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Mini-Review

Microbiota-gut-brain axis in autism spectrum disorder

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ABSTRACT

Extensive studies, largely during the past decade, identify the dynamic and bidirectional interaction between the bacteria resident in the intestines and their host brain along the "microbiota-gut-brain axis". This interaction modulates the development and function of the central nervous system and is implicated in neurological disorders. As a neurodevelopmental disorder, autism spectrum disorder (ASD) is considered a historically defect in the brain. With accumulating evidence showing how the microorganisms modulate neural activities, more and more research is focusing on the role of the gut microbiota in mitigating ASD symptoms and the underlying mechanisms. In this review, we describe the intricate and crucial pathways via which the gut microbiota communicates with the brain, the microbiota-gut-brain axis, and summarize the specific pathways that mediate the crosstalk of the gut microbiota to the brain in ASD.

Introduction

Autism spectrum disorder (ASD), a group of heterogeneous neurodevelopmental disorders, is characterized by deficits in social communication and repetitive and stereotyped behaviors (Association, 2013). Affecting 1 in 54 children and adolescents in the United States (Maenner et al., 2020), ASD poses serious medical and social problems. Besides the neurological abnormities, patients with ASD exhibit gastrointestinal (GI) symptoms, such as abdominal pain, gaseousness, diarrhea, constipation, and flatulence (Chaidez et al., 2014). Furthermore, the observed GI disturbances have shown a strong correlation with the severity of ASD (Adams et al., 2011). These GI problems in ASD suggest that the intestine may play an important role in the pathogenesis of ASD.

The adult human intestine is home to a variety of microorganisms. The collections of these intestinal microorganisms, termed the gut microbiota, exhibit intimate interaction with their hosts rather than passive passengers. In recent years, extensive attention has been paid to gut microbiota's pivotal role in modulating the host neural function and central nervous system (CNS)-related behaviors (Sherwin et al., 2019). Moreover, gut microbiota dysbiosis has been extensively reported in population-based cohort studies of ASD, and probiotics may alleviate the symptoms (Patusco and Ziegler, 2018). With increasing evidence showing how the microorganisms modulate the neural activities (Morais et al., 2021), more and more studies turn to the role of the gut microbiota in treating ASD and its underlying mechanisms (Li et al., 2017). In this review, we discuss the existing and emerging evidence about the complicated and critical pathways via which the gut microbiota connects the brain in health and disease.

The microbiota-gut-brain axis

Over the past decade, studies from preclinical and clinical research strongly support the directional crosstalk between the gut microbiota and the brain, the microbiota-gut-brain axis. In this review, we focus on the "bottom-up" influence of how the gut microbiota affects the brain. The gut microbiota communicates with the CNS through several parallel and interacting pathways involving chemical, neuronal, and immune signaling, which will be discussed in the following sections in detail (Fig. 1).

Neuronal pathways

The neural pathways, the direct pathways that physically connect the gut and the brain, mainly include the vagus nerve and the enteric nervous system (ENS). The vagus nerve extends from the brainstem and innervates the viscera, making it the fastest and most direct pathway for the gut microbiota to influence the brain (Fulling et al., 2019). The vagus nerve is a paired nerve consisting of afferent and

