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Neurogastroenterological Dysregulation in Autism Spectrum Disorder: Barrier Function and Neural Communication

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ABSTRACT

Autism Spectrum Disorder is a heterogeneous neurodevelopmental condition characterized by impairments in social communication and interaction, restricted interests, and repetitive behavioral patterns. Although the etiopathogenesis of autism has not yet been fully elucidated, increasing evidence suggests that gastrointestinal, immunological, metabolic, and neuroendocrine mechanisms may contribute to its clinical complexity.

In this context, the microbiota–gut–brain axis has gained growing attention as a biological framework linking intestinal function with neurodevelopmental and behavioral processes. This review aims to provide a comprehensive overview of the relationship between ASD and the gut–brain axis, with particular emphasis on intestinal permeability, gut microbiota composition, dysbiosis, enteric nervous system function, vagal signaling, and microbiota-derived metabolites.

Current findings indicate that impaired intestinal barrier integrity may facilitate the systemic translocation of bacterial products, toxins, and microbial metabolites, potentially contributing to immune activation and neuroinflammatory responses. Alterations in microbial taxa, including changes in Clostridia, Desulfovibrio, Sutterella, Bifidobacterium, Lactobacillus, Bacteroidetes, and Firmicutes, have been associated with gastrointestinal symptoms and behavioral manifestations in individuals with autism.

Moreover, microbial metabolites such as short-chain fatty acids, tryptophan derivatives, neurotransmitters, and neuropeptides may influence central nervous system function through neural, endocrine, immune, and metabolic pathways. The enteric nervous system and vagus nerve appear to represent key anatomical and functional components of this bidirectional communication. However, existing clinical findings remain heterogeneous due to differences in age, diet, medication use, environmental factors, sampling procedures, and methodological approaches. Overall, a deeper understanding of the microbiota–gut–brain axis may contribute to clarifying the biological heterogeneity and pathophysiological mechanisms underlying autism.

Keywords: Autism Spectrum Disorder, microbiota- brain, gut axis, enteric nervous system, microbial metabolites.

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by persistent impairments in social communication and interaction, accompanied by restricted interests, repetitive behavioral patterns, and sensory-related differences[1]. Although ASD is primarily defined on the basis of behavioral and developmental features, it is increasingly recognized as a multidimensional condition involving a broad range of biological systems. The marked clinical heterogeneity of ASD, the variability in symptom severity, and the frequent presence of comorbid medical conditions suggest that its etiopathogenesis cannot be explained by a single mechanism[2]. Instead, ASD is thought to arise from the dynamic interaction of genetic susceptibility, environmental influences, immune dysregulation, metabolic alterations, and neurodevelopmental processes[4].

In recent years, growing attention has been directed toward the gastrointestinal system and its potential contribution to the biological complexity of ASD[2, 3]. Gastrointestinal symptoms such as constipation, diarrhea, abdominal discomfort, bloating, reflux, and altered bowel habits are frequently reported in individuals with ASD and may negatively affect quality of life, emotional regulation, sleep, and behavioral outcomes[3]. The observation that gastrointestinal disturbances often coexist with behavioral manifestations has led researchers to investigate whether intestinal dysfunction may be linked to neurodevelopmental and neuropsychiatric processes. Within this framework, the microbiota–gut–brain axis has emerged as a key conceptual model for understanding how intestinal, immune, endocrine, metabolic, and neural pathways may interact with central nervous system function[4].

The gut microbiota represents a highly diverse microbial ecosystem that contributes to digestion, nutrient metabolism, immune maturation, epithelial barrier integrity, and the production of biologically active metabolites[4]. Alterations in gut microbiota composition, commonly referred to as dysbiosis, have been associated with changes in intestinal permeability, immune activation, neuroinflammation, and metabolic signaling. In individuals with ASD, studies have reported differences in several microbial taxa, including Clostridia, Desulfovibrio, Sutterella, Bifidobacterium, Lactobacillus, Bacteroidetes, and Firmicutes[5]. Although findings across studies remain heterogeneous, these microbial alterations may have functional consequences through the production of bacterial toxins, short-chain fatty acids, tryptophan metabolites, neurotransmitters, neuropeptides, and inflammatory mediators. These molecules may influence the central nervous system by affecting the blood–brain barrier, neurotransmitter balance, neuroimmune responses, and synaptic plasticity[6,7].

