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REVIEW ARTICLE

Relationship Between Autism Spectrum Disorder and The Brain-Gut Axis

Otizm Spektrum Bozukluğu ile Beyin-Bağırsak Ekseni Arasındaki İlişki

[1]Behiye Nur KARAKUŞ, Faik OZDENGUL

[1]Necmettin Erbakan University, Institute of Health Sciences, Department of Physiology, Konya, Türkiye
[2]Necmettin Erbakan University, Meram Faculty of Medicine, Physiology Department, Konya, Türkiye

Correspondence

Behiye Nur KARAKUŞ
Behiye Nur KARAKUS, Necmettin Erbakan University, Institute of Health Sciences, Department of Physiology, Konya, Türkiye

E-Mail: bhynrgs@gmail.com

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by a rising prevalence, deficits in social communication and interaction, and repetitive behavioral patterns, the etiology of which remains elusive. The collective assembly of microorganisms inhabiting the gastrointestinal tract (GI) is termed the microbiota. Metabolites and molecules synthesized by the microbiota exert regulatory effects on the nervous system, modulating various brain functions. Acting as a pivotal communication conduit, the microbiota mediates interactions between the GI system and the brain, known as the brain-gut axis. Extensive scholarly literature indicates that perturbations in the microbiota composition can profoundly influence brain functions.
Studies indicate that individuals with ASD exhibit alterations in microbiota profiles compared to the general population. Patients with ASD may harbor distinct microbial communities in their intestines, with a general decrease in microbiota diversity. However, whether these changes are a cause or a consequence of ASD remains to be fully determined.
It has been hypothesized that ASD may arise from any disturbance that affects the balance of the microbiota-brain-gut axis, and the disruption of any component of this delicate mechanism potentially triggers disturbances that could occur in the chain.
Research into the causes and treatment of ASD is ongoing, and studies in this area hold promising potential. It is believed that future research will contribute to the development of new treatment approaches for individuals with ASD.

Keywords: Autism spectrum disorder, brain-gut axis, microbiota

ÖZ

Otizm spektrum bozukluğu, prevalansı giderek artan, sosyal iletişim ve etkileşim bozuklukları, tekrarlayıcı davranışlarda bozukluklar ile karakterize, sebebi bilinmeyen gelişimsel bir farklılıktır. Bağırsaklarda yaşayan mikroorganizmaların tamamına mikrobiyota denir. Mikrobiyotanın ürettiği metabolik ürünler ve moleküller, sinir sistemi üzerinde etkili olmakta ve beyin fonksiyonlarını düzenlemektedir. Mikrobiyota, beyin-bağırsak aksı, bağırsaklar ile beyin arasındaki iletişimi sağlamaktadır. Mikrobiyotadaki değişikliklerin beyin fonksiyonları üzerinde etkili olduğuna dair literatürde pek çok çalışma bulunmaktadır.
Çalışmalar, otizm spektrum bozukluğu (OSB) olan bireylerde mikrobiyota profilinde normal popülasyona göre değişiklikler olduğunu göstermektedir. Otizm spektrum bozukluğu olan hastaların bağırsaklarında farklı mikroorganizma toplulukları bulunabilmekte ve genel olarak mikrobiyota çeşitliliği azalmaktadır. Bununla birlikte, bu değişikliklerin otizmin nedeni mi yoksa sonucu mu olduğu henüz tam olarak belirlenmemiştir.
Otizm Spektrum Bozukluğunun mikrobiyota-beyin-bağırsak ekseni dengesini etkileyebilecek herhangi bir bozukluktan kaynaklanabileceği hipotez edilmiştir ve bu hassas mekanizmanın herhangi bir halkasının bozulması potansiyel olarak zincirde meydana gelebilecek bozuklukları tetiklemektedir.
Otizm spektrum bozukluğunun nedenleri ve tedavisi konusunda araştırmalar halen devam etmekte olup bu alanda yapılan araştırmalar umut verici bir potansiyele sahiptir. Gelecekte otizm spektrum bozukluğu (OSB) olan bireylere yönelik yeni tedavi yaklaşımlarının geliştirilmesine katkıda bulunacağı düşünülmektedir.