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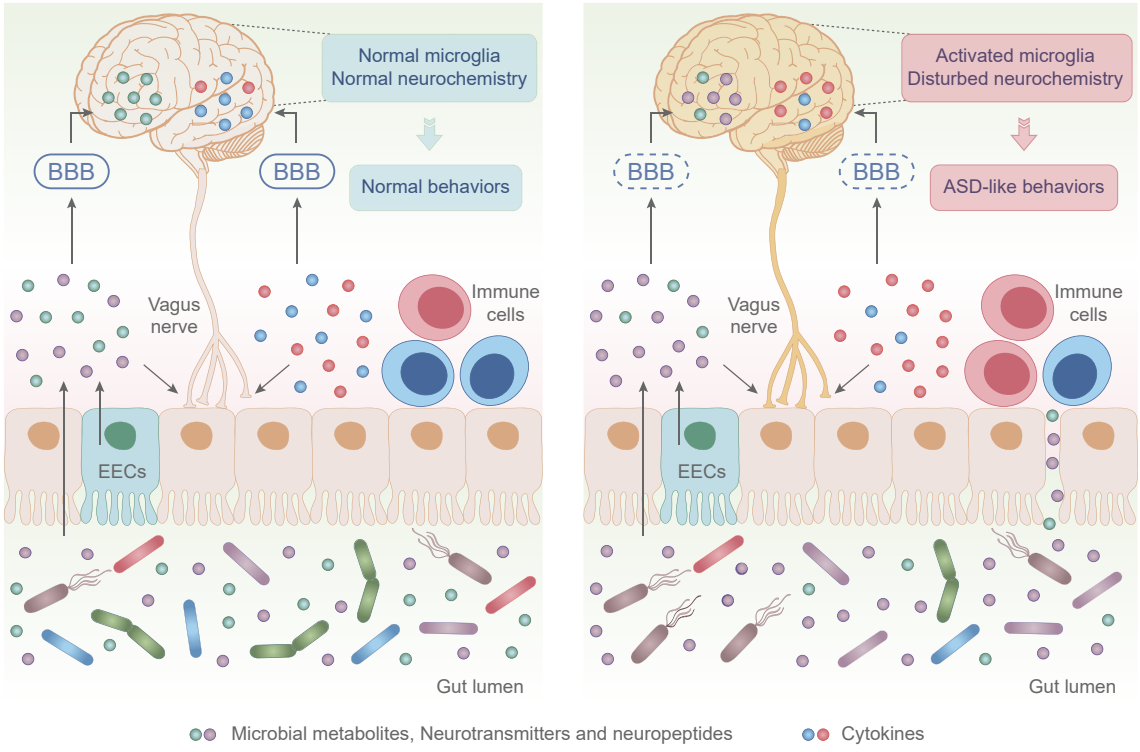

Fig. 1. The microbiota-gut-brain axis in health (left panel) and ASD (right panel). The gut microbiota communicates with the brain via several parallel and interacting pathways involving the autonomic nervous system, such as the vagus nerve, chemical signaling, and immune system. Neuroactive molecules produced by EECs and microbial metabolites such as SCFAs and neurotransmitters can serve as chemical signals. These compounds can modulate CNS activities directly by passing through the BBB or indirectly by influencing the vagus nerve and the mucosal immune response. The gut microbiota also communicates with the brain by the immune system. The cytokines produced by mucosal immune cells can influence brain function directly or indirectly. In ASD, the components in the microbiota-gut-brain axis have been changed. Gut microbiota dysbiosis in ASD leads to dysregulated chemical signals in the gut lumen and circulation. Besides, the altered profiles of mucosal immune cells result in disturbed cytokines, which exasperate the neuroinflammation in the brain. The activated microglia and dysregulated neurochemistry in the ASD brain, including glutamate, GABA, 5-HT, and oxytocin, are related to the disturbed gut microbiota and can be restored by some probiotics. Furthermore, the broken intestinal epithelial barrier in ASD may increase the penetration of chemical signals into the lamina propria from the gut lumen, and the damaged BBB accelerates the chemicals and cytokines to penetrate the brain from circulation. ASD, autism spectrum disorder; EECs, neuroendocrine cells; BBB, blood-brain barrier, CNS, central nervous system; SCFAs, short-chain fatty acids; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine.

efferent neurons, and thus, information can be transmitted directionally between the gut and the brain. Some probiotics have been demonstrated to communicate with the brain and modulate the CNS-related behaviors via the vagal nerve pathway. For example, the improvement of anxiety-related and depressive behaviors by *Lactobacillus rhamnosus* JB1 has been blocked by vagotomy (Bravo et al., 2011). The modulation of *L. reuteri* on ASD-relevant behaviors and oxytocin signaling pathways have been shown to depend on the vagus nerve (Sgritta et al., 2019). Notably, 90% of the vagal fibers between the gut and brain are afferent (Rao and Gershon, 2016), indicating the pivotal role of the vagus nerve in the perception of intestinal signals. The vagal afferents end in the muscle layer and the mucosa of the intestine (Fulling et al., 2019) and sense the mechanical stimuli such as luminal volume and chemical stimuli, such as neurotransmitters, hormones, and cytokines, which may be influenced by the gut microbiota.

