

Gut-Brain Axis in ADHD: A Review of Current Evidence

Oś jelitowo-mózgowa w ADHD: przegląd aktualnych doniesień naukowych

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder traditionally linked to monoaminergic dysregulation within the brain's reward circuitry. Recent evidence points to the potential role of the gut-brain axis (GBA),

a bidirectional communication network linking the central nervous system with the enteric microbiota. This narrative review explores the proposed associations between intestinal dysbiosis and ADHD symptoms, as well as the potential for GBA-targeted therapeutic interventions. Research suggests that individuals with ADHD may exhibit distinct microbial profiles, characterized by an increased abundance of genera such as *Bifidobacterium* and *Bacteroides*, and a depletion of anti-inflammatory taxa like *Faecalibacterium*. These shifts are hypothesized to contribute to “leaky gut” syndrome, potentially triggering systemic inflammation and neuroinflammation that could disrupt neural circuits responsible for executive function. Furthermore, experimental models indicate that gut microbes may modulate the availability of dopamine precursors, indirectly influencing reward processing. Preliminary clinical data suggest that “psychobiotics,” synbiotics, and targeted micronutrient supplementation (e.g., iron, zinc, and magnesium in cases of confirmed deficiencies) might serve as supportive interventions and potentially improve quality of life. While standard pharmacotherapy remains the primary treatment, GBA-focused strategies are being investigated as adjunctive therapies, offering a promising yet preliminary avenue for personalized management. Integrating these interventions may help manage common comorbidities across the lifespan, though further robust clinical trials are required.

Keywords: ADHD, Gut-brain axis, Microbiota, Probiotics, Neuroinflammation, Dopamine, Nutrition.

Streszczenie

Zespół nadpobudliwości psychoruchowej z zaburzeniami uwagi (ADHD) to powszechne zaburzenie neurorozwojowe, tradycyjnie powiązane z dysregulacją układu monoaminergicznego w obrębie struktury pętli nagrody w mózgu. Najnowsze doniesienia wskazują na potencjalną rolę osi jelitowo-mózgowej (GBA), dwukierunkowej sieci komunikacyjnej łączącej ośrodkowy układ nerwowy z mikrobiotą jelitową. Niniejszy przegląd piśmiennictwa analizuje sugerowane powiązania między dysbiozą jelitową a objawami ADHD, a także skuteczność interwencji terapeutycznych ukierunkowanych na oś jelitowo-mózgową. Badania wskazują, że osoby z ADHD mogą wykazywać odmienny profil mikrobiomu, charakteryzujący się zwiększoną liczebnością rodzajów takich jak *Bifidobacterium* i *Bacteroides* przy jednoczesnym zubożeniu taksonów o działaniu przeciwwzapalnym, np. *Faecalibacterium*. Przypuszcza się, że zmiany te przyczyniają się do rozwoju zespołu „nieszczelnego jelita”, co potencjalnie wywołuje uogólniony stan zapalny oraz następcze zapalenie układu

nerwowego, zdolne do zaburzenia funkcji sieci neuronalnych odpowiedzialnych za funkcje wykonawcze. Ponadto modele eksperymentalne wskazują, że mikroorganizmy jelitowe mogą modulować dostępność prekursorów dopaminy, wpływając pośrednio na procesy przetwarzania nagrody. Wstępne dane kliniczne sugerują, że psychobiotyki, synbiotyki oraz celowana suplementacja mikroskładników (np. żelaza, cynku i magnezu w przypadku potwierdzonych niedoborów) mogą służyć jako interwencje wspomagające i potencjalnie poprawiać jakość życia pacjentów. Choć standardowa farmakoterapia pozostaje podstawą leczenia, strategie zorientowane na oś jelitowo-mózgową są badane jako terapie adiuwantowe, oferując obiecujący, choć wciąż wstępny kierunek w spersonalizowanym podejściu terapeutycznym. Integracja tych interwencji może pomóc w kontrolowaniu powszechnych zaburzeń współistniejących na przestrzeni całego życia pacjenta, aczkolwiek konieczne jest przeprowadzenie dalszych, rzetelnych badań klinicznych.