Anahtar Kelimeler: Beyin bağırsak aksı, mikrobiyota, otizm spektrum bozukluğu

Introduction

The human body is inhabited by a multitude of microorganisms, including bacteria, fungi, viruses, and protozoa. Most of these microorganisms are localized in the intestines (1). This complex community of microorganisms residing in the intestines is referred to as the microbiota or microbiome. There exists a mutualistic and symbiotic relationship between these microorganisms and humans (1,2).

Microbiota refers to the intricate communication and interaction among millions of microorganisms residing in the brain-gut axis, central nervous system (CNS), gastrointestinal (GI) system, and intestines (1,2).

Autism spectrum disorder is a neurodevelopmental

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Complaints: geneltip@selcuk.edu.tr

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condition marked by clinical heterogeneity. It is characterized by communication and interaction difficulties, and repetitive and restricted behaviors, and involves developmental and connectivity abnormalities in the brain (3).

The exact etiology of autism remains unknown. Recent studies aiming to understand the condition have highlighted brain functions, and genetic, immunological, and neurochemical factors (4). Additionally, it is thought that an underlying dysbiosis (imbalance) in the intestinal microbial community may also play a role (5). This is supported by the GI disorders observed in individuals with autism, which can range from severe constipation to diarrhea. Recent studies have shown that approximately 40% of those diagnosed with autism experience GI symptoms (3). Recent clinical and preclinical studies on the microbiota-brain-gut axis indicate a significant interaction between gut microbiota and the brain (5,6). It is also known that a significant subset of autism spectrum disorder (ASD) is caused by dysfunction in the brain-gut axis. There is a high correlation between psychiatric comorbidities and GI system dysfunction in these patients (5,6). In this review, we will address the potential role of the brain-gut axis in ASD and focus on the current understanding of the gut microbiota in this population.

Maternal Microbiota

The impact of microbiota and bacterial colonization on human health has been extensively studied in recent years. Research in the field of microbiota links the pathophysiology of many diseases to changes in the microbiota and the brain-gut axis (3,6).

Birth marks the beginning of bacterial colonization in the microbiota. The formation of bacterial microbiota begins during pregnancy and continues through labor and delivery (whether by vaginal birth or cesarean section) and into infancy.

During these periods, numerous factors influence this process, including the mother's nutrition and lifestyle, smoking or alcohol consumption, breastfeeding or formula feeding, and nutrition during the transition periods to complementary and solid foods. Additionally, genetic makeup is another factor shaping the microbiota (7).

As a result of the various changes occurring in the mother's body from the onset of pregnancy, differences in microbiota emerge. Some studies suggest that bacteria in the GI microbiota of the mother during pregnancy and lactation periods reach the mammary glands through a mechanism associated with immune system cells (8). The mother's diet and lifestyle, as well as bacteria from the vagina, GI tract, and breast milk, significantly influence the baby's microbiota. Additionally, it has been suggested that harmful bacteria may pass into breast milk and impact the microbiota, influenced by factors such as the mode of delivery (vaginal birth or cesarean section), certain hormones, and exposure to physiological stress (8,9). It is also suggested that changes in the microbiota occur as a result of babies being born via cesarean section, as they do not come into contact with the beneficial vaginal bacteria that they would be exposed to during a normal birth process through the birth canal. Studies also suggest that the bacteria encountered during a cesarean section may lead to alterations in the baby's intestinal microbiota, potentially contributing to the development of ASD (10).

Microbiota colonization, especially during infancy, plays a crucial role in the development and maturation of the GI mucosa. It is also well-established that breastfeeding is particularly important during the first months of infancy. It is also recognized that breast milk contains numerous beneficial bacteria, particularly Bifidobacterium (10).

Bifidobacterium, often referred to as oriented microbiota or microbiome, plays a significant role in protecting against infections during infancy and certain chronic diseases in adulthood (8).