The ENS is an important component of the autonomic nervous system and controls GI behaviors, such as intestinal transit and secretion (Rao and Gershon, 2016). Although most enteric neurons are not innervated by the CNS, the ENS and the CNS communicate with each other via sympathetic nerve and vagus nerve (Furness et al., 2014). The gut microbiota can modulate the activities and the functions of ENS through chemical signals, such as short-chain fatty acids (SCFAs), neurotransmitters, and polysaccharides (Morais et al., 2021). Microbiota-induced expression of aryl hydrocarbon receptor (AHR) in the enteric neurons can regulate intestinal motility (Obata et al., 2020), indicating the modulation of ENS activities by the gut microbiota. The gut microbiota can influence the neuroanatomy of the ENS as shown by the evidence that the germ-free (GF) mice show an immature ENS that can be normalized by colonization with the gut microbiota (De Vadder et al., 2018).

Neural immune pathways

The immune system can directly modulate and be modulated by both the gut microbiota and the CNS (Fung et al., 2017). The gut microbiota has been demonstrated to serve as a regulator of intestinal, systemic, and CNS-resident immune cell function (Zheng et al., 2020). Previous studies have elucidated, using GF mice, that the development and function of microglia, the tissue macrophages of the CNS responsible for neuronal networks maintenance and injury repair (Lenz and Nelson, 2018), can be influenced by the gut microbiota. For example, GF mice have shown immature and malformed microglia with diminished response to infection, and these defects in microglia can be restored by recolonization with a complex microbiota or administration with SCFA (Erny et al., 2015). Moreover, modulation of microglia by the gut microbiota occurs in a time and sex-dependent manner (Thion et al., 2018). In addition, microbial metabolites of tryptophan can modulate CNS inflammation by activation of astrocyte aryl hydrocarbon receptor (Rothhammer et al., 2016).

The gut microbiota can also communicate with the brain by regulating intestinal and peripheral immune cells (Arrieta and Finlay, 2012). The impact of mucosal immune responses in the intestines

by the gut microbiota has been well demonstrated in the GF mice. A reduced number of pro-B cells and regulatory T cells have been observed in the intestinal lamina propria of GF mice (Atarashi et al., 2011; Wesemann et al., 2013). Colonization of GF mice with segmented filamentous bacteria sufficiently promotes the differentiation of Th17 cells in the intestinal lamina propria (Ivanov et al., 2009), suggesting the vital role of commensal microbes in sculpting the features of specific mucosal immune cell subsets. The intestinal immune cells can affect the neural activities of the brain in both direct and indirect ways. The intestinal immune cells modulate the neural activities in the brain by directly penetrating through the blood-brain barrier (BBB) under some circumstances, such as brain injury, or indirectly by connecting with afferent fibers and enteric nerves (Powell et al., 2017).

The gut microbiota can also communicate with the CNS by peripheral immune responses via circulating cytokines. *Bifidobacterium infantis* has been shown to correct the interleukin (IL)-10/IL-12 level released from the peripheral blood mononuclear cells of irritable bowel syndrome patients (O'Mahony et al., 2005). Probiotics consisting of *B. bifidum* A218, *B. catenulatum* A302, *B. longum* A101, and *L. plantarum* A87 decrease the levels of serum tumor necrosis factor (TNF)-α, IL-5, and IL-6 and increase the level of serum IL-10 in peritoneal dialysis patients (Wang et al., 2015). Some cytokines can pass through the BBB by direct transport and alter the inflammatory status of the CNS (Banks, 2005). For example, elevated brain IL-6 disrupts the balance of excitatory/inhibitory synaptic transmissions and contributes to autism-like behaviors (Wei et al., 2012). TNF-α, one of the well-studied proinflammatory cytokines, increases the local connectivity of neural circuits during neurodevelopment and leads to increased epilepsy (Lee et al., 2010). Importantly, the development and integrity of BBB can be affected by the gut microbiota. The GF mice display increased BBB permeability which can be restored by the colonization of the gut microbiota (Braniste et al., 2014). Furthermore, injury in BBB integrity increases the accessibility of the brain to pathogens and microbial products in the circulating system (Kim, 2008).

Chemical signaling pathways

The gut microbiota can regulate the homeostasis of the host CNS directly or indirectly through a variety of chemical signals, such as SCFAs, serotonin (5-hydroxytryptamine [5-HT]), bile acids, gamma-aminobutyric acid (GABA). Some chemical molecules produced by the gut microbiota can cross the intestinal epithelial barrier as well as the BBB and directly act in the brain. Besides, some chemical molecules propagate signals indirectly through the interaction with enteroendocrine cells, which are interspersed between gut epithelial cells throughout the intestine.

