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REVIEW

THE MICROBIOTA–GUT–BRAIN AXIS AND ITS POTENTIAL THERAPEUTIC ROLE IN AUTISM SPECTRUM DISORDER

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Abstract—Autism spectrum disorder (ASD) is a series of neurodevelopmental disorders that are characterized by deficits in both social and cognitive functions. Although the exact etiology and pathology of ASD remain unclear, a disorder of the microbiota–gut–brain axis is emerging as a prominent factor in the generation of autistic behaviors. Clinical studies have shown that gastrointestinal symptoms and compositional changes in the gut microbiota frequently accompany cerebral disorders in patients with ASD. A disturbance in the gut microbiota, which is usually induced by a bacterial infection or chronic antibiotic exposure, has been implicated as a potential contributor to ASD. The bidirectional microbiota–gut–brain axis acts mainly through neuroendocrine, neuroimmune, and autonomic nervous mechanisms. Application of modulators of the microbiota–gut–brain axis, such as probiotics, helminthes and certain special diets, may be a promising strategy for the treatment of ASD. This review mainly discusses the salient observations of the disruptions of the microbiota–gut–brain axis in the pathogenesis of ASD and reveals its potential therapeutic role in autistic deficits.

Key words: autism spectrum disorder, microbiota, brain, microbial metabolites, probiotics.

Contents

INTRODUCTION

Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders, and the symptoms of autism were first described by Kanner (1943). Individuals with ASD display a wide range of symptoms, including difficulty with social interaction and communication skills, restricted activities and interests, and repetitive behavior (Lai et al., 2013). In addition to these core symptoms, children/young adults with ASD often have comorbid medical conditions, including intellectual disability, gastrointestinal (GI) symptoms, feeding difficulties and sleep disruption (Kohane et al., 2012; Mannion et al., 2013). The early symptoms of ASD can be recognized as early as one year of age, and the incidence rate in the United States is approximately 14.7 cases per 1000 children (Osterling et al., 2002; Baoi, 2014). Treatments and educational interventions usually last for the entire duration of their lives for those who are diagnosed with ASD (Aman, 2005). With its large financial cost and high prevalence, ASD has become a heavy economic burden to both families and society.

ASDs are etiologically heterogeneous. It is believed that both genetic and environmental factors influence the onset and development of ASD (Risch et al., 2014). The genetic architecture of ASD has been shown to be complex. More than 100 genes and genomic regions have been implicated in the etiology of ASD, and approximately

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Abbreviations: 4EPS, 4-ethylphenylsulfate; 5-HT, 5-hydroxytryptamine; AA, acetic acid; ANS, autonomic nervous system; ASD, autism spectrum disorder; BBB, blood–brain barrier; CHD8, chromodomain helicase DNA-binding protein 8; CNS, central nervous system; CRH, corticotropin-releasing hormone; ENS, enteric nervous system; GABA, gamma-aminobutyric acid; GF/CF, gluten-free, casein-free; GF, germ-free; GI, gastrointestinal; HPA, hypothalamus–pituitary–adrenal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; KD, ketogenic diet; MIA, maternal immune activation; PPA, propionic acid; SCFAs, short-chain fatty acids; TeNT, tetanus neurotoxin; TSO, *Trichuris suis* ova; VA, valeric acid; WAS, water-avoidance stress.

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350–400 genes have been suggested to be autism susceptibility genes (Betancur, 2011; Iossifov et al., 2012). A malfunction in some of these genes may result in the abnormal development of the nervous system, including the central nervous system (CNS) and the enteric nervous system (ENS) (Bernier et al., 2014; Kozol et al., 2015). Additionally, accumulating evidence supports a significant contribution of environmental factors to the pathology of ASD, including gut bacteria, oxidative stress, and physical condition (Heberling et al., 2013).

Although the exact etiology and pathology of ASD are still unclear, the interactions between the gut and the brain within ASD have received considerable attention. Recently, studies on gut microbiota have provided important observations concerning this complex bidirectional axis (Mayer et al., 2015). In ASD, characteristic neurodevelopmental deficits are often associated with a series of GI symptoms, such as abdominal pain, diarrhea and flatulence (Adams et al., 2011). Altered gut microbiota composition and metabolic activities have also been detected in both children affected with ASD and a murine model of ASD (de Theije et al., 2014b). Recent studies have further demonstrated that a disturbance of the gut microbiota, which is critical for cerebral development and activity, may contribute to ASD behavioral deficits (Critchfield et al., 2011). The potential therapeutic benefit of the gut microbiota is also demonstrated on the mouse model of ASD (Hsiao et al., 2013). These studies support the hypothesis that communication along the microbiota–gut–brain axis plays an important role in ASD. In this review, we summarized the involvement of the microbiota–gut–brain axis in the pathology of ASD and the results of microbiota-based treatments.