Intestinal Microbiota

Microbiota is a community of microorganisms, including symbiotic, commensal, mutualistic, and pathogenic microorganisms, residing in various parts of our body. This community may vary depending on factors such as diet, lifestyle, medication use, and inflammation (1).

In this symbiotic and mutual relationship, microorganisms can benefit from human substrates, while humans can benefit from microbial activities such as the digestion of carbohydrates, production of essential vitamins (such as B vitamins and K, biotin, cobalamin, folates, nicotinic acid, pantothenic acid, riboflavin, and thiamine), immune system modulation,

and production of secondary bile acids and short-chain fatty acids (11).

Intestinal bacteria such as Bifidobacteria and Lactobacillus synthesize gamma-aminobutyric acid (GABA) from monosodium glutamate. Similarly, Bacillus, Escherichia, and Saccharomyces synthesize norepinephrine, while streptococci, candida, escherichia, and enterococci synthesize serotonin. Bacillus and Serratia are associated with dopamine synthesis (11).

Microbiota is distributed throughout the body, colonizing areas such as the skin, upper and lower respiratory tract, urogenital system, eyes, and especially the intestines, which harbor the majority of the microbiota (12). The colonization of GI by the microbiota begins during the prenatal period. There is evidence of microorganism presence in the placenta, amniotic fluid, meconium, and umbilical cord blood. In the first days after birth, the infantile microbiota changes due to exposure to various physiological and non-physiological factors, such as breast milk, formula use, antibiotic administration, prolonged hospital stays, and early weaning. Our microbial components are influenced by various external factors, including genetics, medication use, dietary habits, lifestyle, and hygiene. Indeed, it is evident that we are exposed to numerous bacterial organisms from the beginning to the end of our existence. Many studies have demonstrated the role of the GI tract microbiota in symptoms of ASD. Approximately 70-80% of children with ASD experience GI system disorders, including bloating, constipation, and diarrhea (13,14). This provides evidence for a relationship between gut physiology and altered microbiota in ASD. Children with ASD generally consume fewer vegetables compared to other children in the same age group (14,15). Additionally, their diet lacks fibrous foods as they tend to consume more foods with higher energy density (14).

The microbiota of children with ASD differs from that of other children in terms of bacterial species and metabolites, such as short-chain fatty acids (SCFAs) (16). In these children, beneficial bacterial species such as Bifidobacterium were found in lower numbers, whereas potentially pathogenic bacterial species such as Desulfovibrio and Clostridium were found in higher numbers (17). A recent study detected Clostridium perfringens bacteria and its toxin genes in the intestines of children with ASD and linked this toxin to digestive system diseases (17,18). Intestinal microbiota also encompasses the array of microorganisms and genomes present in the intestinal environment. The intricate role of the gut microbiota in the brain-gut axis underscores the bidirectional communication between the enteric nervous system (ENS) and CNS (3). Research in this field provides several strategic approaches to assessing the impact of communication between the gut microbiota and the brain-gut axis on behavior. Treatment methods such as probiotic therapy, antibiotic therapy, fecal transplantation procedures, and exposure to various infections can be cited as examples (3,17).

Some studies have noted a correlation between GI symptoms and the severity of clinical symptoms in ASD (18), suggesting that autism symptomatology might be more prevalent and severe in children with GI issues compared to those without. As for the " microbiota-brain-gut axis" concept, recent scientific advancements propose that gut microbiota influences brain development and function via the endocrine, immune, and nervous systems. Consequently, alterations in the gut microbiota could potentially trigger not only some GI symptoms observed in autistic children but also certain neuropsychiatric symptoms. (18,19).

Brain Intestinal Axis Communication Pathways

The microbiota communicates through neuronal, hormonal, and immunological pathways within the brain-gut axis and plays a critical role in maintaining brain-gut homeostasis (3). Generally, the microbiota-brain-gut axis encompasses ENS, CNS, neuroendocrine and neuroimmune systems, parasympathetic and sympathetic pathways of ANS, the hypothalamic-pituitary-adrenal axis, and intestinal microbiota (20).

