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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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THE GUT-BRAIN AXIS IN NEURODEGENERATIVE DISEASES AND MOOD DISORDERS: MECHANISMS AND SCIENTIFIC EVIDENCE

Jakub Przerwa *(Corresponding Author, Email: przerwa50@o2.pl)*
7th Navy Hospital in Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0005-4280-2209

ABSTRACT

The gut–brain axis (GBA) is a complex, bidirectional communication system between the central and enteric nervous systems and the gut microbiota. Increasing evidence points to its key role in the pathogenesis of neurodegenerative diseases and mood disorders, such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, depression, and anxiety disorders. Communication within the GBA occurs through neural, immune, and endocrine pathways, with microbial metabolites-including short-chain fatty acids, tryptophan derivatives, and cytokines-playing a crucial role in neuroinflammatory and neurodegenerative processes. Gut dysbiosis, increased intestinal barrier permeability, and vagus nerve dysfunction link intestinal abnormalities with brain dysfunction.

Preclinical and clinical studies suggest that modulation of the microbiota-through diet, probiotics, prebiotics, or fecal microbiota transplantation-may have therapeutic potential in neuropsychiatric and neurodegenerative diseases. However, individual variability, methodological limitations, and ethical considerations hinder the practical implementation of these strategies in clinical practice.

Understanding the functioning of the gut–brain axis may open new avenues for the prevention and treatment of neurological and psychiatric disorders through targeted interventions on the gut microbiota.

KEYWORDS

Gut-Brain Axis, Gut Microbiota, Neurodegenerative Diseases, Depression, Neuroinflammation, Short-Chain Fatty Acids, Serotonin, Probiotics, Dysbiosis, Psychobiotics

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Introduction

The gut-brain axis (GBA) is a bidirectional system of interactions between the central nervous system (CNS) and the gastrointestinal tract, encompassing metabolic, immunological, hormonal, and neuronal connections [1–3]. In recent years, it has become a focus of research in fields such as psychiatry, gastroenterology, and neurology. A key component of the GBA is the gut microbiota, which influences the CNS by affecting brain inflammation, neurogenesis, and neuroplasticity, thereby directly impacting brain function, including neuropsychological abilities [4,5].

The mechanisms through which the gut microbiota interacts with the CNS include the production of neuroactive metabolites (short-chain fatty acids – SCFAs, serotonin, dopamine, GABA), modulation of the hypothalamic-pituitary-adrenal (HPA) axis, and influence on the immune system [6–8].Dysfunction of this axis may contribute to various CNS disorders, including neurodegenerative diseases [9–12]. For example, it has been shown that gut dysbiosis in Alzheimer's disease may promote increased synthesis of hyperphosphorylated tau and amyloid-β [13,14]. In Parkinson's disease, evidence suggests that neurodegenerative processes may originate in the gut and spread to the CNS via the vagus nerve [15,16].The gut–brain axis and its dysregulation also play a crucial role in the pathogenesis of anxiety and depressive disorders. In mood disorders, dysbiosis can lead to disturbances in serotonin and tryptophan metabolism [17–

20].Clinical studies also suggest potential therapeutic effects on the GBA through diet, fecal microbiota transplantation, probiotics, and prebiotics, thereby influencing mood, neuroplasticity, and the rate of neurodegeneration [21–24]. These findings highlight the important role of gut microbiota in maintaining neuroimmunological homeostasis and its potential as a therapeutic target in neurodegenerative and psychiatric diseases.The aim of this article is to elucidate the mechanisms of gut–brain axis function, its role in the development of mood disorders and neurodegeneration, and to present potential therapeutic interventions.

Methodology

This article is a narrative literature review. Its purpose was to provide a concise overview of current evidence regarding the involvement of the gut-brain axis in the pathogenesis of neurodegenerative diseases and mood disorders, including biological mechanisms, clinical studies, and potential therapeutic implications.The literature search was conducted in PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect. Publications in English and Polish from 2013 to 2025 were included. The review included peer-reviewed articles, including reviews, original research, and meta-analyses, addressing the role of the gut-brain axis in disease development, as well as publications containing clinical and experimental data. Analysis was qualitative, focusing on key findings related to communication mechanisms within the GBA and their significance for neurodegeneration and affective disorders.