Another important mechanism linking intestinal function with ASD-related processes is impaired epithelial barrier integrity, often described as increased intestinal permeability or "leaky gut"[8]. Disruption of the intestinal barrier may facilitate the translocation of bacterial products, toxins, and microbial metabolites into the systemic circulation, thereby promoting inflammatory and immune-mediated responses[8]. Such processes may contribute to systemic inflammation and potentially influence neurodevelopmental pathways through immune, metabolic, and neuroendocrine mechanisms[9]. In this context, intestinal inflammation, dysbiosis, altered cytokine profiles, and microbial metabolites are considered interconnected components of a broader biological network rather than isolated phenomena.

The enteric nervous system also occupies a central position within this network[10]. Often referred to as the "second brain," the enteric nervous system regulates gastrointestinal motility, secretion, epithelial barrier function, mucosal immunity, and intestinal blood flow[11]. Its close anatomical and functional connections with the autonomic nervous system and central nervous system provide a structural basis for bidirectional gut–brain communication. The vagus nerve, in particular, serves as a major neural pathway through which intestinal signals may be transmitted to the brain[9]. Through afferent and efferent fibers, vagal signaling participates in the regulation of immune responses, inflammatory reflexes, metabolic homeostasis, and behavioral processes. Therefore, dysfunction at any level of the enteric nervous system, vagal pathways, intestinal microbiota, or immune signaling may have consequences for both gastrointestinal and neurobehavioral outcomes[11].

Microbiota-derived metabolites further strengthen the biological link between the gut and the brain. Short-chain fatty acids, tryptophan derivatives, serotonin, gamma-aminobutyric acid, dopamine, and other neuroactive compounds produced or modulated by gut microorganisms may influence neuronal signaling, immune regulation, mitochondrial function, oxidative stress, and inflammatory pathways[11,12]. Similarly, short-chain fatty acids may exert both beneficial and potentially harmful effects depending on their concentration, metabolic context, and interaction with host physiology. These findings suggest that the gut microbiota may affect ASD-related processes not only through microbial composition but also through its metabolic activity[12,78].

Taken together, current evidence supports the view that ASD should be evaluated within a broader biological framework that integrates neurodevelopmental, gastrointestinal, immunological, metabolic, and neuroendocrine mechanisms. However, the relationship between the gut microbiota and ASD remains complex, and existing findings are not entirely consistent across studies[12]. Differences in age, diet, medication use, symptom severity, environmental exposure, sampling procedures, and methodological approaches may contribute to this variability. Therefore, a comprehensive understanding of ASD requires an integrated perspective that considers the microbiota–gut–brain axis as a dynamic and bidirectional system. In this context, the present article aims to examine the potential roles of intestinal permeability, gut microbiota composition, dysbiosis, enteric nervous system function, vagal signaling, and microbiota-derived metabolites in the pathophysiological mechanisms associated with ASD[12,62,63].

The aim of this review is to provide a comprehensive overview of the potential role of the gut–brain axis and gut microbiota in the pathophysiology of Autism Spectrum Disorder. In this context, the article seeks to examine the bidirectional communication mechanisms between the gastrointestinal system and the central nervous system, with particular emphasis on neuroimmune, neuroendocrine, metabolic, and vagal signaling pathways. Furthermore, this review aims to discuss how alterations in gut microbiota composition, microbial metabolites, gastrointestinal dysfunction, and inflammation may contribute to neurodevelopmental processes and behavioral manifestations observed in ASD.

2. Leaky gut syndrome and ASD

The term "leaky gut" refers to the translocation of bacteria, toxins, and microbial metabolites into the systemic circulation as a consequence of impaired barrier integrity within the intestinal wall of both the small and large intestines[13]. This intestinal barrier is composed of tight junctions, paracellular spaces, and various protein structures located within epithelial cells. Recent studies have demonstrated that disruption of this barrier function is frequently observed in individuals with autism spectrum disorder (ASD)[14].

The majority of studies investigating the relationship between autism spectrum disorder (ASD) and the gut microbiota have been conducted using experimental animal models. However, some researchers argue that the animal models currently employed do not fully replicate the core clinical features observed in individuals with ASD. Based on the proposed association between autism and the gut microbiota, numerous studies have evaluated the effectiveness of probiotic and prebiotic interventions, as well as specialized dietary programs, in individuals with ASD. Findings from these studies indicate that neither probiotic and prebiotic supplementation nor specific dietary interventions exert a consistent or definitive effect on the core symptoms of autism[15]. In addition, studies have reported that the dietary patterns of individuals with ASD, particularly those exhibiting selective eating behaviors, may substantially influence gut microbiota composition, thereby contributing to microbial differences compared with healthy controls[16].