OVERVIEW OF THE MICROBIOTA–GUT–BRAIN AXIS

Communication between the gut and the brain, which is regarded as the gut–brain axis, is a well-known bidirectional neurohumoral communication system. Previous studies of the gut–brain axis mostly focused on its involvement in functional GI syndromes, such as irritable bowel syndrome (IBS) (Sanger and Lee, 2008). Recently, growing evidence has shown that the microbiota that resides in the gut can modulate brain development and produce behavioral phenotypes via the gut–brain axis (Diaz et al., 2011). Thus, a growing interest has developed focusing on the potential effects of the microbiota–gut–br ain axis in neurodevelopmental disorders.

The gut microbiota

The human gut harbors up to 100 trillion micro-organisms, including at least 1000 different species of known bacteria (Bermon et al., 2015). Over the past several years, substantial advances have been made in the ability to assess the microbiota composition, substituting high-throughput sequencing at the genetic level for culture-based approaches (Fouhy et al., 2012). Two predominant bacterial species in the human microbiota are the *Bacteroidetes* and *Firmicutes* phyla, with the *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* phyla occurring relatively rarely (Eckburg et al., 2005). The colonization of the gut microbiota commences at birth, when the infant is exposed to a complex microbiota during vaginal delivery (Di Mauro et al., 2013). The host's genome persistently influences the diversity and activity of the gut microbiota. Other environmental factors, including infection, antibiotics, diet, stress, and disease, may also alter the natural composition of the gut microbiota (Nicholson et al., 2012).

The microbiota that colonize the intestinal tract normally have a balanced compositional state. Carbohydrates are important energy sources for the body as well as the growth of microbial cells. Non-digestible carbohydrates, including cellulose, xylans and inulin, are fermented in the gut by microbiota to yield energy and produce metabolites, such as short-chain fatty acids (SCFAs) (Tremaroli and Backhed, 2012). The gut microbiota and their metabolites confer a number of beneficial effects on human health and physiology, including the regulation of polysaccharide degradation, nutrient absorption, fat distribution, gut motility, and epithelial barrier integrity (Backhed et al., 2004; Collins and Bercik, 2009; Liu et al., 2016). The SCFAs, mainly acetic acid (AA), propionic acid (PPA) and butyric acid (BA), also profoundly affect the immune and inflammatory responses (Maslowski et al., 2009). Studies have reported that SCFAs can reduce the production of proinflammatory factors *in vitro*, including IL-1β, IL-6 and TNF-α, and enhance the production of the anti-inflammatory cytokine IL-10 (Vinolo et al., 2011).

The bidirectional communication between gut microbiota and the brain

Communication along the microbiota–gut–brain axis mainly describes how signals from the gut microbiota influence brain function, as well as how brain messages impact microbiota activity and GI physiology. This bidirectional communication acts mainly through both neuroendocrine and neuroimmune mechanisms involving the autonomic nervous system (ANS) and the ENS.

Pivotal morphologic components of brain to gut microbiota signaling are the sympathetic and parasympathetic branches of the ANS. The sympathetic system exerts an inhibitory effect on the gut, such as inhibiting intestinal motor function and decreasing gut secretion (Al Omran and Aziz, 2014). Under conditions of stress, the sympathetic system is over activated, as well as the integrity of the gut epithelium is destroyed and the gut motility and secretions are changed (Zou et al., 2008; Snoek et al., 2010). The stress-induced changes of gut alter the habitat of resident bacteria and promote alterations to microbiota composition or activity (Collins et al., 2012). The hypothalamus–pituitary–adrenal (HPA) axis is another critical mechanism by which the brain influences the composition of the gut microbiota. When the HPA axis was over activated, the levels of circulating cortisol and proinflammatory cytokines are significantly elevated (Dinan et al., 2006). Mice that were subjected to water-avoidance stress (WAS) developed intestinal inflammation and compositional alterations in

gut microbiota, and these pathological processes may be associated with increased levels of corticotropin-releasing hormone (CRH) (Sun et al., 2013). Mice that were subjected to an olfactory bulbectomy displayed chronic depression-like behaviors and elevated central CRH, which led to increased motility in the colon and an altered microbial profile in the gut (Park et al., 2013).

