

Gut-Brain Axis and Microbiota's Role in Neurotoxicity Modulation

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Abstract

The gut-brain axis is a complex communication system that connects the gastrointestinal tract and the central nervous system. It is bidirectional in nature. Also, it occurs through neural, hormonal and immune pathways.

Research is starting to show that gut microbiota affects certain neurotoxic effects by controlling inflammation, maintaining the blood-brain barrier, and making neurotransmitters. The changes in the microbes of the gut cause the condition named dysbiosis. If it is disturbed due to heavy metals, pesticides, drugs and chemicals, it would interfere with the neurotoxic response. Microbial metabolites like SCFAs, bile acids, and tryptophan derivatives can potentiate or antagonize neurotoxicity by regulating oxidative stress, excitotoxicity and immune activation. Also, new findings show that probiotics, prebiotics, and fecal microbiota transplantation treatments may reverse neurotoxic damage and neurophysiological balance. Even though tests have helped us understand this well, it is still hard to know for sure that these things happen in humans. The growing area of microbiome science and its association with the field of neurotoxicology has tremendous importance in sub-fields of prevention, diagnostics and personalized therapeutics. More is known about the link between our gut microflora and the brain, will open new ways to reduce neurotoxicity and achieve better neurological health.

Keywords: Gut-Brain Axis; Microbiota; Neurotoxicity; Neuroinflammation; Dysbiosis

Introduction

The gut-brain axis represents bidirectional communication between the gastrointestinal tract and the brain, facilitating physiological and molecular connections through diverse signaling pathways [1]. This axis links complex structures and functions-such as stress responses and immunomodulation-to neural targets, either independently or in combination [2]. The gut microbiota comprises a highly

diverse and variable microbial population that establishes both symbiotic and homeostatic relationships with the host [3]. Several molecular and cellular mechanisms underpin microbiota-brain interactions, including signaling molecules, immune system modulation, autonomic neural pathways, and enteric nervous system activity, which in turn influence neurodevelopment, neuroinflammation, and neurotransmitter production [4]. Together, the microbiota and central nervous system contribute to host function throughout life [5]. A century after the enteric nervous system was identified, connections between gut microbes and the central nervous system have expanded the understanding of the gut-brain axis, suggesting mediating roles in health and disease [6]. Robust evidence from animal models indicates that the gut microbiota is crucial for proper neurodevelopment and neuronal function, while its composition and metabolic activity can significantly affect behavior [1]. Microbiome-brain communication can be described through indirect or direct pathways, providing a stronger rationale than traditional concepts of gut-microbiota-brain interaction [2].

Understanding the gut-brain axis

The gut-brain axis comprises the bidirectional communication between the gastrointestinal tract and the brain [1]. Signals from the brain influence gastrointestinal functions such as motility and secretion, and sensory information from the digestive tract is transmitted to CNS structures implicated in homeostatic and behavioral control [7]. Pathways of communication include multiple physiological processes, ranging from neural and hormonal to molecular mechanisms [8].

Microbiota composition and diversity

Gut microbiota encompass a broad range of microbial populations (including bacteria, archaea, yeasts, and fungi) residing in the enteric lumen, with bacterial counts reaching up to 10^{14} organisms belonging to at least 12-18 different phyla and approximately 1,000 species [7]. This microbiota maintains general organ integrity and homeostasis of the intestinal mucosa, exhibiting considerable interindividual variability in diversity and abundance [9]. The most prevalent bacterial phyla are *Firmicutes* and *Bacteroidetes*; species from the former include *Clostridium*, *Enterococcus*, *Lactobacillus*, and *Ruminococcus*, while *Bacteroidetes* are represented by *Bacteroides* and *Prevotella* [10]. *Actinobacteria* (mainly *Bifidobacterium*), *Proteobacteria* (*Escherichia* and *Desulfovibrio*), and *Verrucomicrobia* (*Akkermansia*) are present at lower abundance (~10 - 15%). The human gut microbiome encompasses over 22 million genes and encodes tens of thousands of different metabolic pathways [2].

Human microbiota composition undergoes continuous development and changes from the prenatal stage through birth, infancy, and childhood, reaching adult configuration during early adolescence before declining with ageing/pre-geriatric stages [11]. Microbiota-gut-brain axis communication systems may maintain healthy microbial colonization and significantly influence host physiology and brain development throughout life via specific pathways [12].

