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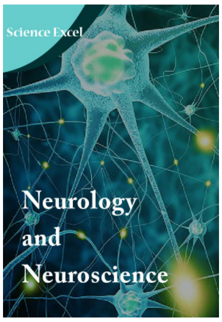
Review Article



Influence of Gut Microbiota on Neurodevelopment: A Literature Review

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Abstract

The gut microbiota plays a crucial role in the development of the central nervous system (CNS) from the gestational period through the early years of life. Growing evidence shows that changes in its composition—known as dysbiosis—are associated with neurological and behavioral disorders such as autism spectrum disorder (ASD), ADHD, and anxiety. This study aims to review the current literature on the relationship between the microbiota and neurodevelopment, highlighting the involved mechanisms, influencing factors, and potential clinical applications. Scientific articles were selected from databases such as PubMed, Scopus, and Web of Science. The findings point to a bidirectional communication between the gut and the brain, mediated by immunological, metabolic, and neuroendocrine pathways, with therapeutic potential through interventions such as probiotics, prebiotics, and fecal microbiota transplantation. It is concluded that modulating the microbiota represents a promising pathway to promote neurological health in children.

Introduction

Neurodevelopment is a complex process involving the formation, differentiation, and maturation of nerve cells, as well as the consolidation of neural circuits. Traditionally, genetic and environmental factors such as nutrition and sensory stimuli have been identified as the main modulators of this process. However, in recent decades, interest has grown in the role of the gut microbiota—a community of microorganisms that inhabit the gastrointestinal tract—as a direct influencer of neurological development, especially in childhood [1].

Studies show that the microbiota is involved in cognitive, behavioral, and emotional functions through the so-called gut-brain axis, a bidirectional communication network between the central nervous system, enteric nervous system, immune system, and microbial metabolism [2]. Understanding this interaction may clarify the pathophysiology of various neurodevelopmental disorders and open doors for innovative therapeutic interventions.

Justification

Despite advances in neuroscience and microbiology, integration between these fields is still recent. With the increasing prevalence of disorders such as ASD, ADHD, and childhood depression, identifying new risk factors and prevention strategies has become urgent. The gut microbiota, being modifiable through diet, medications, and probiotics, represents a modifiable risk or protective factor that can be managed early. Therefore, it is relevant to critically review the scientific literature to understand the real impact of the microbiota on neurodevelopment and its possible clinical applications.

Methodology

This is a narrative literature review. The search was conducted in PubMed, Scopus, and Web of Science databases using the following keywords: "microbiota," "neurodevelopment," "gut-brain axis," "infant," "child," "autism," "ADHD," "probiotics," and "dysbiosis," combined with Boolean operators AND/OR. Articles published between 2010 and 2024, available in English or Portuguese, that directly addressed the influence of the microbiota on human or animal neurodevelopment were included. Duplicates, editorials, and systematic reviews with unclear methodology were excluded.

Results

Analysis of the selected studies revealed that gut microbiota plays an active role in several stages of neurodevelopment, influencing processes ranging from neuronal proliferation and differentiation to the modulation of

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Table 1 – Effects of Absence or Dysbiosis of Gut Microbiota in Animal Models

Study	Experimental Model	Observed Changes	Reference
Clarke et al. (2013)	Germ-free mice	Reduced BDNF in the hippocampus, anxiety-related behavioral alterations	(3)
Ogbonnaya et al. (2015)	Germ-free mice	Decreased adult hippocampal neurogenesis	(4)
Braniste et al. (2014)	Germ-free mice	Increased blood–brain barrier permeability	(17)
Hsiao et al. (2013)	Microbiota transplant (ASD)	Autism-like behaviors after microbiota transfer to germ-free mice	(20)
Kelly et al. (2016)	Microbiota transplant (depression)	Depressive behaviors in recipient animals after microbiota transplant	(21)

synaptic circuits. In germ-free animal models, the absence of microbiota resulted in significant structural changes in the brain, including reduced hippocampal volume, altered myelination, and decreased expression of neurotrophic factors such as BDNF [3,4].