Neuronal Communication Pathways

Communication between the brain and intestine occurs through neurotransmitters, neurohormones, neuropeptides, cytokines, chemokines, growth factors, and other regulatory molecules (3,21). Factors facilitating brain-gut communication include serotonin, cytokines released from mucosal cells, the vagus nerve, as well as afferent and efferent nerve pathways (3,22). Bacteria within the GI microbiota possess the capability to produce a wide array of neuromodulatory and neurotransmitter substances. Several studies indicate that neurochemicals synthesized by gut bacteria play

a role in influencing behavior in both human and animal models of ASD (20). However, certain foods may contain neurochemical substances such as histamine, and excessive consumption of these foods can alter the composition of the microbiota. Symptoms such as vomiting, hypertension, and headache may manifest as a result of overconsumption of foods with high histamine concentrations (23). The GI system is regulated by a distinct nervous system known as ENS (24). Often referred to as the "second brain," ENS boasts an extensive neural network. Both intestinal physiology and microbiota are governed by both ENS and CNS. Comprising sensory neurons, interneurons, and motor neurons, ENS oversees and senses functions such as secretion, absorption, motility, and visceral sensitivity (24).

Communication between CNS and ENS occurs through the vagus nerve, pelvic nerve, and sympathetic pathways. ENS and ANS communicate with afferent and efferent neurons innervating the intestine, utilizing neurotransmitters such as noradrenaline, adrenaline, and acetylcholine (25). CNS plays a significant role in governing the GI system, overseeing acid secretion and contractile activity through vago-vagal reflexes (26). Moreover, research has demonstrated that certain probiotics establish communication with the brain and regulate behaviors associated with CNS via the vagus nerve (27). For instance, the correction of anxiety and depressive behaviors induced by Lactobacillus rhamnosus JB1 bacteria was achieved through vagotomy. The modulatory effect of Lactobacillus reuteri on behaviors linked to ASD and oxytocin signaling pathways has been demonstrated to rely on the vagus nerve (27). Notably, 80% of vagal fibers between the gut and the brain are afferent, underscoring the crucial role of the vagus nerve in the perception of gut signals (25).

Vagal afferents terminate within the intestinal muscular layer and mucosa, detecting mechanical stimuli like luminal volume and chemical stimuli such as neurotransmitters, hormones, and cytokines, which could be modulated by the intestinal microbiota (24,25). Three key regions in CNS are linked to the GI system. Vagal afferents convey chemosensitive and mechanosensitive information from the esophagus, stomach, and intestine to CNS, but they are not capable of transmitting pain. Thoracolumbar and lumbosacral afferents, however, perceive pain originating from the intestines (25).

Chemical Signalling Pathways or Endocrine Communication Pathways

Enteroendocrine cells, numbering over 20 different types in the body, secrete endocrine hormones within the GI tract. They play a role in regulating digestive activities via ENS, as well as through endocrine and paracrine signaling via vagal afferents. While enteroendocrine cells are responsible for the release of intestinal hormones, their regulation is influenced by the intestinal microbiota (28). Gut hormones such as ghrelin, gastrin, leptin, galanin, and orexin play crucial roles in regulating energy homeostasis, feeding behavior, sexual behavior, circadian rhythm, and anxiety. Additionally, hormones like calcitonin gene-related peptide (CGRP), substance P, neuropeptide Y (NPY), somatostatin, vasoactive intestinal peptide (VIP), and corticotropin-releasing factor (CRF) are believed to play significant roles in facilitating bidirectional communication within the brain-gut axis (29).