Mechanisms of gut microbiota interaction with the brain

Bidirectional communication between the gut and brain connects the digestion of food with mood, behavior, and quality of life [2]. Several pathways mediate this microbiota influence on the central nervous system [13]. Gut bacteria significantly impact neuro-immune and neuro-endo-crine functions in the gut-brain axis, although definitions of “immune” and “endocrine” vary [14]. The diversity of commensal microorganisms implies a broad range of metabolites and molecules that can influence central nervous system physiology [7]. Chemicals produced by or induced via bacteria in the digestive tract signal to the brain through various mechanisms, including stimulation of enteric nerves; interaction with intestinal epithelium to activate neuropeptides or hormones; modulation of immune cells; or entry into circulation, thereby reaching the brain through blood flow [15].

Role of gut microbiota in neurodevelopment

Because of its location, the gastrointestinal tract constitutes the anatomical interface between the external environment and the interior of an organism in charge of regulating the host's homeostasis [16]. Within the framework of the accidental exposure to environmental contaminants that everyday products and food are a source of, the digestive system represents the principal route of intake and a potential target of the toxicity of these substances [17]. Models available to study the toxic effects of contaminants in the intestine are diverse, and they all have in common the use of isolated cells, two-dimensional (2D) cultures, or animal models for the study of toxicity [18]. These poorly physiological models represent, in many cases, a barrier for the predictive extrapolation of data to humans [19]. Under this premise, the present contribution highlights the potential application of organoids as a reliable tool for the toxicological assessment of environmental pollutants and drugs that affect the intestine [20].

Impact of microbiota on neuroinflammation

Microbiota can regulate neuroinflammation, a key factor in the development of neurotoxicity [21]. Conversely, these microorganisms may also contribute to neurotoxicity by promoting inflammatory cascades and accumulation of toxic metabolites in the nervous system [7]. The human microbiome shapes the immune response, modulating inflammatory activity within the brain [22]. Altered intestinal bacterial populations frequently coincide with central nervous system disturbances, suggesting a role for microbiota-derived inflammation in nerve damage [23]. Probiotic *Bifidobacterium longum* NCC3001 alleviates symptoms in patients with irritable bowel syndrome, attenuating depressive components and modifying brain activation patterns [24]. The gut-brain axis provides a conceptual framework for mutual influence between gastrointestinal and cerebral functions [25].

Altered gut flora often predates and may accelerate neuroinflammatory processes, particularly in Alzheimer's disease [24]. Exposure to bacterial lipopolysaccharides induces neuroinflammation by activating inflammatory pathways [23]. Moreover, gut bacteria generate amyloids that could modulate neuroinflammatory responses [26]. Dietary interventions that preserve beneficial microbiota reduce neuroinflammation, as demonstrated in Tg2576 transgenic mice [27]. Bacterial load also influences inflammatory responses: antibiotic-mediated reductions in colonization prevent alcohol-induced neuroinflammation in mice [28]. Comparable phenomena occur in Gulf War Illness, characterized by concurrent neurological and gastrointestinal disturbances [29]. Microbiota modulates neuroinflammatory processes, whereas interactions with foreign compounds can exacerbate these and other adversities [30]. This dual capacity profoundly affects neurotoxic mechanisms, in line with the modulation exercised throughout other domains of neural function [30].

Microbiota and neurotransmitter production

The gut microbiota can produce and modulate neurotransmitters involved in neural signalling and neurotoxicity pathways, including γ -aminobutyric acid (GABA), serotonin, glutamate, dopamine, and norepinephrine [31]. GABA is produced by *Bacteroides*, *Parabacteroides*, and *Escherichia* species; their relative abundance positively correlates with depression-trait behaviors [2]. Early colonization enhances enteric-spinal GABA receptor expression, and germ-free mice have reduced colonic and plasma GABA, but normal brain levels [32]. Serotonin is generated mainly by enterochromaffin cells under microbiota influence; metabolites such as α -tocopherol, tyramine, and p-aminobenzoate increase peripheral 5-HT concentrations while the microbiota also supplies precursors and intermediates that influence serotonin biosynthesis [33]. Glutamate is synthesized by bacteria including *Corynebacterium glutamicum* and *Lactobacillus plantarum*, and microbes such as *Escherichia coli* produce dopamine and norepinephrine, although the mechanisms regulating their systemic effects are poorly understood [22]. Microbial fermentation generates short-chain fatty acids (SCFAs) that affect behaviors such as those associated with depression, neurodevelopment, anorexia, and colorectal cancer; SCFAs are absorbed in the colon and transported to the bloodstream, where acetate concentrations reach 100 - 200 μ M [34]. Through the generation and modulation of neuroactive compounds-especially alkaloids-the microbiota shapes the circulating pool of these molecules and modulate host signalling pathways at multiple levels [35]. This control over neurotransmitters constitutes a significant mechanism by which gut microbes influence brain function [36].