SCFAs, a cluster of lipids produced from the fermentation of dietary fiber in the intestinal lumen by the gut microbiota, are speculated to directly or indirectly mediate the microbiota-gut-brain crosstalk (Dalile et al., 2019). Because of the abundant expression of monocarboxylate transporters in endothelial cells (Vijay and Morris, 2014), SCFAs can cross the BBB and directly affect neurological processes (Oldendorf, 1973). In the brain, SCFAs act extracellularly as endogenous ligands for G protein-coupled receptors (Kimura et al., 2011) and intracellularly modulate the gene expression by inhibiting histone deacetylases (Waldecker et al., 2008). However, given the minimal amount of SCFAs taken up by the brain (Song et al., 2009), more and more studies suggest that SCFAs affect brain function through indirect pathways. SCFAs can also affect the microbiota-gut-brain crosstalk through neuroimmune pathways by reducing systemic inflammation and regulating the neuroinflammation-associated microglia activation (Huuskonen et al., 2004). SCFAs reduce systemic inflammation mainly in two ways. SCFAs improve the intestinal epithelial barrier and reduce the entry of pathogenic bacteria and metabolites into peripheral blood (Feng et al., 2018). As SCFAs can reach the peripheral blood, they can directly interact with a variety of immune cells and ameliorate the systemic inflammation (Correa-Oliveira et al., 2016). In addition, SCFAs might also mediate the microbiota-gut-brain communication by modulating the enteroendocrine pathways (Shackley et al., 2020) and the vagal pathways (Goswami et al., 2018).

5-HT is an important neurotransmitter with diverse effects in CNS as well as peripheral nervous system (Mohammad-Zadeh et al., 2008). In the intestine, 5-HT is produced by enterochromaffin cells from tryptophan, and this process is regulated by the gut microbiota (Yano et al., 2015). In GF and antibiotic-treated mice, biosynthesis of 5-HT has been found to be significantly decreased, and inoculation with spore-forming bacteria rescues the 5-HT level (Yano et al., 2015). The gut-derived 5-HT contributes more than 90% of the 5-HT in the body, and the peripheral 5-HT level does not directly affect its level in the brain since 5-HT cannot pass through the BBB (Yano et al., 2015). The role of the gut-derived 5-HT in modulating the physiological function of GI tract has been well demonstrated. The coordinated transit of the GI tract is dependent on 5-HT-mediated regulation of smooth muscle tone, mucosal secretion, and visceral perception through an interaction with ENS and smooth muscle cells (Beattie and Smith, 2008). However, how the gut-derived 5-HT affects CNS function remains largely unknown. As 5-HT can act via both proinflammation and anti-inflammation mechanisms to influence mucosal immunity in the intestine (Spohn and Mawe, 2017), how 5-HT would affect the systemic inflammation and the CNS need further investigation.

In addition to modulating the production of neurotransmitters by the hosts, the gut microbes are capable of synthesizing neurotransmitters themselves. Several gut microbes such as *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and *Parabacteroides* are demonstrated to produce GABA (Yunes et al., 2016, 2020; Otaru et al., 2021), a main inhibitory neurotransmitter. As an acid-resistance mechanism, GABA secretion by the gut microorganisms can be influenced by the environmental pH (Barrett et al., 2012), and *Bacteroides* shows the strongest potential to produce GABA within the pH range of the human large intestine (Strandwitz et al., 2019). Intestinal microbes-derived GABA participates in the gut-brain connections possibly through enteroendocrine pathways and neuroimmune pathways (Mazzoli and Pessione, 2016). Besides, the presence of GABA transporters on brain capillary endothelial cells (Takanaga et al., 2001) suggests that GABA may pass through the BBB and directly function as an inhibitory neurotransmitter in CNS.

Potential roles of the microbiota-gut-brain axis in ASD

Increasing evidence has proved the potential roles of the gut microbiota in treating ASD. In this review, we discuss the dysregulated gut microbiota, intestinal metabolites, and brain function, as well as the pathways that mediate the microbiota-gut-brain connections in ASD (Fig. 2).