Serotonin is a pivotal neurotransmitter in the brain-gut axis. Peripheral 5-hydroxytryptamine (5-HT) contributes to intestinal motility, regulation of GI functions, and pain perception, while also influencing mood changes and the regulation of perception (29). Different subtypes of serotonergic receptors are found in enteric neurons, CNS, and the smooth muscles of the GI tract. The concentration of 5-HT in the plasma is believed to originate primarily from enterochromaffin cells. Intestinal 5-HT contributes to over 90% of the body's 5-HT, yet its peripheral levels do not directly impact its levels in the brain due to the inability of 5-HT to cross the blood-brain barrier. The role of intestinal 5-HT in regulating the physiological function of the GI tract has been well-established (29-31). Certain members of the Lactobacillus and Escherichia coli families within the GI tract lumen convert glutamic acid to Gamma-aminobutyric acid (GABA) (32). Locally produced GABA by the resident bacterial microbiota plays a significant role in signaling among intestinal bacteria (32,33).

The gut microbiota directly or indirectly regulates the homeostasis of CNS through various chemical signals, including short-chain fatty acids, serotonin, bile acids, and gamma-aminobutyric acid (GABA) (33). Many intestinal bacteria such as Lactobacillus, Bacteroides, Parabacteroides, and Bifidobacterium produce GABA, the primary inhibitory neurotransmitter (32,33). As an acidic mechanism, GABA secretion by

intestinal microorganisms influences the environmental pH in the intestine. Bacteroides exhibits a high capacity to produce GABA within the pH range of the human large intestine. GABA synthesized in the gut microbiota facilitates brain-gut communication through enteroendocrine and neuroimmune pathways (33). Certain chemical molecules produced by the intestinal microbiota directly affect the brain by crossing both the intestinal epithelial barrier and the blood-brain barrier. Additionally, some chemical molecules indirectly transmit signals by interacting with enteroendocrine cells situated among the intestinal epithelial cells (34).

SCFAs are one of the lipid clusters produced by the intestinal microbiota through the fermentation of dietary fiber in the intestinal lumen. They are believed to mediate microbiota-brain-gut interactions directly or indirectly. Additionally, SCFAs directly influence neurological processes by crossing the blood-brain barrier (34).

Brain-Gut Axis and Immune System Pathways

The immune system plays a crucial role in brain development. A significant portion of the body's immune cells are located in the GI tract. Cytokines can influence intestinal hormones and vagal afferent neurons, thereby facilitating brain-gut interaction (35). Enterocytes contribute to the release of certain cytokines and chemokines and produce innate immune receptors. Alterations in the microbiota are key factors that can trigger GI immune activation (36). The interaction between ENS and mast cells further contributes to the bidirectional communication between the gut and CNS.

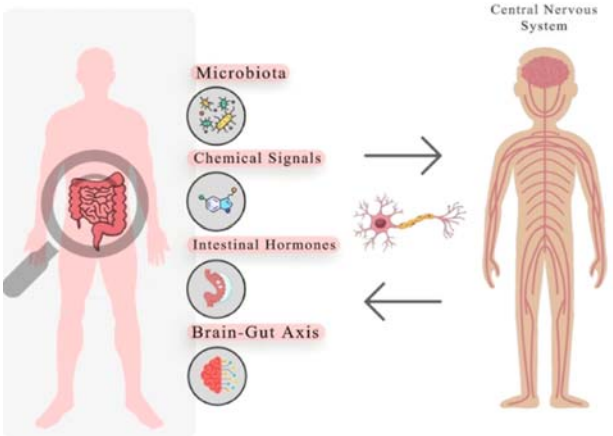

Figure 1. The communication pathways of the brain-gut axis and central nervous system

Additionally, serotonin is known to regulate immune system responses and influence inflammatory events in the intestinal system. Some 5-HT receptors have been observed to play an immunomodulatory role. Studies have found that changes in 5-HT concentration in the GI tract and alterations in enterochromaffin cells are associated with conditions such as ulcerative colitis and Crohn's disease (30,36).