Słowa kluczowe: ADHD, oś jelitowo-mózgowa, mikrobiota, probiotyki, neuroinflamacja, dopamina, żywienie.

Introduction

Neurobiological Foundations of the Gut-Brain Axis

Contemporary neuroscience is increasingly conceptualizing psychiatric disorders through the lens of complex inter-systemic communication networks. Central to this paradigm is the gut-brain axis (GBA), a bidirectional communication network that links the central nervous system (CNS) with the enteric nervous system (ENS). This tripartite conversation involves signaling between the brain, the gut, and the vast microbial community residing in the digestive tract. The ENS is often referred to as the “second brain” due to its immense complexity and its ability to manage gastrointestinal functions semi-autonomously while staying in constant contact with cognitive and emotional centers in the CNS [1-3].

The primary physical link in this axis is the vagus nerve, which serves as the fastest route for signal transmission between the two systems. Approximately 80% of vagal fibers are sensory (afferent), conveying information from the gut to the brain, while 20% are motor (efferent), allowing the brain to influence gut motility and secretion. Within the bowel wall, intrinsic primary afferent neurons (IPANs) detect chemical and mechanical changes, often responding to microbial metabolites or signals from enteroendocrine cells. This neural architecture allows the gut to communicate its state directly to the brain, potentially influencing everything from basic digestion to complex feeling states and intuitive decision-making [1-4].

Biochemical and Endocrine Signaling Pathways

Beyond direct neural connections, the gut microbiota is hypothesized to exert an influence through the production of neuroactive chemicals, such as short-chain fatty acids (SCFAs), GABA, and serotonin. These microbial products can influence neural response, demonstrating how intestinal bacteria may modulate host neurochemistry and behavior [1, 4-5].

The axis also functions through endocrine channels, specifically the hypothalamic-pituitary-adrenal (HPA) axis, which manages the body's physiological response to stress. Environmental stress can disrupt the microbial balance and increase gut permeability, while a healthy microbiome is conversely thought to be required for the normal development of the brain's stress circuitry. Evidence from germ-free animal studies indicates that without microbial colonization, the HPA axis becomes hyper-reactive, and levels of brain-derived neurotrophic factor (BDNF) - a protein essential for neuroplasticity - are significantly altered in areas like the hippocampus. This underscores the proposed importance of the gut microbiome for emotional regulation and healthy neurodevelopment from early life in experimental models [1,6-7].

Dysfunction within the GBA is increasingly linked to various neuropsychiatric and gastrointestinal disorders, including anxiety, depression, autism, and irritable bowel syndrome (IBS). The brain interprets signals from the gut through interoception, where internal states are translated into "gut feelings" within areas like the insular cortex; failures in updating these internal predictions are hypothesized to lead to chronic symptoms. Targeting this axis through "psychobiotics" - probiotics or prebiotics that influence the brain - offers a promising but still exploratory therapeutic avenue for potentially improving mental health by modulating systemic inflammation and neural signaling [1, 3-4, 6-7].

Microbial Modulation of Dopaminergic Pathways in ADHD

ADHD is a prevalent neurodevelopmental disorder, affecting approximately 5-6% of the pediatric population and often persisting into adulthood. It is clinically characterized by pervasive patterns of inattention, impulsivity, and motor hyperactivity. Its neurobiological substrates are predominantly linked to dysregulation in monoaminergic neurotransmission, specifically involving the dopaminergic and noradrenergic pathways within the mesocorticolimbic reward circuitry. Neuroimaging evidence frequently corroborates this, demonstrating attenuated ventral striatal activation during reward anticipation in ADHD cohorts, which is considered a hallmark of the disorder's pathophysiology [5, 8].

The hypothesis connecting microbial ecology to ADHD postulations suggests that gut-derived microbes modulate the availability of essential amino acid precursors required for central dopamine biosynthesis. Empirical data have identified a significant increase in the abundance of the genus *Bifidobacterium* among individuals with ADHD. These taxa encode the enzyme cyclohexadienyl dehydratase (CDT), which facilitates the conversion of precursors into phenylalanine - a direct precursor of dopamine. Crucially, higher concentrations of these specific bacteria correlate with alterations in the neural processing of rewards, implying that microbial metabolic activity may indirectly influence the patient's neurofunctional architecture based on current theoretical models [5, 8].