Dysregulated gut microbiota and related abnormal intestinal metabolites and brain function in ASD

Extensive clinical evidence has demonstrated gut microbiota dysbiosis in ASD (Kelly et al., 2017). In general, feces from individuals with ASD exhibits compositional alteration in microbiota characterized by increased Firmicutes/Bacteroidetes ratio (Vuong and Hsiao, 2017). Despite the inconsistency on microbiota composition in terms of specific bacterial species across cohort studies on ASD, what these studies have in common is the finding that most bacteria with altered abundance in ASD show potentially beneficial or harmful

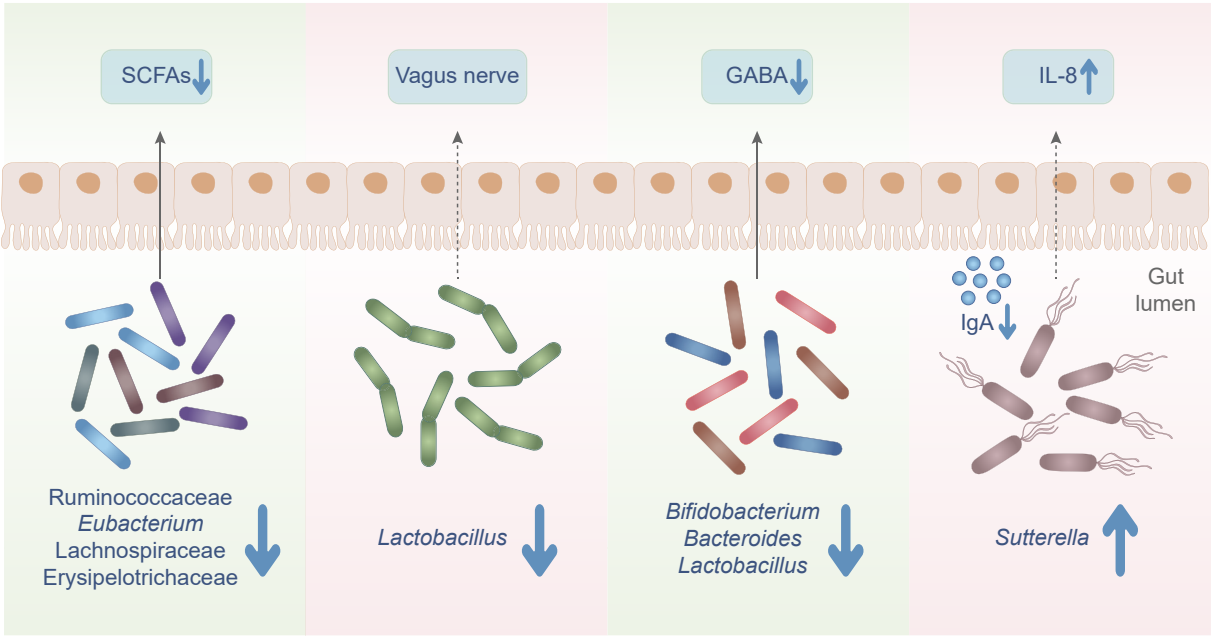

Fig. 2. Dysregulated gut microbiota and related intestinal abnormities in ASD. Decreased abundance of butyrate-producing bacteria, Ruminococcaceae, *Eubacterium*, Lachnospiraceae, and Erysipelotrichaceae, and relevant reduced fecal butyrate have been found in the feces of children with ASD. GABA-synthesizing microbiomes, *Bacteroides*, *Lactobacillus,* and *Bifidobacterium*, and related fecal GABA have been reported reduced in patients with ASD and animal models. Besides, *Lactobacillus*, which acts through the activation of the vagus nerve, has been demonstrated to decrease in ASD. *Sutterella*, which shows its detrimental effect by degrading IgA in the mucosa and increasing proinflammatory cytokine IL-8. ASD, autism spectrum disorder; SCFAs, short-chain fatty acids; GABA, gamma-aminobutyric acid; IgA, immunoglobulin A; IL, interleukin.