Microbiota's Role in Autism Spectrum Disorder (ASD)

With the increasing understanding of the brain-gut axis, the communication pathways between the gut microbiota and CNS are gaining significant attention. The gut microbiota influences CNS activity through microbial metabolites, immune system mediators, gut hormones, and the vagus nerve (37). Dysbiosis in the gut microbiota is prevalent in individuals (38). Recent reviews have emphasized the importance of nutrition in modulating the gut microbiome to alleviate GI symptoms. The use of oral probiotics and prebiotics may reduce ASD-related symptoms via the brain-gut axis. Several clinical studies have suggested that probiotics and prebiotics could serve as promising therapeutic options for ASD (37,38).

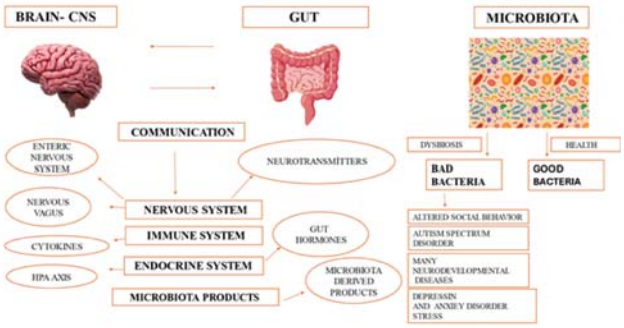

Figure 2. Relationship between brain- gut axis and microbiota

Probiotics are beneficial live microorganisms that aid human health by regulating intestinal transit, enhancing the renewal rate of enterocytes (39), and increasing the production of SCFAs (40). Well-known bacterial species such as Lactobacillus and Bifidobacterium are widely utilized as probiotic supplements. Prebiotics, in contrast, are organic compounds that selectively stimulate the growth and metabolic activity of beneficial microorganisms, thereby improving gut microbiota composition and intestinal health. Notable examples of prebiotics include oligosaccharides, galactans, and fructans. Due to their high tolerability and minimal side effects,

the application of prebiotics and probiotics presents significant therapeutic potential for ASD (41).

Clinical studies suggest that the use of prebiotics and probiotics can improve symptoms of autism and regulate the distribution and content of bacteria in the gut microbiota. In a 2018 study by Shaaban SY et al., stool samples were collected from patients aged five to nine years diagnosed with ASD after three months of probiotic supplementation. Bacterial analysis was performed using quantitative real-time PCR. To assess the severity of GI symptoms in autistic children, the Gastrointestinal Severity Index questionnaire was modified, and the Autism Treatment Evaluation Checklist was used to evaluate autism symptoms. The analysis focused on the bacterial species Lactobacillus rhamnosus, Lactobacillus acidophilus, and Bifidobacterium longum. The study reported a decrease in body weight, GI symptoms, and autism scale scores in children with ASD. Additionally, the bacterial analysis revealed an increase in the numbers of Bifidobacteria and Lactobacilli (42).

In a study where probiotics and prebiotics were administered simultaneously, researchers compared differences in gut microbiota profiles (using 16S rRNA sequencing), fecal SCFAs, and plasma neurotransmitters between 26 children with ASD and 24 neurotypical children. All 26 children with ASD participated in the intervention phase, receiving either probiotics + fructooligosaccharide (FOS) (n=16) or placebo supplementation (n=10). The gut microbiota profiles, SCFAs, and neurotransmitter levels were measured both before and after the intervention. During the intervention phase, it was observed that children with ASD had dysbiotic gut microbiota, characterized by significantly lower levels of Bifidobacteriales and Bifidobacterium longum. Following the probiotics + FOS intervention, an increase in beneficial bacteria (Bifidobacteriales and B. longum) and a suppression of pathogenic bacteria (Clostridium) were noted, along with a marked reduction in autism severity and GI symptoms. Moreover, post-intervention, the SCFAs levels in children with autism significantly increased and approximated those of the control group. The probiotics + FOS intervention was associated with improvements in ASD symptoms, including the regulation of gut microbiota, SCFAs, and serotonin levels, thus addressing the hyperserotonergic state and dopamine metabolism disorder observed in ASD (43).