One of the principal mechanisms influencing intestinal permeability is intestinal inflammation[17]. Alterations in the composition of the gut microbiota have been shown to significantly affect immune system function[18]. In particular, toxins produced by *Clostridia* and *Desulfovibrio* species, as well as lipopolysaccharides (LPS) present in the cell walls of Gram-negative bacteria such as *Bacteroides*, are thought to contribute to inflammatory processes. Additionally, heavy metals and phenolic compounds that cannot be effectively eliminated from the body due to deficiencies in detoxification and antioxidant defense mechanisms may further exacerbate inflammation[17].

Studies examining fecal microbiota profiles in individuals with autism spectrum disorder (ASD) have demonstrated increased levels of *Clostridia* accompanied by reduced *Bifidobacteria* abundance. This microbial imbalance may promote a shift in cytokine homeostasis toward a predominantly pro-inflammatory profile[19]. It has been proposed that this dysregulation among inflammatory cytokines triggers intestinal inflammatory responses and that prolonged exposure of the intestinal epithelium to such inflammation may damage epithelial barrier integrity, ultimately leading to increased intestinal permeability[19].

3. Microbiota Composition, Dysbiosis and ASD

The diverse collection of microorganisms inhabiting the human body consists predominantly of bacteria, but also includes viruses, protozoa, fungi, and archaea. Collectively, these microorganisms are referred to as the human microbiota. Those residing within the gastrointestinal tract are specifically known as the gut flora or gut microbiota[20].

The gut microbiota exerts a wide range of essential physiological and pathological functions within the host, particularly in relation to the gastrointestinal system. It contributes to digestive processes by facilitating nutrient absorption through intestinal cells and by producing key metabolites, including short-chain fatty acids[21]. In addition, the microbiota participates in intestinal mucus formation and supports the enzymatic activity of the mucosal layer[22].

Furthermore, the gut microbiota provides protection against pathogenic microorganisms through the secretion of antimicrobial substances, thereby contributing to antibacterial defense and protection against toxins[23]. It also plays a supportive role in immune system regulation and promotes the synthesis of essential vitamins, including B vitamins[24].

The gut microbiota, together with the metabolites it produces, constitutes a critical component of the continuous bidirectional communication between the gastrointestinal system and the brain. The gut–brain axis, which encompasses the vagus nerve, the immune and endocrine systems, as well as bacterial metabolites and microbial products, has emerged as a key neuro–immuno–humoral signaling network linking the gut and the central nervous system[25].

In addition to the gut–brain axis, the gastrointestinal system—particularly through the involvement of the microbiota—has increasingly been referred to as the "second brain"[26]. Dysbiosis, defined as the disruption of microbial homeostasis resulting from imbalances in microbial composition and metabolic activity, may lead to dysfunction within these interconnected networks. Such disturbances have been associated with alterations in blood–brain barrier permeability, neuroinflammation, and the development of neurodevelopmental and neurodegenerative disorders[27].

Bacterial colonization begins at birth, and the establishment of the neonatal microbiota is strongly influenced by the mode of delivery. The microbiota of infants born via vaginal delivery closely resembles the maternal vaginal microbiota, whereas infants delivered by cesarean section tend to develop a microbiota more similar to the maternal skin microbiota[28]. Recent studies have further demonstrated that bacterial colonization may begin during the perinatal period and that the maternal gut microbiota can be partially transmitted to the infant's intestinal microbiota[29]. In adulthood, diet is considered one of the most significant factors influencing microbiota composition. In addition, various other factors, including stress, medication use, environmental exposures, and medical conditions, are also known to affect the gut microbiota[30].

The gut microbiota is classified into microbial groups known as phyla. Four major phyla predominate within the human gastrointestinal tract: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*. Among these, *Firmicutes* and *Bacteroidetes* constitute the most abundant and prevalent phyla[31]. Numerous studies have demonstrated that the gut microbiota influences a wide range of neurological functions through the gut–brain axis. Communication between the gut microbiota and the brain occurs primarily through three major pathways: the neural pathway (including the vagus nerve and enteric nervous system), the immune pathway (mediated by cytokines), and the endocrine pathway (involving the hypothalamic–pituitary–adrenal axis and gut hormones). Dysregulation in any of these pathways may contribute to the development of neuropsychiatric disorders[31].

Alterations in bacterial populations, particularly involving *Bacteroides* and *Bifidobacterium* species associated with the *Firmicutes* and *Actinobacteria* phyla, have been linked to dysbiosis and disturbances in mental health. The gut microbiota regulates the gut–brain axis by maintaining intestinal permeability through modulation of tight junction integrity within the intestinal epithelium, as well as through the production of neurotransmitters, short-chain fatty acids, amino acids, and various bioactive metabolites[32].