While current clinical evidence is still limited and requires further verification in longitudinal studies, the correlation between intestinal dysbiosis and reward system disturbances in ADHD provides a theoretical foundation for considering nutritional and probiotic interventions as potential adjunctive support for standard pharmacotherapy [8-9]. This paper aims to provide a narrative analysis of these connections and evaluate the preliminary therapeutic potential resulting from the modulation of the gut-brain axis in patients with ADHD.

Literature Search Strategy

A comprehensive literature search was conducted to inform this narrative review across major medical databases, including PubMed (MEDLINE), Embase, and the Cochrane Library. The search strategy employed a combination of keywords and indexed terms (MeSH/Emtree) related to Attention-Deficit/Hyperactivity Disorder (ADHD) and the gut-brain axis (e.g., “microbiota”, “microbiome”, “gut-brain signaling”).

The search was primarily restricted to articles published between 2021 and 2026 to capture the most contemporary evidence. The selection prioritized high-level evidence study designs, specifically Randomized Controlled Trials (RCTs), systematic reviews, and meta-analyses, while acknowledging the heterogeneity of the available data.

After screening the initial results for thematic relevance to the intersection of ADHD and gut-brain interactions, 18 of the most recent publications were selected for detailed narrative analysis. Additionally, a select number of foundational older studies were included to provide essential pathophysiological context and a comprehensive overview of the field's development.

Differences in Microbiota Composition in ADHD

In individuals with ADHD, the gut-brain axis is often characterized by dysbiosis involving significant taxonomic shifts compared to healthy controls. Research suggests a potential increased abundance of certain genera, such as *Odoribacter*, *Bifidobacterium*, and *Bacteroides*, alongside a notable depletion of anti-inflammatory taxa like *Faecalibacterium* [10]. While some meta-analyses show no significant differences in microbial α -diversity, specific shifts including an increased population of *Fusobacterium* have been documented. These microbial profiles have been correlated with clinical symptom severity; for instance, higher *Bacteroides* levels are associated with increased hyperactivity and impulsivity, while a scarcity of *Faecalibacterium* is linked to heightened ADHD severity [10-12].

From an ecological perspective, the ADHD microbiome is defined by a reorganization of microbial co-occurrence networks. While healthy gut ecosystems are characterized by integrated competitive interactions, the ADHD microbiome shifts toward larger, more isolated, and cooperative clusters. Specifically, a *Bacteroidetes*-dominant community becomes more prominent in ADHD, driven by *Bacteroides* as a central centroid. In this environment, *Bifidobacterium* shifts from competing with ADHD-associated taxa to cooperating with them, while its overall participation in the ecosystem decreases. These ecological perturbations are hypothesized to disrupt neurotransmitter pathways, such as dopamine and serotonin, which are essential for the neurocircuitry of executive function and emotional regulation [13].

Proposed Biological Mechanisms Based on Experimental Models

A proposed pathophysiological consequence of this dysbiosis is the compromise of the intestinal mucosal barrier, frequently referred to as the “leaky gut” hypothesis. It is postulated that when the barrier is weakened, bacterial components such as lipopolysaccharides (LPS) can enter the systemic circulation, triggering a chronic, low-grade inflammatory response. This disruption of the intestinal epithelium is thought to promote the penetration of bacterial toxins into the bloodstream, which ultimately may contribute to the destabilization of the blood-brain barrier (BBB) and the activation of microglia. This systemic and neuroinflammatory state is a transdiagnostic feature often shared with other psychiatric disorders, potentially contributing to the disruption of neural circuits responsible for cognitive control and emotional regulation [12, 14-15].

Metabolic pathways within the gut influence the synthesis of neurotransmitters critical for attention and reward processing. Certain gut bacteria are thought to be involved in the production of dopamine precursors, such as phenylalanine - specifically linked to

increased *Bifidobacterium* in ADHD patients - while others contribute to the potential synthesis of γ -aminobutyric acid (GABA) and serotonin. Furthermore, the fermentation of dietary fibers by beneficial bacteria produces short-chain fatty acids (SCFAs) like butyrate, which possess neuroactive properties and support mitochondrial function. In ADHD, the observed depletion of SCFA-producing microbes, such as *Faecalibacterium*, may reduce the availability of compounds that protect the blood-brain barrier (BBB) and stimulate brain-derived neurotrophic factor (BDNF), thereby potentially affecting neuronal plasticity and catecholaminergic signaling [10, 12].