effects to the host. A cohort study shows decreased abundance of Ruminococcaceae, *Eubacterium*, Lachnospiraceae, and Erysipelotrichaceae, key butyrate-producing bacteria, in the feces of children with ASD, and this disturbed microbiota is correlated with lower levels of fecal butyrate level (Liu et al., 2019). Besides, decreased abundance of *Bifidobacterium*, which is used as probiotics through its anti-inflammatory activity, has been reported, and *Prevotella*, *Coprococcus*, and Veillonellaceae, which are responsible for carbohydrate fermentation (Fattorusso et al., 2019). On the other hand, *Clostridium*, *Desulfovibrio*, *Alistipes*, *Akkermansia*, and *Sutterella* have been demonstrated to be more abundant in the feces of children with ASD (Fattorusso et al., 2019). *Sutterella* can degrade immunoglobulin A in the mucosa, an immunoglobulin that protects the epithelial cells from pathobiont invasion and thus shows its detrimental effect on the host intestinal microenvironment (Kaakoush, 2020). Besides, *Sutterella* induces modest intestinal inflammation by producing IL-8 (Hiippala et al., 2016). Together, these findings suggest dysregulated composition and function of the gut microbiota in ASD.

As a neurodevelopmental disorder, ASD demonstrates several neurological alterations, including abnormal synapse remodeling, impaired neurocircuitry, and disturbed neurochemistry. Here we focus on the abnormities that have been reported to be influenced by the gut microbiota. Clinical studies demonstrate the activation of microglia across different brain regions in both postmortem tissues and *in vivo* brain during the development of ASD (Liao et al., 2020). In addition to their classic inflammatory function, microglia is highly active during CNS development and modulates the activity-dependent synapse and dendritic spine remodeling by interacting with the neurons during the crucial period of synaptogenesis (Edmonson et al., 2016). Abnormal synapse pruning is involved in the synaptic excitatory/inhibitory imbalance, a commonly accepted pathogenesis of ASD (Koyama and Ikegaya, 2015).

Some neurochemical alterations in the brain, such as GABA, glutamate, 5-HT, and oxytocin, have been considered etiologies for ASD (Marotta et al., 2020). GABA and glutamate are the main excitatory and inhibitory neurotransmitters in the human brain, respectively. Changes in concentrations of GABA and glutamate may lead to excitatory/inhibitory imbalance, which has been demonstrated in ASD individuals (Puts et al., 2017; Horder et al., 2018). As one of the best-known neurotransmitters, 5-HT plays a crucial role in brain development by modulating numerous developmental events, including neuronal migration, cell differentiation, and synaptogenesis, some of which have been implicated in ASD (Gaspar et al., 2003). 5-HT in the brain is also responsible for positive prosocial interactions, as evidenced by the fact that genetic deletion of 5-HT recapitulates decreased sociability, and 5-HT released in the nucleus accumbens rescues the social deficits (Walsh et al., 2018). It is reported that the dynamic changes of 5-HT synthesis capacity from childhood to adulthood are disrupted in patients with ASD (Chugani et al., 1999). Besides, the oxytocin signaling pathway attracts more and more attention in the etiology and treatment of ASD in recent years. As a neuropeptide, oxytocin has been proved to modulate social behaviors in preclinical and human studies. Accumulating evidence supports the important role of oxytocin signaling dysregulation in the social impairment of ASD (Insel, 2010), and exogenous oxytocin administration shows improvement in social function in some clinical trials (Guastella and Hickie, 2016).

Pathways that mediate the microbiota-gut-brain crosstalk in ASD

ASD is highly inheritable with many *de novo* mutations and copy number variations involved. Many ASD susceptible genes are considered to be involved in synaptic transmission (Varghese et al., 2017) and immune pathways (Wong et al., 2019), affecting the microbiota, microbial metabolites, and the crosstalk between gut microbiota and the brain. How the microbiota-gut-brain axis works in the altered genetic background in ASD needs to be further investigated.