Infants, who are traditionally assumed to be born with a relatively sterile microbiota, rapidly acquire intestinal microbial colonization after birth, thereby contributing to the maturation and regulation of the immune system. Within the gut microbiota, certain bacterial populations associated with anti-inflammatory activity, such as *Bifidobacterium* and *Lactobacillus*, coexist in balance with pro-inflammatory bacteria, including *Clostridium* and *Ruminococcus* species[33].

A substantial number of clinical and experimental studies have investigated the relationship between the gut microbiota and autism spectrum disorder (ASD). Clinical studies examining bacterial phyla colonizing the intestinal tract have reported that the *Bacteroidetes* phylum is more abundant in individuals with ASD, whereas the *Firmicutes* phylum predominates in healthy control groups[34]. In another study, significant reductions in both *Bacteroidetes* and *Firmicutes* phyla were observed in individuals with ASD, accompanied by an increase in *Lactobacillus* spp+. These findings were further supported by a study conducted by Adams and colleagues, which also demonstrated markedly elevated levels of *Lactobacillus* spp. in individuals with autism[36]. Additionally, another study performed in different populations and at different time points reported increased abundance of *Clostridium* spp. in individuals with ASD[37].

In a sequencing-based study, *Clostridia* levels were not found to be significantly elevated in individuals with autism; however, the abundance of *Bacteroidetes* and *Desulfovibrio* was reported to be moderately higher. Notably, *Desulfovibrio*, which is present at a frequency of less than 0.3% in the general population, was observed to be approximately 10 times more abundant in individuals with autism. In addition, researchers investigating the etiopathogenesis of autism have suggested that, alongside *Clostridia* and its associated toxins, *Desulfovibrio* species and their toxic metabolite hydrogen sulfide (H_2S) should also be considered as potential targets of investigation[34,35].

In experimental studies on this topic, although the causal relationships and underlying mechanisms have not yet been fully elucidated, the maternal immune activation (MIA) mouse model is widely used to investigate certain features of autism. In one study, alterations in the gut microbiota composition of offspring derived from the MIA mouse model were identified, with notable differences observed particularly in the *Clostridia* and *Bacteroidia* phyla[38,39].

One of the most widely used animal models for inducing autism-like features is prenatal exposure to valproic acid (VPA). In mouse models exposed to VPA during the prenatal period, an increase in the abundance of *Firmicutes* has been reported, accompanied by a decrease in *Bacteroidetes* and *Desulfovibrionales* levels[39]. Furthermore, particularly in male offspring exposed to VPA, alterations have been observed in several bacterial taxa, including *Alistipes*, *Enterorhabdus*, *Mollicutes*, and *Erysipelotrichales*[39].

Another notable finding from this study is that these microbial alterations occur in parallel with increased butyrate levels in the cecum and neutrophil infiltration in the ileum. Moreover, an inverse relationship has been reported between intestinal serotonin levels and social behavior scores, suggesting a potential link between microbial changes, intestinal immune responses, and behavioral outcomes[40,41].

In a study conducted by Kang and colleagues, the gut microbiota of twenty children with ASD presenting with intestinal problems was compared with that of twenty neurotypical children. The authors found that children with ASD exhibited reduced bacterial diversity, which was associated with the severity of gastrointestinal symptoms. No significant differences were detected at the phylum level; however, this inconsistency may have been due to the fact that fecal samples were collected by parents rather than directly by researchers. When compared with neurotypical children, fecal samples from children with ASD showed a significantly higher abundance of the genus *Coprococcus* and the phylum *Prevotella*.

Prevotella species are commensal gut bacteria involved in the degradation of plant polysaccharides and the synthesis of vitamin B1. Therefore, a reduced abundance of the *Prevotella* phylum may potentially contribute to vitamin B1 deficiency. In addition, members of the *Veillonellaceae* family were found to be less abundant in individuals with ASD. Subtle differences were also observed in the genus *Sutterella*, which was present at lower levels in the ASD group. Overall, these findings suggest that alterations in gut microbiota composition in individuals with autism may lead to biochemical and functional consequences for the host[32].

The reduction of beneficial microorganisms such as *Bifidobacterium* and *Lactobacillus*, which support intestinal peristalsis, together with an increase in methane-producing microorganisms that slow intestinal transit time, may contribute to the development of constipation. In addition, prolonged retention of fecal matter within the intestine may enhance bacterial fermentation, thereby increasing the absorption of microbial toxins. This process has been proposed to potentially contribute to behavioral disturbances and alterations in neurological function in individuals with ASD[43,44].