Neuroimaging studies have suggested that the gut microbiota significantly influences the functional and structural organization of the brain, including systems involved in reward processing and emotional regulation. Evidence suggests that the relative abundance of GABA-producing taxa, such as *Bacteroides*, correlates with alterations in the functional connectivity of the Default Mode Network (DMN), a mechanism particularly evident in stress-related and depressive disorders. In patients with ADHD, the microbiome appears to modulate the reward system's sensitivity by enhancing the synthesis of neurotransmitter precursors, such as phenylalanine, which is associated with reduced ventral striatal response during reward anticipation. By regulating the systemic inflammatory environment and the availability of neuroactive metabolites like short-chain fatty acids (SCFAs), the gut microbiome is proposed to act as a potential modifier of the neural pathways responsible for motivation, reinforcement, and cognitive health [15-16].

The assembly of the microbiota-gut-brain axis occurs during 'critical time-windows' in early development, where primordial gut colonization is thought to be essential for infant neurogenesis and cognitive outcomes. Ecological disruptions during these periods - stemming from cesarean delivery, prenatal antibiotic exposure, or maternal dysbiosis - significantly correlate with an increased susceptibility to ADHD. These 'microbial missteps' may persistently alter the host's neuro-immune maturation and blood-brain barrier integrity. Throughout the lifespan, the gut microbiome functions as a dynamic modulator of host physiology, where continuous ecological shifts potentially influence the clinical presentation and neurodevelopmental trajectory of ADHD through mechanisms involving neuroinflammation and neurotransmitter regulation [11,17].

Interventional Studies with Probiotics and Synbiotics

Modern approaches to managing Attention Deficit Hyperactivity Disorder (ADHD) are evolving toward integrated models that look beyond traditional pharmacology, specifically

focusing on the gut-brain axis (GBA). Interventions such as specific probiotic strains, prebiotic fibers, synbiotic formulas, and targeted micronutrient supplementation are being analyzed for their potential ability to alleviate symptoms in children and adults [9].

Probiotics are explored as the foundation of GBA interventions, particularly “psychobiotics” hypothesized to be capable of modulating neurotransmitters like dopamine and GABA. Long-term studies indicate that early exposure to specific bacterial cultures may provide protective developmental benefits. For instance, infants supplemented with *Lactobacillus rhamnosus* GG (LGG) during their first six months showed a significantly lower risk of ADHD diagnosis by age 13 compared to placebo groups. In already diagnosed children, while LGG may not always eliminate core symptoms, it has been associated with improvements in health-related quality of life, specifically emotional and social functioning [8-9, 18-20].

Other strains, such as *Bifidobacterium bifidum* Bf-688, have shown clinical promise in reducing inattention and hyperactivity/impulsivity scales in pediatric populations. Interestingly, this intervention has also been linked to increased weight and BMI, which provides a critical clinical advantage for patients experiencing appetite suppression as a side effect of stimulant medications. While current meta-analyses indicate that multi-strain preparations may show a trend toward higher therapeutic efficacy compared to single-strain regimens, these differences have not yet reached statistical significance. Nonetheless, it is hypothesized that multiple strains could offer advantages through more comprehensive colonization of intestinal niches and potential synergistic metabolic effects [9, 18, 20-21].

In adult populations, particularly university students with ADHD, multi-strain probiotic mixtures have demonstrated the potential to improve clinical and functional outcomes. Supplementation has been associated with a reduction in hyperactivity (measured by computerized performance tests like MOXO) and is correlated with enhanced academic performance. These benefits are often accompanied by a significant reduction in gastrointestinal symptoms. While the intervention did not significantly change overall long-term physiological stress markers, correlations were observed between fingernail cortisol concentrations (a biomarker of long-term HPA axis activity) and the severity of attention and impulsivity symptoms [9, 21].