More recent research has indicated that the effect of the gut microbiota extends much beyond the modulation of the gut itself. The metabolites that are derived from the microbiota can be absorbed and transported by blood before crossing the blood–brain barrier (BBB) to modulate cerebral function. For example, strains of *Lactobacillus rhamnosus* YS9 are able to produce gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter in the brain. Monoamines, such as noradrenaline, dopamine and serotonin are also produced by several strains of bacteria (Clarke et al., 2014). Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine that plays an important regulatory role in many organ systems (Luo et al., 2015). Recent studies have revealed a link between serotonin synthesis and microbiota activities. For instance, the indigenous spore-forming bacteria (Sp) from mouse microbiota could promote 5-HT biosynthesis from colonic enterochromaffin cells (ECs) and modulate 5-HT concentrations in both colon and blood. Furthermore, they have identified several fecal metabolites, which are increased by Sp, elevate 5-HT in chromaffin cell cultures, suggesting a direct metabolic signaling of gut microbiota to 5-HT release (Yano et al., 2015). Another study by Reigstad et al. also found that microbiota from conventionally raised mice significantly increase the expression of colonic Tph1 (tryptophan hydroxylase 1), which is the rate-limiting enzyme for mucosal 5-HT synthesis. And the gut microbiota act through SCFAs to promote the enteric 5-HT production and homeostasis (Reigstad et al., 2015). In 2014, Fischbach et al. first identified two enzymes that are found in the human microbiome that decarboxylate tryptophan to form the neurotransmitter tryptamine. This indicates a direct mechanism by which the gut microbiota influences host neurotransmitters (Williams et al., 2014).

The germ-free (GF) animal model, which displays a wide range of deficits in brain (and gut) biochemistry, HPA axis responses, and social behaviors, is a crucial tool for the investigation of the activity of the gut microbiota in host physiology (Desbonnet et al., 2014). When comparing control GF mice and GF mice that were inoculated with gut microbiota, researchers observed significant differences in the cerebral concentration of 38 metabolites, many of which were known to modulate brain activity (Matsumoto et al., 2013). These circulating metabolites from the gut were then able to enter the cerebrospinal fluid (CSF) by crossing the BBB. Studies have reported that the monocarboxylate transporters of SCFAs are abundantly expressed at the BBB, thereby allowing the SCFAs to cross the BBB and enter the brain (Pierre and Pellerin, 2005). The G protein-coupled receptor (GPR) 41, a receptor that is activated by PPA, is also highly expressed in rat brain tissue (Bonini et al., 1997). Additionally, GF mice have shown an increased BBB permeability and an altered expression of tight junction proteins, which alters the levels of circulating neuroimmune signaling molecules and microbiota metabolites that reach the brain. This may be another underlying mechanism by which the microbiota affects brain activity (Braniste et al., 2014).

The gut microbiota also participates in cerebral disorders by modulating the immune response of the host. Pathogenic microbiota as well as bacterial metabolites and their components are able to stimulate the secretion of pro-inflammatory cytokines (including IL-1, IL-6 and IL-18) by intestinal epithelial cells, intestinal dendritic cells and macrophages (Maynard et al., 2012,). The increased levels of circulating cytokines are closely associated with various neuropsychiatric disorders, including depression, anxiety, schizophrenia and ASD (Liu et al., 2015; Petra et al., 2015). In one study, a *Trichuris muris* infection induced significant anxiety-like behaviors, increased chronic mononuclear infiltration and elevated levels of the circulating pro-inflammatory cytokines TNF-α and interferon-γ (Bercik et al., 2010). Meanwhile, the probiotics *Lactobacillus helveticus* and *Bifidobacterium longum* reversed the myocardial infarction-induced depression and apoptosis in the limbic system (amygdala, dentate gyrus), which is associated with a reduction of pro-inflammatory cytokines (Girard et al., 2009; Arseneault-Bréard et al., 2012).

Another possible mechanism by which the microbiota–gut–brain axis mediates communication may be through the use of established neuronal circuits. Vagal afferents are critical neuronal pathways allowing the information flow from the viscera to CNS. The gut microbiota can deliver their signals to the brain via the vagus nerve. Administration of *B. longum* significantly reversed the chronic colitis-induced anxiety-like behaviors in mice, but this anxiolytic effect was absent in previously vagotomized mice. As *B. longum* could decrease the excitability of enteric neurons, it may signal to the CNS by activating vagal pathways (Bercik et al., 2011). In an inflammatory bowel disease (IBD) model infected with *Citrobacter rodentium*, *C. rodentium* significantly increased the anxiety-like behaviors after infection. And there were significantly more c-Fos protein-positive neurons in the vagal sensory ganglia of *C. rodentium*-treated animals, consistent with vagal afferent transmission of *C. rodentium*-related signals to the brain (Lyte et al., 2006). In addition to the modulating effects on behavior, another study has shown that ingestion of *L. rhamnosus* reduced the stress-induced elevation of corticosterone and induced region-dependent alterations in central GABA receptor expression. Nevertheless, these neurochemical effects were not found in vagotomized mice (Bravo et al., 2011). In addition to the vagal afferents, sensory fibers traveling from the GI tract to spinal dorsal horn could also transmit the information from the viscera to CNS (Mayer, 2011). It has been reported that mucosal release of cytokines and other inflammatory mediators can activate the spinal afferent terminals and result in the visceral hyperalgesia (Holzer, 2006). And the gut microbiota may also deliver their signals to CNS via the spinal afferents. Nohr et al. have