Structure of the Gut-Brain Axis

The gut-brain axis is a complex system encompassing multiple overlapping pathways: neuronal (vagus nerve and enteric nervous system), immunological (cytokines and immune cells), metabolic (amino acids, neurotransmitters, SCFAs produced by microbiota), and endocrine (hypothalamic-pituitary-adrenal axis) [25–28]. These connections maintain metabolic and neurophysiological homeostasis.The most direct pathway in the GBA is neuronal, in which the vagus nerve transmits signals from the gut to the CNS, reaching the amygdala and hippocampus [29,30]. The vagus nerve can be stimulated by gut bacteria, such as *Lactobacillus rhamnosus*, modulating GABA receptor expression in the brain [31].

Another important neuronal component is the enteric nervous system (ENS), which operates partially independently of the CNS and regulates blood flow, secretion, and gastrointestinal motility [32]. The ENS communicates with the CNS through afferent and efferent fibers, forming a dynamic regulatory network [33].Gut microbiota also influence cytokine balance, microglial activation, and T-cell regulation, modulating inflammatory responses in the CNS [34,35]. Dysregulation of the GBA can increase proinflammatory mediator synthesis, enhance intestinal permeability, and activate neuroinflammatory pathways, promoting neurodegeneration [36,37].

The hypothalamic-pituitary-adrenal (HPA) axis is another key element. Gut microbiota can modulate HPA activity, affecting corticotropin-releasing hormone (CRH) and cortisol secretion [38].Additionally, gut bacteria produce metabolites that affect CNS function, including SCFAs - butyrate, propionate, and acetate - which exhibit neuroprotective, anti-inflammatory, and antioxidant properties [39,40]. Tryptophan metabolites influence serotonin synthesis in enteric neurons and modulate NMDA and GABA receptor activity in the brain [41,42].Gut dysbiosis also contributes to neuroinflammation. Disruption of tight junctions in the intestinal epithelium allows bacterial translocation into the bloodstream, impairs blood-brain barrier function, and triggers microglial inflammatory responses [43,44].

Gut–Brain Axis in Neurodegenerative Diseases

Dysfunction of the GBA may play a central role in the pathogenesis of neurodegenerative diseases such as Parkinson’s disease (PD), Alzheimer’s disease (AD), and multiple sclerosis (MS). Gut microbiota can modulate disease onset and progression through effects on inflammation, neurotransmitter metabolism, and blood-brain barrier integrity [45–47].

PD is characterized by degeneration of dopaminergic neurons, resulting in bradykinesia, rigidity, resting tremor, and gait and postural disturbances. Evidence suggests that α-synuclein aggregates may originate in enteric plexuses and travel to the CNS via the vagus nerve, indicating that PD could begin in the gut [48–50]. Patients with PD often show reduced *Prevotella*, *Roseburia*, and *Faecalibacterium* and increased *Enterobacteriaceae*, promoting inflammation [51,52]. In animal models, colonization with PD patient-derived microbiota exacerbated motor and neuroinflammatory symptoms compared with healthy donor microbiota [53]. In AD, gut microbiota influence disease progression and cognitive function. Patients with AD have reduced butyrate synthesis due to decreased *Butyricicoccus* and *Eubacterium* [54]. Gut microbiota also affect

β-amyloid and hyperphosphorylated tau deposition, contributing to cognitive decline [55,56]. Bacterial lipopolysaccharide and amyloids may induce β-amyloid aggregation and microglial activation [57,58]. Dysregulation of tryptophan and serotonin metabolism further disrupts HPA axis function, increasing oxidative stress and neuronal apoptosis [59].

In MS, a chronic inflammatory demyelinating CNS disease, patients show characteristic gut microbiota changes, including reduced anti-inflammatory bacteria (*Prevotella*, *Parabacteroides distasonis*) and increased potentially proinflammatory species (*Akkermansia muciniphila*, *Methanobrevibacter smithii*) [62,63]. Treg/Th17 imbalance promotes CNS inflammation [64], and fecal microbiota transplantation (FMT) from MS patients exacerbated disease in animal models [65]. SCFAs exhibit neuroprotective and immunomodulatory effects by inhibiting microglial activation [66].