In a study conducted by Billeci and colleagues (2023), potential alterations in brain activity induced by probiotic therapy were examined in 46 children diagnosed with ASD, aged between 12 and 72 months, using electroencephalography (EEG). This investigation was carried out as a randomized controlled trial. After the probiotic intervention, a reduction in gamma and beta band power in the frontopolar regions, along with modifications in frontal asymmetry, was detected among the participants. These changes suggest a shift towards typical healthy brain functioning. Furthermore, notable correlations were identified between EEG findings and various clinical and biochemical parameters (44).

In a placebo-controlled study involving individuals diagnosed with ASD, children were stratified into two groups based on the presence or absence of GI issues. These groups consisted of individuals with GI symptoms and those without such symptoms. Both cohorts underwent probiotic treatment for five months. Upon completion of the treatment regimen, the group without GI symptoms displayed amelioration in core autism symptoms, while the group experiencing GI symptoms exhibited enhancements in adaptive functions and sensory profiles compared to the placebo-administered group (45). Furthermore, researchers noted a positive correlation between the plasma levels of 25(OH)D and the response to probiotic intervention in mitigating the severity of autism (46).

Numerous clinical studies have been conducted to explore the role of gut microbiota in the onset and progression of ASD. These studies have noted that individuals with ASD exhibit dysbiosis in both the diversity and abundance of gut bacteria, unlike neurotypical individuals (47). Despite conflicting results, meta-analyses in the literature suggest a correlation between ASD and changes in microbiota composition, underscoring the need for further cohort studies to assess this relationship (47). Moreover, a thorough investigation into gut microbiota may facilitate the customization of microbiological interventions and serve as a supplementary treatment approach for ASD (37). Indeed, certain clinical trials and animal studies have indicated that restoring gut microbiota balance through antibiotics, prebiotics, probiotics, or fecal microbiota transplantation (FTT) can induce alterations in neurological functions, behaviors, and associated symptoms in children with autism (48).

Therapeutic Approaches to Target Gut Microbes in

Autism Spectrum Disorder

Probiotic Therapy

Probiotic therapy is proposed as a non-pharmacological treatment method to alleviate the severity of GI symptoms in children diagnosed with ASD (49). Due to its lack of potential side effects, it is also recommended as an adjunctive therapy for children with ASD (49, 50). The literature indicates that patients with ASD frequently suffer from GI complaints, and probiotics are hypothesized to address gut inflammation, mitigate GI symptoms in children with Inflammatory Bowel Disease (IBD), and enhance behavioral symptoms in autistic children (50). Numerous studies indicate that probiotic consumption fosters beneficial modifications in gut microflora, thereby conferring numerous health benefits (51).

Although the precise mechanisms by which probiotics exert their effects remain unclear, several hypotheses have been proposed (51). Firstly, probiotics alter the function and composition of gut-residing microbes and directly interact with the host, facilitating immune system engagement (52). Secondly, probiotics can sustain the integrity of the mucosal barrier by enhancing mucin production, mitigating bacterial overgrowth, promoting antioxidant synthesis, and modulating Immunoglobulin A (IgA) secretion to bolster mucosal immunity (52).

Dietary Intervention

Numerous environmental factors can influence the microbiota-brain-gut axis, with daily food intake being one of the most significant. Dietary components can modify the composition of gut microbiota and affect serum metabolites, thereby modulating brain activity in the host. Consequently, various dietary supplements can help restore microbial balance in the gut and exert therapeutic effects on ASD-related deficits (53). While dietary interventions are increasingly popular for children with autism, they can also lead to adverse effects, as restrictive diets may result in other nutritional deficiencies. Parents of children with autism frequently report issues with their children's selective eating habits. Currently, a range of dietary interventions is employed, including gluten- and casein-free diets, ketogenic diets, yeast-free diets, food allergen restrictions, and supplementation with vitamins A, C, B6, folic acid, B12, minerals such as magnesium, and omega-3 fatty acids (53,54).