Conclusion

The gut-brain axis is a bidirectional communication pathway linking the gut and brain, primarily influenced by the commensal microbiota [7]. The microbiota contributes to the neuro-immune-endocrine connection, and emerging evidence shows that xenobiotics interact with it [37]. Most evidence derives from animal models, which, although limited, demonstrated that the gut microbiota is essential for proper neurodevelopment and neuronal function [1]. The gut hosts a broad diversity of microbial populations that modulate neurotoxicity related to the central nervous system (CNS) via the gut-brain axis, conferring differential effects on a wide range of xenobiotics [36]. Various molecular mechanisms mediate these interactions [38]. Neuronal development and function are influenced by the microbiota, which plays a pivotal role in the modulation of neuroinflammation [26]. Through neurotransmitter production, the microbiota participates in neurotoxicity pathways [39].

Bibliography

1. Gubert C., *et al.* "Convergent pathways of the gut microbiota-brain axis and neurodegenerative disorders". *Gastroenterology Report (Oxford)* 10 (2022): goac017.
2. Ojeda J., *et al.* "Gut microbiota interaction with the central nervous system throughout life". *Journal of Clinical Medicine* 10.6 (2021): 1299.
3. Dash S., *et al.* "Understanding the role of the gut microbiome in brain development and its association with neurodevelopmental psychiatric disorders". *Frontiers in Cell and Developmental Biology* 10 (2022): 880544.
4. Wang Q., *et al.* "The microbiota-gut-brain axis and neurodevelopmental disorders". *Protein and Cell* 14.10 (2023): 762-775.
5. He Y., *et al.* "Unraveling the interplay between metabolism and neurodevelopment in health and disease". *CNS Neuroscience and Therapeutics* 31.5 (2025): e70427.
6. Bicknell B., *et al.* "Neurodegenerative and neurodevelopmental diseases and the gut-brain axis: the potential of therapeutic targeting of the microbiome". *International Journal of Molecular Sciences* 24.11 (2023): 9577.
7. Balaguer-Trias J., *et al.* "Impact of contaminants on microbiota: linking the gut-brain axis with neurotoxicity". *International Journal of Environmental Research and Public Health* 19.3 (2022): 1368.
8. Mayer EA., *et al.* "The gut-brain axis". *Annual Review of Medicine* 73 (2022): 439-453.
9. Doroszkiewicz J., *et al.* "The role of gut microbiota and gut-brain interplay in selected diseases of the central nervous system". *International Journal of Molecular Sciences* 22.18 (2021): 10028.
10. Engevik AC and Engevik MA. "Exploring the impact of intestinal ion transport on the gut microbiota". *Computational and Structural Biotechnology Journal* 19 (2021): 134-144.
11. Jeong S. "Factors influencing development of the infant microbiota: from prenatal period to early infancy". *Clinical and Experimental Pediatrics* 65.9 (2022): 439-447.
12. Sarkar A., *et al.* "The association between early-life gut microbiota and long-term health and diseases". *Journal of Clinical Medicine* 10.3 (2021): 459.
13. Pérez-Morales M., *et al.* "Steering the microbiota-gut-brain axis by antibiotics to model neuro-immune-endocrine disorders". *Neuroimmunomodulation* 31.1 (2024): 89-101.