Gut–Brain Axis in Depression and Anxiety Disorders

Dysfunction of the GBA directly affects depressive and anxiety disorders by promoting oxidative stress, HPA axis dysregulation, and gut microbiota disturbances [67–69]. Increased intestinal permeability allows lipopolysaccharide translocation, triggering systemic inflammation and altering tryptophan metabolism, reducing brain serotonin synthesis [70,71].

Gut bacteria influence mood via modulation of neurotransmitters, the immune system, and tryptophan metabolism. Animal studies show germ-free mice exhibit increased depressive and anxiety-like behaviors, while colonization with probiotic strains (*Bifidobacterium longum*, *Lactobacillus rhamnosus*) normalizes behavior and cortical GABA receptor expression [72,73].Depressed patients often show reduced butyrate-producing bacteria (*Faecalibacterium*, *Coprococcus*) and increased potentially pathogenic species (*Enterobacteriaceae*, *Alistipes*) [74–76]. Clinical studies indicate probiotics reduce inflammatory markers, lower cortisol, and improve mood in mild depression [77–79].

HPA axis hyperactivity is prominent in depression. Strains such as *Bifidobacterium infantis* and *Lactobacillus helveticus* can regulate HPA activity and reduce stress-related symptoms [81,82]. Gut microbiota also influence serotonergic and GABAergic neurotransmission, hippocampal and amygdala function, affecting psychiatric symptom severity and potential clinical applications [83,84]. Prebiotics, probiotics, and FMT can alleviate anxiety and support mood disorder treatment [85–91]. Chronic stress promotes dysbiosis and proinflammatory species, creating a feedback loop between stress and microbiota imbalance [92,93].

Therapeutic Interventions Targeting the Gut-Brain Axis

Key therapeutic strategies influencing neurodegenerative diseases and mood disorders via the GBA include probiotics, prebiotics, synbiotics, dietary interventions, and fecal microbiota transplantation (FMT) [94,95]. Probiotics are live microorganisms that confer health benefits when administered in adequate amounts. Lactic acid bacteria (*Lactobacillus* spp., *Bifidobacterium* spp.) are particularly important. Psychobiotics - probiotics beneficial to mental health - have been shown to improve mood, reduce cortisol, and alleviate anxiety in healthy individuals [96–100]. Probiotics also positively affect neurogenesis and BDNF levels, supporting hippocampal function [101].

Diet plays a critical role in shaping gut microbiota. The Mediterranean diet supports microbial diversity and may reduce depression risk, while diets high in sugars and saturated fats promote inflammation and mood disturbances [104–106]. Fermented foods can enhance gut–brain communication [107]. FMT involves transferring healthy donor microbiota to the patient's gut to restore microbial balance, initially used for recurrent *Clostridioides difficile* infections. Evidence suggests FMT may also benefit PD, AD, and depression [108–110], though further research on safety and standardization is required [111]. Future studies should focus on elucidating GBA mechanisms using metagenomics and proteomics, optimizing psychobiotic composition and dosage, and identifying specific neuroactive bacterial strains [112,113].

Conclusions

Current evidence highlights the significant role of the gut-brain axis in the pathophysiology of depressive, anxiety, and neurodegenerative disorders. Dysbiosis affects neurotransmitter function, promotes oxidative stress and neuroinflammation, disrupts metabolic and immune homeostasis, and impairs HPA axis function. Consequently, it may influence the course of Alzheimer's and Parkinson's disease, depression, mood disorders, and anxiety symptoms.

Therapeutic interventions targeting gut microbiota composition and quality offer opportunities to modulate the GBA and alleviate neuropsychiatric symptoms. These include probiotics, prebiotics, diet, and

FMT, which can be effective and safe adjuncts to pharmacotherapy.Although many mechanisms remain unclear, translational research suggests the gut–brain interface is a promising therapeutic target in 21st-century medicine. Further clinical studies are needed to evaluate long-term effects and standardize interventions. Integrating knowledge from neurology, psychiatry, microbiology, and nutrition may lead to a new generation of neuroprotective and neuromodulatory therapies aimed at maintaining microbiome homeostasis and promoting mental and neurological health.

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