Antibiotic Intervention

The treatment of GI infections can be managed with antibiotics, which tend to alter the composition of gut microbiota. Research indicates that early antibiotic exposure may be a potential trigger for autism; however, certain antibiotics, such as aminoglycosides, have shown efficacy in alleviating autism symptoms to some extent (55). One hypothesis proposed by researchers is that aminoglycoside antibiotics might ameliorate autism symptoms by correcting a premature stop codon mutation in a polymorphic gene potentially linked to autism. Several studies have demonstrated that antibiotics can be beneficial in alleviating ASD symptoms by selectively eliminating residual microbiota. Vancomycin and Metronidazole have been employed in the treatment of ASD symptoms (56).

However, Metronidazole is generally not preferred due to its systemic side effects. In a study involving 11 children with ASD treated with Vancomycin, significant communication, and behavioral improvements were observed following the planned 8-week treatment. Another study reported that a 10-day course of amoxicillin led to improvements in autism symptoms in a child, as reported by the parents. Contrarily, there are studies suggesting that early antibiotic exposure may indeed trigger autism (56). In a rodent model study, maternal use of oral antibiotics (non-absorbable Sulfonamide, Neomycin, Bacitracin) resulted in offspring exhibiting impaired social interactions. Fecal samples from these offspring exposed to antibiotics showed a 50% reduction in Lactobacillus abundance and an increase in Clostridium, indicating that early antibiotic exposure can cause behavioral outcomes in offspring. The association between gut microbiota and antibiotic treatment remains to be fully confirmed and continues to be a subject of ongoing research (56,57).

Fecal Microbiota Therapy (FMT) and Microbiota Transfer Therapy (MTT)

The FMT technique represents a notable approach to treating ASD. Here, the gut microbiota from a healthy individual is transferred to the patient, offering a diverse array of thousands of bacterial species naturally occurring in the gut. This stands in stark contrast to probiotic treatments, which typically involve only a limited number of bacterial species derived from milk cultures. FMT therapy holds promise in

addressing chronic inflammatory conditions like insulin sensitivity (58). Research further suggests that FMT can ameliorate symptoms of constipation and contribute to normalizing the gut microbiota in conditions such as irritable bowel syndrome. Consequently, researchers have shown a keen interest in employing FMT for the treatment of children with ASD. Recently, an advanced version of the FMT protocol, known as Microbiota Transfer Therapy (MTT), has gained traction (58,59). This approach involves a two-week course of antibiotics followed by bowel cleansing, succeeded by a seven-to-eight-week period of administering a substantial initial dose of standardized human gut microbiota. MTT has demonstrated significant improvements in GI symptoms, including constipation, indigestion, abdominal pain, and diarrhea, while also alleviating ASD-related symptoms (59, 60). Additionally, there have been instances where recipients of FMT from obese donors developed new-onset obesity (60).

Kang and colleagues conducted a clinical trial involving 18 children diagnosed with autism to investigate the effects of microbiota transplant therapy on gut microbial composition and the alteration of GI and ASD symptoms. The study observed substantial improvements in behavioral symptoms persisting for eight weeks post-treatment, coupled with an 80% reduction in gastrointestinal symptoms (61).

Conclusion

In conclusion, there are many pathways through which the gut microbiota influences neurodevelopment in ASD. The effects of these pathways can be both simultaneous and interconnected. Despite extensive research, there are still many issues to be addressed regarding how the gut microbiota regulates or influences autism. The studies conducted give rise to numerous inquiries. In this review, we discussed various treatments aimed at addressing ASD concerning its pathogenesis and the gut microbiome. These treatments may help manage problems and symptoms associated with autism. Research has shown promising results in a variety of therapies including probiotics, prebiotics, FMT, MTT, and dietary changes. However, to achieve meaningful outcomes in autism research, more rigorously conducted randomized controlled trials are needed. In the future, further elucidation of the relationship between the microbiota-brain-gut axis and ASD will be an important area where we can improve the quality of life of patients and develop potential treatment strategies.

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