Synbiotics, which combine probiotics with prebiotics like inulin and pectin, aim to optimize the survival of beneficial bacteria while reducing systemic inflammation. Formulas like Synbiotic 2000 have been reported to significantly lower pro-inflammatory cytokines (IL-12/IL-23p40) and vascular adhesion molecules (sICAM-1), particularly in children

on psychostimulant medication. Since elevated sICAM-1 is linked to blood-brain barrier dysfunction and neuroinflammation, its reduction suggests that synbiotics may stabilize the neurological environment and improve comorbid traits such as emotion dysregulation. These interventions also increase plasma levels of propionic acid - often alongside formic and acetic acids - which are short-chain fatty acids (SCFAs) that protect against vascular inflammation and contribute to immunomodulation within the microbiota-gut-brain axis [9, 22-23].

Metagenomic sequencing reveals that these interventions modulate microbial community structure by significantly altering taxonomic and functional β -diversity while influencing specific functional gene modules, such as those related to osmoprotection and environmental stress response. Furthermore, postbiotics - preparations of heat-killed bacteria like *Lactobacillus acidophilus* LB - have emerged as a safe and effective adjunctive therapy in preliminary studies. When used alongside atomoxetine, these inactivated cultures may improve focused attention and executive functions, including cognitive flexibility, providing a favorable safety profile compared to live bacteria for sensitive clinical populations [9, 22-24].

Current meta-analytic evidence indicates that GBA-targeted interventions may yield higher therapeutic efficacy when used as adjunctive therapies rather than stand-alone treatments. Specifically, the effect size for probiotics used alongside stimulants like methylphenidate was notably higher (SMD = 0.84) than when used as simple supplementation (SMD = 0.07), although this difference has not yet reached statistical significance ($p = 0.16$) due to the limited number of available trials. Furthermore, RCTs involving atomoxetine support the potential of probiotics to improve core ADHD symptoms and cognitive functions. These findings suggest that modulating the microbiota may enhance overall treatment outcomes and help manage comorbidities, potentially addressing the side effects or stigma that often lead to the discontinuation of standard pharmacotherapy [9, 18, 21, 24].

Targeted Micronutrient Supplementation in Confirmed Deficiencies

Oxidative stress (OS) and micronutrient status are investigated as potential non-genetic factors that may exacerbate the pathophysiology of ADHD. Individuals with the disorder often exhibit a diminished total antioxidant status (TAS/TAC), characterized by significantly reduced activity of key enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). This oxidative imbalance is frequently linked to deficiencies in essential minerals such as iron (Fe), zinc (Zn), and magnesium (Mg).

Iron is particularly significant as it serves as a mandatory cofactor for tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines, including dopamine and norepinephrine. Consequently, iron deficiency may impair neurotransmitter production, thereby contributing to core behavioral symptoms such as inattention and impulsivity. [25] Prebiotic intervention, specifically using galactooligosaccharides (β -GOS) or bovine colostrum, has been suggested to enhance pro-social behavior and reduce irritability by strengthening the gut barrier and promoting the growth of beneficial *Bifidobacterium* populations. Clinical evidence indicates that targeted nutritional therapy can effectively mitigate core symptoms in specific patient subsets; high-dose zinc supplementation (150 mg/day) and iron replacement for individuals with confirmed low serum ferritin levels have demonstrated improvements in attention and hyperactivity. Furthermore, the synergistic administration of magnesium and vitamin D may contribute to lower levels of anxiety and aggression, likely by bolstering the intestinal barrier and protecting the central nervous system against oxidative stress [8-9, 19-20, 25].

Elimination Diets as Selected Strategies

In addition to essential minerals, vitamins B6, B12, and D, alongside omega-3 polyunsaturated fatty acids (EPA/DHA), are fundamental for neurotransmitter synthesis, maintaining membrane fluidity, and protecting against oxidative neuronal damage. Dietary patterns act as potential modulators of the gut-brain axis; while the Mediterranean diet promotes microbial diversity and mitigates ADHD symptom severity, “Western” diets high in processed sugars and additives can exacerbate systemic inflammation and oxidative stress. Evidence-based protocols, such as the “Few-Foods” elimination diet, might serve as valuable clinical tools in highly selected cases, rather than as a universal dietary intervention, to identify food sensitivities that trigger pro-inflammatory cytokine production, subsequently driving the neuroinflammatory processes associated with ADHD pathogenesis [9, 19, 22, 25].