14. Sun Z., *et al.* "A review of neuroendocrine immune system abnormalities in IBS based on the brain-gut axis and research progress of acupuncture intervention". *Frontiers in Neuroscience* 17 (2023): 934341.
15. De la Fuente M. "Interactions between the gut microbiota and the nervous system. Microbiota-gut-brain axis in health and mental diseases". *Journal of Spanish Society of Anti-Aging Medicine and Longevity and Latin-American Federation of Anti-Aging Medicine Societies* (2021): 65.
16. Priyadarshane M., *et al.* "Mechanism of toxicity and adverse health effects of environmental pollutants". In *Microbial biodegradation and bioremediation* (2022): 33-53.
17. Pironti C., *et al.* "Microplastics in the environment: intake through the food web, human exposure and toxicological effects". *Toxics* 9.9 (2021): 224.
18. Sandys O and Te Velde A. "Raising the alarm: environmental factors in the onset and maintenance of chronic (low-grade) inflammation in the gastrointestinal tract". *Digestive Diseases and Sciences* 67.9 (2022): 4355-4368.
19. Jomova K., *et al.* "Heavy metals: toxicity and human health effects". *Archives of Toxicology* 99.1 (2025): 153-209.
20. Zhang H., *et al.* "Gut microbiota contributes to bisphenol A-induced maternal intestinal and placental apoptosis, oxidative stress, and fetal growth restriction in pregnant ewe model by regulating gut-placental axis". *Microbiome* 12.1 (2024): 28.
21. Khalid Farooq R., *et al.* "Varied composition and underlying mechanisms of gut microbiome in neuroinflammation". *Microorganisms* 10.4 (2022): 705.
22. Tinkov AA., *et al.* "Gut microbiota as a potential player in Mn-induced neurotoxicity". *Biomolecules* 11.9 (2021): 1292.
23. Solanki R., *et al.* "Emerging role of gut microbiota dysbiosis in neuroinflammation and neurodegeneration". *Frontiers in Neurology* 14 (2023): 1149618.
24. Mou Y., *et al.* "Gut microbiota interact with the brain through systemic chronic inflammation: implications on neuroinflammation, neurodegeneration, and aging". *Frontiers in Immunology* 13 (2022): 796288.
25. Balaguer-Trias J., *et al.* "Impact of contaminants on microbiota: linking the gut-brain axis with neurotoxicity". *International Journal of Environmental Research and Public Health* 19.3 (2022): 1368.
26. Bairamian D., *et al.* "Microbiota in neuroinflammation and synaptic dysfunction: a focus on Alzheimer's disease". *Molecular Neurodegeneration* 17.1 (2022): 19.
27. Padhi P., *et al.* "Mechanistic insights into gut microbiome dysbiosis-mediated neuroimmune dysregulation and protein misfolding and clearance in the pathogenesis of chronic neurodegenerative disorders". *Frontiers in Neuroscience* 16 (2022): 836605.
28. Makdissi S., *et al.* "Towards early detection of neurodegenerative diseases: a gut feeling". *Frontiers in Cell and Developmental Biology* 11 (2023): 1087091.
29. Kurowska A., *et al.* "The role of diet as a modulator of the inflammatory process in the neurological diseases". *Nutrients* 15.6 (2023): 1436.
30. Kurhaluk N., *et al.* "Role of antioxidants in modulating the microbiota-gut-brain axis and their impact on neurodegenerative diseases". *International Journal of Molecular Sciences* 26.8 (2025): 3658.

31. D'Alessandro G., *et al.* "Neuro-signals from gut microbiota: perspectives for brain glioma". *Cancers (Basel)* 13.11 (2021): 2810.
32. Wang W., *et al.* "Neurotransmitter disturbances caused by methylmercury exposure: Microbiota-gut-brain interaction". *Science of the Total Environment* 873 (2023): 162358.
33. Dicks LMT. "Gut bacteria and neurotransmitters". *Microorganisms* 10.9 (2022): 1838.
34. Chen Y., *et al.* "Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders". *Nutrients* 13.6 (2021): 2099.
35. Duan J., *et al.* "Podophyllotoxin-mediated neurotoxicity via the microbiota-gut-brain axis in SD rats based on the toxicological evidence chain (TEC) concept". *Science of the Total Environment* 907 (2024): 168106.
36. Teng M., *et al.* "Polystyrene nanoplastics toxicity to zebrafish: dysregulation of the brain-intestine-microbiota axis". *ACS Nano* 16.5 (2022): 8190-8204.
37. Guzzardi MA., *et al.* "Maternal pre-pregnancy overweight and neonatal gut bacterial colonization are associated with cognitive development and gut microbiota composition in pre-school-age offspring". *Brain, Behavior, and Immunity* 100 (2022): 311-320.
38. Kerna NA., *et al.* "The gut-brain axis in neurodevelopmental disorders: mechanistic insights, clinical implications, and public health strategies". *Gut* 29 (2024): 5.
39. Jabbari Shiadeh SM., *et al.* "Bidirectional crosstalk between the gut microbiota and cellular compartments of brain: Implications for neurodevelopmental and neuropsychiatric disorders". *Translational Psychiatry* 15.1 (2025): 278.

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