In individuals with autism spectrum disorder (ASD) who experience chronic diarrhea, carbohydrate malabsorption and dysbiosis are commonly observed. Autism has been reported to be associated with the overgrowth of bacterial taxa such as *Clostridiaceae* and *Sutterella*, which may contribute to alterations in stool consistency[45]. In addition, deficiencies in digestive enzymes—particularly disaccharidases—are frequently reported in autism, leading to incomplete carbohydrate digestion. This condition may further disrupt the balance of the gut microbiota[45]. Moreover, some children diagnosed with ASD exhibit alternating episodes of diarrhea and constipation that are often associated with psychological stress, alongside clinical features resembling irritable bowel syndrome (IBS)[46].

4. Enteric Nervous System and ASD

The enteric nervous system (ENS) is the most complex component of the peripheral nervous system, encompassing neural structures within the esophagus, stomach, intestines, gallbladder, and pancreas[47]. In mammals, the intestinal tract performs functions beyond digestion and possesses several additional essential physiological roles. The enteric nervous system is characterized by its intrinsic and highly specialized neural network[43]. This network, embedded within the intestinal wall, is referred to as the enteric nervous system and is also known as the "little brain" or "second brain." The ENS plays a crucial role in numerous gastrointestinal functions, including barrier integrity, secretion, peristalsis, motility, fluid homeostasis, and regulation of intestinal blood flow. It also modulates the activity of enteric neuroendocrine and epithelial cells and contributes to immune responses. Functionally, the system exhibits both excitatory and inhibitory properties, thereby ensuring the coordinated regulation of gastrointestinal physiology[47].

The enteric nervous system consists of three main cellular components: neurons, interneurons, and glial cells. These cells originate from the neural crest (crista neuralis) and migrate to the gastrointestinal tract during development. Their migration, maturation, and organization continue throughout gestation and, in some species, extend into the postnatal period[47]. A study has demonstrated that, alongside postnatal maturation of the enteric nervous system, the emergence of gut microbiota diversity may play an important role in the development and functional regulation of the ENS[46].

Ganglia form two major plexuses: the submucosal plexus (Meissner's) and the myenteric plexus (Auerbach's). Each plexus contains a heterogeneous population of neurons with distinct neurochemical coding, projections, and functional roles[47]. Although the enteric nervous system (ENS) appears to function as an autonomous system, it is closely interconnected with the autonomic nervous system. It maintains functional connections with both the sympathetic and parasympathetic nervous systems[48]. In addition, it receives a substantial number of afferent fibers via the vagus nerve and spinal afferent pathways[47]. Through these connections, the ENS establishes extensive bidirectional communication and interaction between the sympathetic prevertebral ganglia and the central nervous system (CNS)[48]. This system also incorporates a broad endocrine signaling network[49].

Dysfunction of the ENS is generally associated with gastrointestinal disorders[50,51]. Due to its anatomical location, the ENS is considered to be protected by the mucosal layer, epithelial barrier, and the regulation of ion and fluid balance within the intestinal environment[43,52]. In addition, the ENS, in cooperation with glial cells, contributes to the maintenance of epithelial barrier integrity between the intestinal wall and the cells and tissues within the intestinal lümen[43].

This neuroendocrine network, which forms a bridge between the gastrointestinal system and the central nervous system, constitutes the structural basis of gut microbiota–gut–brain axis functions[53]. Any neurological disturbance occurring at any level of this system may affect both intestinal and brain function[53]. Neural communication between the gut and the brain occurs directly via the vagus nerve, and bacteria are capable of stimulating afferent neurons within the enteric nervous system[53,54]. Vagal signaling originating from the intestine may trigger an anti-inflammatory response against microbial sepsis[53]. Gut microorganisms can influence brain function through the vagus nerve; accordingly, it has been observed that after vagotomy, microbial regulation of behavior is no longer effective[53].

Enteric nervous system dysfunction has been implicated in the etiopathology of several neurological and neurodegenerative disorders, including autism spectrum disorder (ASD), Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease[54]. Children with neurodevelopmental disorders frequently experience a range of chronic gastrointestinal symptoms, such as gastroesophageal reflux, vomiting, gastrointestinal pain, inflammatory bowel disease (IBD), constipation, and gastrointestinal hypomotility[55,56]. These symptoms are recognized as significant clinical indicators that contribute to a reduced quality of life[55,56].