Previous studies have shown the multiple pathways of crosstalk between the gut microbiota and the brain and demonstrated how the chemical, neural, and immune-related signals modulate the ASD-relevant phenotypes in animal models (Table 1). Neural pathways, especially the vagus nerve pathway, have been well demonstrated to mediate the connection of the gut microbes to the CNS. Optogenetic activation of gut vagal afferents produces reward-related behavior, suggesting that the vagus nerve connects the gut to the brain reward system (Han et al., 2018), a system whose dysfunction is implicated in ASD (Kohls et al., 2013). Notably, vagus nerve stimulation in the treatment of neurodevelopment disorders has been studied for many years, and vagus nerve stimulation has been shown to improve behavior in patients with ASD and epilepsy (van Hoorn et al., 2019). The pivotal role of the vagus nerve in the crosstalk of the gut microbiota to the brain has been demonstrated by vagotomy in different ASD models. Using genetic, environmental, and idiopathic ASD models, *L. reuteri* has been shown to rescue the social deficits in a vagus nerve dependent, as evidenced by the fact that *L. reuteri* fails to show the beneficial effects after vagotomy in these mice (Sgritta et al., 2019). Vagus nerve-mediated restoration of ASD-relevant behavior by *L. reuteri* also depends on the oxytocinergic and dopaminergic signaling in the brain (Sgritta et al., 2019).

Multiple preclinical and clinical studies have shown altered fecal or intestinal luminal metabolites in ASD, possibly because of gut microbiota dysbiosis. Some gut microbiota-derived metabolites, such as SCFAs, neurotransmitters, and amino acids, influence CNS development and ASD-relevant phenotypes in animal models. For example, mice colonized with gut microbiota from human ASD donors recapitulate the hallmark ASD-like behaviors and metabolomic analyses of serum and intestinal contents from these mice reveal the decreased level of 5-aminovaleric acid and taurine (Sharon et al., 2019), both of which act as GABA receptor agonists. Supplement with these two compounds improves the behaviors and rescues neuronal excitability in idiopathic ASD mice (Sharon et al., 2019). In addition, the role of SCFAs in ASD development and treatment seems to be diverse and depends on the specific compound. While butyrate can attenuate the behavioral deficits in ASD mice by modifying cortex development (Kratsman et al., 2016), propionic acid, another SCFA, induces ASD-like behaviors and shows neuro damage effects (MacFabe et al., 2011). In addition, microbe-induced metabolite BH4 rescues ASD-relevant behaviors by improving the social reward-mediated synaptic transmission in *Cntnap2*$^{-/-}$ mice (Buffington et al., 2021).

The role of the immune pathway in mediating the connection between the gut microbiota and the brain is well described in an ASD model induced by maternal polycytidylic acid (poly [I:C]) (Estes and McAllister, 2016), a double-strand RNA analogue that induces maternal immune activation (MIA). This model, based on epidemiological studies that maternal infection increases the risk for ASD, depends on the activation of T helper 17 cells by the specific maternal gut bacteria, segmental filamentous bacteria (Choi et al., 2016; Kim et al., 2017). Not only maternal immune response plays a pivotal role in modulating fetus brain development, but also the dysregulated immune profiles in offspring can influence the symptoms of ASD. For example, offspring from MIA during pregnancy displays abnormal systemic immune profiles and function, and the MIA offspring irradiated and repopulated with immunologically normal bone marrow no longer display deficits in repetitive and anxiety-like behaviors (Hsiao et al., 2012), implicating the contribution of cellular immune dysregulation during prenatal life in ASD-relevant behavioral defects. In addition, gut microbiota dysbiosis and increased gut permeability have been observed in MIA offspring, and supplementation with *Bacteroides fragilis* corrects these intestinal abnormities as well as behavioral deficits (Hsiao et al., 2013). Increased permeability in the intestinal epithelial barrier, otherwise known as "leaky gut", is alleged to promote mucosal inflammation by enhancing immune activation (Ahmad et al., 2017).

As discussed previously, there are multiple pathways in which the gut microbiota can affect neurodevelopment in ASD. The effects of these pathways may be simultaneous and interconnected. For a specific type of ASD or a particular commensal bacterium, there may be a major pathway that mediates the regulatory effects of the microorganism on ASD. Despite the extensive discoveries, there are still a great number of issues that need to be addressed about how the gut microbiota regulates ASD. For example, how do the commensal bacteria activate the vagus nerve? Is the activation of the vagus nerve by the gut microbiota highly selective for the

Table 1
Microbiota-gut-brain axis pathways in ASD animal models.