Table 1 summarizes the main findings from experimental studies in murine models, highlighting the consequences of absence or dysbiosis of gut microbiota on the brain.

In addition, the composition of the microbiota was found to be influenced by factors such as delivery mode, breastfeeding, antibiotic use, and early childhood diet, with long-term impacts on neurological function [5,6]. Children born via cesarean section and not breastfed are more predisposed to developing disorders such as ADHD and ASD, possibly due to lower colonization by beneficial bacteria like Lactobacillus and Bifidobacterium [7].

In humans, recent meta-analyses show that specific patterns of intestinal dysbiosis are correlated with neurological and psychiatric symptoms. Children with ASD, for example, have higher abundance of pro-inflammatory bacteria such as Clostridium spp. and lower microbial diversity compared to healthy controls [8,9]. Metabolomic analyses revealed changes in levels of short-chain fatty acids (SCFAs), such as butyrate, which are known to be involved in neurogenesis and the integrity of the blood-brain barrier [10].

Table 2 – Clinical Evidence Linking Gut Microbiota and Neurodevelopment

Population/Intervention	Main Finding	Reference
Children with ASD	Higher abundance of Clostridium, lower microbial diversity	(8,9)
Metabolomic analysis (ASD vs. controls)	Reduced levels of SCFAs, especially butyrate	(10)
Probiotics in pregnant women (Pärtty et al.)	Lower risk of ASD, improved early neurodevelopment	(11)
Probiotics in infants (Rhoads et al.)	Reduced colic symptoms and inflammatory markers	(12)
Synbiotics in children (Nettleton et al.)	Increased brain functional connectivity and reduced systemic inflammation	(13)

Randomized clinical trials using probiotics in pregnant women and infants showed positive effects on child neurological development, including improvements in cognitive, language, and adaptive behavior measures [11,12]. Similarly, interventions with synbiotics in pediatric populations showed reductions in inflammatory markers and increased functional connectivity in brain regions related to emotional regulation [13]. Table 2 summarizes these clinical findings.

Discussion

The findings of this review reinforce the idea that the gut microbiota is a key component in orchestrating neurodevelopment. The mechanisms through which the microbiota exerts this influence are multiple and interconnected, including:

- **Production of neuroactive metabolites,** such as SCFAs, dopamine, GABA, and serotonin, which directly affect neuronal activity and synaptic plasticity [14,15].
- **Modulation of systemic and local inflammation,** through activation of regulatory T cells and reduction of pro-inflammatory cytokine production, creating a favorable environment for neural development [16].
- **Interference with the maturation of the blood-brain barrier**, with direct implications for CNS protection and regulation of neurotoxic substance entry [17].

It is important to highlight that the gut-brain axis is not unidirectional. Neurological factors, such as maternal stress and anxiety, also negatively affect microbiota composition through hormonal and immune changes during pregnancy. This bidirectional cycle between brain and gut is particularly relevant in early childhood, a period when both the nervous system and microbiota are developing in parallel [18,19].

Studies in germ-free murine models provide robust evidence of causality, as microbiota transplants from individuals with ASD or depression into mice led to the emergence of behaviors similar to those observed in human donors. This indicates that microbiota can modulate complex behavioral traits [20,21].

Despite these advances, significant gaps remain. Many studies are observational, making it difficult to establish causality in humans. There is also great heterogeneity in sequencing techniques and in defining an "ideal" microbiome, which complicates comparisons across studies. Additionally, the response to probiotic interventions is highly individualized, reinforcing the need for personalized approaches such as customized microbiota and precision psychiatry [22].

Future research should prioritize controlled, longitudinal clinical trials that evaluate not only microbiota composition but also its metabolic products and interactions with the immune and central nervous systems. The use of integrated omics tools will enable a deeper understanding of this interface.

Conclusion

Gut microbiota directly influences the development of the central nervous system through multiple mechanisms, and early modulation may represent a promising strategy for preventing and treating neurodevelopmental disorders. The consolidation of evidence in humans, through robust clinical studies, will be essential for advancing this approach in the context of child health.

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