Bidirectional communication between the gut and the brain is regulated through neuronal, endocrine, and immunological pathways[57]. Interaction between the gut and the brain occurs via two primary neuroanatomical routes. The first involves direct reciprocal information exchange mediated by the vagus nerve and the autonomic nervous system at the level of the spinal cord. The second consists of bidirectional communication between the enteric nervous system in the gut and the vagus nerve[57]. This bidirectional communication is known as the gut–brain axis and represents a fundamental regulator of homeostasis and gastro-neuronal signaling[58]. Multiple systems, including the neuroendocrine, neuroimmune, enteric nervous system, and gastrointestinal microbiota, contribute to the modulation of the gut–brain axis[58].

Through this reciprocal interaction, gastrointestinal (GI) symptoms observed in neurodevelopmental disorders have become central to several hypotheses. Approximately 50–70% of individuals diagnosed with autism spectrum disorder (ASD) experience gastrointestinal symptoms, including hypomotility. These rates do not differ significantly between sexes but vary according to the severity of ASD, with more severe cases showing a higher prevalence of chronic gastrointestinal symptoms[59,60]. The most commonly reported gastrointestinal symptoms in individuals with autism include constipation, nausea, vomiting, bloating, and diarrhea[56].

5. Vagus stimulation and neural communication mechanisms

The vagus nerve (cranial nerve 10) is the tenth cranial nerve and carries both afferent and efferent fibers associated with motor, sensory, and autonomic nervous system functions[61]. The vagus nerve performs numerous essential physiological roles in the body. It is particularly involved in digestive, respiratory, and cardiovascular regulation, and serves as a direct anatomical and functional link between the gut and the brain[61]. Experimental studies have supported the role of afferent pathways within the vagus nerve in mediating communication between gut microbiota and the brain, suggesting that these neural circuits play a key role in gut–brain signaling[62,63].

Studies have shown that in animals infected with pathogenic bacteria such as *Citrobacter rodentium* and *Campylobacter jejuni*, c-Fos (c-FBJ osteosarcoma oncogene) expression is increased in vagal sensory ganglia as well as in visceral sensory nuclei within specific brain regions, compared with non-infected control animals. Furthermore, it has been proposed that these alterations—observed in brain regions including the paraventricular nucleus, the basolateral nucleus of the amygdala, the bed nucleus of the stria terminalis, the medial prefrontal cortex, and the anterior cingulate cortex—may help explain the relationship between gastrointestinal bacterial changes and anxiety-like behaviors[62,63].

In another study investigating the role of the vagus nerve in immune system function, animal models infected with *Salmonella typhimurium* were used. Following vagotomy, a reduction in c-Fos expression in neurons as well as a decrease in immune system cell activity was observed. These findings provide evidence that the vagus nerve plays a critical role in transmitting signals related to changes in gut microbiota and intestinal immune responses to the central nervous system[10].

Findings reported by Tracey and colleagues support the concept that the immune response is regulated through a pathway termed the "inflammatory reflex." This cholinergic anti-inflammatory pathway is mediated by efferent fibers of the vagus nerve. It is proposed that, following vagus nerve stimulation, acetylcholine signaling via nicotinic acetylcholine receptors plays a central role in this mechanism[64]. This signaling is also thought to be transmitted through a specific T-cell population identified in mice, which produces acetylcholine and exhibits a memory-like phenotype. These cells are considered important mediators in the vagus nerve–induced suppression of cytokine production[65].

The vagus nerve plays an important role in the regulation of metabolic homeostasis[66]. Studies on vagus nerve stimulation have demonstrated that it significantly enhances memory and cognitive performance, promotes neuronal plasticity, and improves decision-making processes in both rodent models and humans[67,68]. Various approaches, including both manual and electrical stimulation of the vagus nerve, have been investigated in experimental and clinical studies[66]. Research findings suggest that vagus nerve stimulation may exert potential beneficial effects on cardiovascular, neurodegenerative, metabolic, and other physiological biomarkers associated with the morbidity and mortality of depression[66].

A comprehensive understanding of the function and impact of the vagus nerve within the gut–brain axis is thought to potentially contribute to the development of alternative therapeutic approaches for behavioral disorders.

6. Gut microbiota-derived metabolites

Neurotransmitters produced in the gut, as well as their precursors, may influence their corresponding levels in the brain. In addition to being derived from dietary nutrient metabolism, neurotransmitters can also be synthesized by gut bacteria. For instance, *Escherichia coli* has been reported to produce dopamine, serotonin, and noradrenaline, whereas Lactobacilli species can generate serotonin, GABA, acetylcholine, and histamine, which may in turn influence the host brain[69]. These microbial products have been suggested to play a significant role in the development of various neurological conditions, including Alzheimer's disease, Parkinson's disease, neurodegenerative disorders, mood disorders such as depression, and autism spectrum disorders[70]. Furthermore, short-chain fatty acids (SCFAs) may indirectly influence the gut–brain axis by stimulating the release of certain gut hormones, such as leptin and glucagon-like peptide-1 (GLP-1), via enteroendocrine cells. These enteric hormones can interact with vagal afferent pathways as well as brain receptors, thereby contributing to gut–brain communication[71].