Pathways	Gut microbes	Animal models	Conclusions and comments	Reference
Neuronal pathways	*L. reuteri*	*Shank3B*$^{-/-}$ and BTBR mice	*L. reuteri* increases oxytocin level and restores ASD-relevant behaviors through the vagus nerve, demonstrating the pivotal role of the vagus nerve in the microbiota-gut-brain axis across different ASD models.	Sgritta et al., 2019
Chemical signaling pathways	Microbiota from patients with ASD	Mice colonized with microbiota from patients with ASD and BTBR mice	Microbial metabolites 5-aminovaleric acid and taurine improve the behaviors and neuronal excitability in ASD, elucidating the role of microbial metabolites in the microbiota-gut-brain axis.	Sharon et al., 2019
	B. fragilis	MIA mice	4EPS, which is increased by MIA and restored by *B. fragilis*, induces anxiety-like behaviors, showing the role of 4EPS in mediating the microbiota-gut-brain connection.	Hsiao et al., 2013
	L. reuteri	*Cntnap2*$^{-/-}$ mice	Microbial metabolite (BH4) rescues the social deficits and synaptic transmission, dissecting the contribution of host genetics and gut microbiota in modulating ASD-relevant behaviors.	Buffington et al., 2021
Neural immune pathways	SFB	MIA mice	Offspring of MIA shows ASD-relevant behaviors and abnormal cortical development, which demonstrates the role of specific maternal gut microbes in triggering MIA.	Kim et al., 2017; Vuong et al., 2020
	L. plantarum	*Kdm5*-deficient *Drosophila* model	*L. plantarum* improves social behaviors and brain 5-HT level, showing how immune deficiency impacts neurodevelopment.	Chen et al., 2019

5-HT, 5-hydroxytryptamine; ASD, autism spectrum disorder; MIA, maternal immue activation.

microorganisms? That is, can all intestinal commensal bacteria activate the vagus nerve, or only a specific type of commensal bacteria can do? In addition, is there a correlation between intestinal commensal bacteria and metabolites since some microbial metabolites have shown to modulate neural activity?

Animal models in dissecting the role of microbiota-gut-brain axis in ASD

Several model organisms, including *Drosophila*, zebrafish, rodents, and nonhuman primates, have been used in dissecting the molecular and cellular mechanisms underlying ASD (Meshalkina et al., 2018; Zhao et al., 2018; Bellosta and Soldano, 2019). Rodent models are the most widely used among these organisms since the availability of genetic manipulation tools and relatively mature evaluation methods for neuropsychiatric behaviors. Various rodent models have been developed based on known ASD risk genes, such as *MECP2*, *SHANK3*, *NLGN3*, *UBE3A*, and *CHD8*, and environmental risk factors during the perinatal period, including maternal VPA exposure, maternal autoantibodies exposure, maternal high-fat diet, and MIA (Varghese et al., 2017). BTBR mice also serve as an idiopathic ASD model (Varghese et al., 2017). Although these rodent models are somewhat capable of mimicking the behavioral and neural abnormalities of patients with ASD and have been applied to investigate the mechanisms underlying the microbiota-gut-brain axis in ASD in the last decade, there are considerable differences between the mouse and the human regarding brain anatomy, cognitive capacity, and behavioral paradigms (Watson and Platt, 2012). To bridge mouse- and human-based investigations of ASD, nonhuman primate models have been developed in recent years mimicking MIA (Bauman et al., 2014) and ASD risk gene mutation (Liu et al., 2016; Zhou et al., 2019). Primates share more similarities with humans than rodents in terms of neural circuits mediating social behavior, information acquisition paradigms, and behavioral repertoire (Watson and Platt, 2012). Using nonhuman primate ASD models to dissect the crosstalk between gut microbiota and brain may show more convincing results and provide better guidance for targeting the commensal gut microbiome in ASD treatment.

Perspectives and future directions

Mounting evidence supports the importance of the microbiota in shaping neurological processes directly through vagus nerve signaling and indirectly through immune response and modulation of host metabolisms via neuroactive compounds. Although how the gut microbes influence the neural activities in ASD has been elucidated in several studies across animal models and research groups, it is still largely unknown how the microbiota-gut-brain connections act in ASD because of the complexities of human neurodevelopment disorders and the limitations of animal models that mimic ASD. The field of microbiome and neuroscience should integrate advanced technology resources and continue to collaborate to develop safe and effective therapeutic options for ASD targeting the microbiota-gut-brain axis in the coming decade.

Conflict of interest

The authors declare no conflict of interests.

Acknowledgments

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