinal factors that may contribute to a neuroprotection mechanism. Therefore, it is possible to inquire about the aggressor and healing role of the intestine in the human brain and, thus, build countless therapeutic and prophylactic possibilities for neuroscience in the field of neurodegenerative diseases.

**Funding:** None.

**Research Ethics Committee Approval:** None.

**Acknowledgments:** None.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Supplementary Materials:** None.

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