The gut microbiome is estimated to contain more than 22 million microbial genes[72], which far exceeds the approximately 22,000 genes present in the entire human genome[73]. This extensive genetic capacity enables the microbiota to synthesize a wide range of enzymes with versatile metabolic functions, allowing the fermentation and degradation of various compounds that the human host is unable to metabolize on its own. As a result, the gut microbiota can produce metabolites with a broad spectrum of bioactivities. Microbiota-derived metabolites can be classified into three main categories based on their origin: (i) metabolites directly produced by the gut microbiota from dietary components, (ii) host-derived metabolites that are subsequently modified by the gut microbiota, and (iii) re-synthesized metabolites generated through microbial metabolic pathway[72].

The gut microbiota plays a significant role in the multifaceted regulation of metabolic disorders. This regulation is based on the production of various microbial metabolites and their interactions with host receptors that can activate or inhibit signaling pathways in host cells, thereby exerting effects that may be either beneficial or detrimental to host health[74].

6.1 SHORT CHAIN FATTY ACIDS (SCFAS)

Fatty acids play multiple essential roles, including serving as an energy source for cells, contributing to membrane structure, participating in cellular functions, regulating gene expression and signaling pathways, and being involved in the synthesis of lipid-based signaling molecules such as eicosanoids, which act as chemical messengers[75]. A significant proportion of fatty acids, including acetate, butyrate, isobutyrate, hexanoate, and propionate, are produced by gut microbiota species such as *Eubacterium*, *Roseburia*, *Faecalibacterium*, *Bifidobacterium*, *Lactobacillus*, and *Enterobacter* present in the intestinal flora[78].

Gut bacteria are capable of producing short-chain fatty acid (SCFA) metabolites that can regulate intestinal motility, secretion, and signaling within the gut–brain axis. They exert these effects through free fatty acid receptors expressed on epithelial cells, enteroendocrine and enterochromaffin immune cells, as well as intrinsic and extrinsic neurons[76,77]. In addition, short-chain fatty acids may influence the production of neurotransmitters in the brain by regulating the expression of enzymes involved in their biosynthesis[78].

Studies investigating the interaction between fatty acids and the gut microbiota have shown that fatty acids can influence intestinal permeability, modify lipoprotein profiles, enhance immune system functions, and acidify colonic pH. These changes are thought to facilitate the entry of cytokines and neuroactive metabolites released from the intestine into the systemic circulation, where they may cross the blood–brain barrier and subsequently affect brain function and human behavior. However, further studies are needed to clarify these mechanisms in detail[79].

In addition, fatty acids may trigger inflammatory responses through binding to specific immune cells such as T lymphocytes, B lymphocytes, and macrophages; however, certain short-chain fatty acids produced via microbial fermentation are known to exert anti-inflammatory effects[80]. Finally, among the short-chain fatty acids that play important roles within the intestinal lumen, butyrate has been shown to be involved in neurotransmitter synthesis and release, while propionate an SCFA with key functions in the production of free oxygen radicals and mitochondrial energy metabolism has been reported to possess neuroactive properties[81,82].

In conclusion, although further studies are required to fully elucidate the mechanisms of action of short-chain fatty acids and their derivatives in relation to the microbiota, the gut–brain axis, and human behavior, these molecules also hold potential as an alternative therapeutic avenue for the treatment of various diseases in the future.

6.2. TRYPTOPHAN

The primary physiological pathway of tryptophan metabolism is the kynurenine pathway. In studies conducted on germ-free mice, an increase in tryptophan levels has been observed as a result of reduced activation of the peripheral kynurenine pathway in these animals[83]. In a study by Agudelo and colleagues, it was reported that in stress-induced depressive states, the conversion of plasma kynurenine to kynurenic acid—known for its neuroprotective effects is reduced[84].

Desbonnet and colleagues investigated the effects of probiotics and observed increased levels of tryptophan and kynurenic acid in rats fed with *Bifidobacterium infantis*[85]. They also reported that probiotic treatment modulates tryptophan metabolism and may exert a therapeutic effect in stress-related conditions by enhancing the peripheral conversion of kynurenine to kynurenic acid[85].