Discussion

The synthesis of current literature indicates that the gut-brain axis may act as a potential modifier of ADHD pathophysiology, extending the neurobiological understanding of the disorder beyond simple neurotransmitter imbalances. The findings regarding *Bifidobacterium* are particularly noteworthy; while often considered beneficial, their reported overabundance in ADHD cohorts is hypothesized to facilitate the conversion

of precursors into phenylalanine, potentially influencing the host's dopaminergic architecture and reward anticipation. This aligns with contemporary neuroscience which views psychiatric conditions through the lens of complex, inter-systemic networks. Furthermore, the "leaky gut" hypothesis provides a theoretical link between gastrointestinal health and neuroinflammation. The postulated translocation of lipopolysaccharides (LPS) into the systemic circulation is thought to destabilize the blood-brain barrier and activate microglia, a transdiagnostic feature shared with other psychiatric disorders such as anxiety and depression. This systemic inflammation may partially explain the high prevalence of emotional dysregulation and comorbid gastrointestinal symptoms in ADHD patients. Regarding therapeutic interventions, the evidence highlights a shift toward integrated care. While single-strain probiotics like *Lactobacillus rhamnosus* GG show potential early developmental benefits in preliminary studies, multi-strain and synbiotic formulas appear to offer more comprehensive metabolic support by potentially modulating both taxonomic diversity and pro-inflammatory cytokine levels. The preliminary observation that GBA-targeted treatments may yield higher effect sizes when used as adjunctive therapies to stimulants such as methylphenidate is a promising clinical insight. This suggests that modulating the microbiome does not replace traditional pharmacotherapy, but rather may optimize the biological environment in which these drugs function. However, the transition from correlation to causation remains a major challenge, underscoring that current evidence is largely associative and necessitating further longitudinal studies to establish definitive clinical protocols.

Conclusions

In conclusion, the gut-brain axis represents a critical component in understanding ADHD pathophysiology, where intestinal dysbiosis has been observationally associated with the severity of core symptoms such as inattention, impulsivity, and hyperactivity. These microbial alterations are hypothesized to facilitate shifts in metabolic pathways, thereby influencing the synthesis of essential dopamine and serotonin precursors and the production of neuroprotective short-chain fatty acids. Current evidence suggests that targeted interventions - including specific probiotics, synbiotics, and micronutrients like iron, zinc, and magnesium (in cases of confirmed deficiencies) - may serve as supportive clinical tools to potentially improve both symptom management and the overall quality of life for patients. Furthermore, such GBA-targeted strategies appear most promising when utilized as adjunctive therapies alongside standard pharmacotherapy, potentially mitigating medication side effects while enhancing the overall therapeutic response. Ultimately,

future ADHD management may eventually move toward personalized treatment protocols based on individual microbial profiles to address the proposed mechanisms of systemic inflammation and maintain gut barrier integrity, though more rigorous clinical trials are needed to validate these approaches.

Conflicts of interests: The authors declare no conflicts of interests.

List of Abbreviations

BBB: Blood-Brain Barrier

BDNF: Brain-Derived Neurotrophic Factor

B-GOS: Galactooligosaccharides

CAT: Catalase

CDT: Cyclohexadienyl Dehydratase

DHA: Docosahexaenoic Acid

DMN: Default Mode Network

EPA: Eicosapentaenoic Acid

GBA: Gut-Brain Axis

GPx: Glutathione Peroxidase

IPANs: Intrinsic Primary Afferent Neurons

LGG: Lactobacillus Rhamnosus GG

LPS: Lipopolysaccharides

RCT: Randomized Controlled Trial

SCFAs: Short-Chain Fatty Acids

sICAM-1: Soluble Intercellular Adhesion Molecule-1

SMD: Standardized Mean Difference

SOD: Superoxide Dismutase

TAS/TAC: Total Antioxidant Status / Total Antioxidant Capacity

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