Unlike serotonin, kynurenine is able to cross the blood–brain barrier. It may also exert adverse effects on brain health by promoting neuroinflammation and neurodegeneration[86]. Indole production, which is largely associated with the gut microbiota, is catalyzed by microbial enzymes. Tryptophan hydroxylase and indole have been detected in the blood, brain, and gastrointestinal system[87]. A growing body of literature supports the concept that the conversion of tryptophan to indole may influence gut–brain axis function[88].

6.3. NEUROTRANSMITTERS AND NEUROPEPTIDES

Neurotransmitters are chemical messenger molecules responsible for signal transmission between neurons[89]. Neuropeptides, on the other hand, facilitate inter-neuronal communication by interacting with different receptors in the brain. These protein-based molecules are responsible for specific behavioral patterns[89]. Recent studies have shown that various microbial taxa within the gut microbiota, including *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Enterococcus*, and *Trichuris*, are capable of producing neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin, as well as certain neuropeptides, including brain-derived neurotrophic factor (BDNF)[90,91]. Although these molecules are associated with neuronal signal transmission, they are also believed to play important roles in the regulation of brain function and behavior.

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain. It acts as a secondary messenger in important physiological processes such as cellular development, homeostasis, and autophagy[92].

An imbalance between excitatory and inhibitory neurotransmitters in the central nervous system, particularly involving GABA, is thought to contribute to the etiopathogenesis of various neuropsychiatric disorders, including autism, epilepsy, anxiety, and depression[92].

Several reports have demonstrated that certain gut microbiota members, including *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*—particularly *Bacteroides fragilis*—are capable of producing GABA within the intestinal microbiota[69]. More recently, a novel "GABA-consuming" species, *Evtepia gabavorous*, belonging to the family *Ruminococcaceae*, has been identified[69]. The GABA dependency of *E. gabavorous* has been clearly demonstrated by its ability to grow only in the presence of GABA-producing *Bacteroides fragilis* strains.

It has also been suggested that bacterial species such as *Akkermansia muciniphila*, *Parabacteroides merdae*, and *Parabacteroides distasonis* may play a role in regulating GABA by altering the GABA/glutamate ratio and increasing brain glutamate levels[93].

There is increasing evidence that the neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) is a key player in the brain, the gut and microbiota, gut–brain axis signaling. Studies have shown that bacteria derived from both humans and mice can increase colonic and serum 5-HT levels in germ-free mice, and that they enhance 5-HT production indirectly by generating SCFAs, which upregulate serotonin synthesis. These changes have also been associated with improved gut motility in germ-free mouse models[77,94].

Recent evidence has demonstrated that 5-HT released from enterochromaffin cells may communicate with the gut microbiota, particularly with *Turicibacter sanguinis*, which possesses serotonin-related mechanisms involved in microbial colonization and host physiology[95].

5-HT plays a regulatory role in appetite, gastrointestinal motility, mood, cognition, and sleep patterns[69]. Enteric serotonin levels are regulated by tryptophan hydroxylase isoforms TPH1 and TPH2[96]. Although 5-HT can also be synthesized in the central nervous system, nearly 90% of the body's total serotonin is produced by enterochromaffin cells in the gut[95].

Some studies have further suggested that a wide range of gut bacteria, including *Escherichia coli*, *Hafnia*, *Bacteroides*, *Streptococcus*, *Bifidobacterium*, *Lactococcus*, *Lactobacillus*, *Morganella*, *Klebsiella*, *Propionibacterium*, *Eubacterium*, *Roseburia*, and *Prevotella*, may contribute to serotonin production, accounting for up to 80% of its synthesis within the gastrointestinal system[97].

7. Conclusion and Future Directions

Elbette. Metnin akademik İngilizce çevirisi aşağıdaki gibidir:

Autism Spectrum Disorder (ASD) is a multidimensional clinical condition that is not limited solely to neurodevelopmental and behavioral manifestations, but also involves gastrointestinal, immunological, metabolic, and neuroendocrine mechanisms. Current evidence suggests that alterations in the gut microbiota may be associated with gastrointestinal symptoms, neuroinflammation, immune system activation, and behavioral manifestations observed in ASD. In particular, dysbiosis, increased intestinal permeability, microbial metabolites, and inflammatory responses are thought to influence neurodevelopmental processes through the gut–brain axis.

However, findings from clinical studies remain inconclusive and not entirely consistent. Therefore, standardized, large-scale, and long-term studies are needed to better elucidate the relationship between ASD and the gut microbiota. Although microbiota-targeted approaches, including probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation, appear promising, their efficacy and safety require further clarification. In this context, the gut–brain axis emerges as an important research field for understanding the etiopathogenesis of ASD and for developing personalized therapeutic strategies in the future.

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