reported that the free fatty acid receptor 3 (FFAR3) is expressed on the sensory neurons in the spinal dorsal root ganglion. So the microbiota metabolites SCFAs could directly act on the afferent fibers projecting to spinal and modulate the activity of central neurons (Nøhr et al., 2015).These results strongly suggest that the neuronal circuits play a significant role in the interaction between the gut microbiota and the CNS.

THE MICROBIOTA–GUT–BRAIN AXIS AND AUTISM

Since the connection between the gut microbiota and autism was described early in the last century, a growing number of studies have demonstrated the importance of the microbiota–gut–brain axis in the occurrence and development of ASD (Bolte, 1998). Furthermore, restoring the balance of the microbiota–gut–brain axis may be a potential therapeutic target for the treatment of ASD.

Manifestations of microbiota–gut–brain axis disturbances in ASD

One manifestation of the disturbances within the microbiota–gut–brain axis in ASD is the comorbidity of neurodevelopmental deficits and intestinal symptoms. In a study of 1513 children of 20–60 months of age, children with ASD were found to be approximately six to eight times more susceptible to frequent gaseousness/bloating, constipation and diarrhea than were the control children. In addition, the GI symptoms were also strongly correlated with the severity of autism (Adams et al., 2011; Chaidez et al., 2014). In a study of 2973 children with ASD, 24% of the subjects experienced at least one type of GI problem. Excessive sensory responsiveness and anxiety were highly associated with GI problems, and each could serve as a predictor for chronic GI problems in ASD (Mazurek et al., 2013). Although the cause of GI complications within autism is unclear, developmental deficits in the nervous system may be one reason. For example, the chromodomain helicase DNA-binding protein 8 (CHD8) gene was identified as an important ASD candidate gene. There is a much higher frequency of constipation in children with CHD8 mutations than in children without the mutation (60–26%). Studies in zebrafish revealed that mutations in chd8 cause motility defects by affecting the neuronal colonization of the GI tract (Bernier et al., 2014). Additionally, in a murine model of ASD induced by prenatal exposure to valproic acid (VPA), apparent epithelial cell loss and neutrophil infiltration were found in the intestinal tract of the male offspring. This intestinal inflammation is most likely associated with increased neuroinflammatory markers and reduced serotonin levels in the brain (de Theije et al., 2014a).

Another manifestation of the disturbances within the microbiota–gut–brain axis in ASD includes changes in microbiota composition. Children are typically diagnosed with autism between the ages of 1 and 3 years (Howlin and Asgharian, 1999). A study of 54 children (23 ASD, age 123 ± 9 (37–208) month; 22 typically developing siblings and nine control subjects, 136 ± 9 (42–221) month; age mean ± SEM (range)) showed that the number of *Sutterella* spp. is elevated in the feces of ASD children compared to those of controls and that the number of *Ruminococcus torques* is higher in the ASD children with functional GI disorders than in those without disorders (Wang et al., 2013). An additional study with 33 ASD subjects, seven non-ASD siblings and eight control subjects (2–13 years) revealed that the level of Bacteroidetes was higher in the stools of severely autistic children and that the level of Firmicutes was higher in the control group. The sibling control data appeared to be between the autistic and control group data, which suggests that both genetic and environmental factors contribute to the disturbances of gut microbiota in ASD (Finegold et al., 2010; Louis, 2012). In VPA-exposed ASD model rats, the operational taxonomic units (OTUs) that were assigned to genera within the main phyla of Bacteroidetes and Firmicutes were significantly altered; this corroborated ASD studies in humans (de Theije et al., 2014b). These studies demonstrated that autistic behaviors were often associated with gut microbiota dysbiosis.

Microbiota–gut–brain axis disturbances as a possible contributor to ASD

Disturbances within the microbiota–gut–brain axis have been suggested as potential contributors to the occurrence and development of ASD. SCFAs, the critical mediators within the microbiota–gut–brain axis, can cross the BBB and modulate brain activity directly. The study by Adams et al. has found that children with autism had much lower levels of total SCFAs in their stool samples, including lower levels of AA, valeric acid (VA) and PPA (Adams et al., 2011; MacFabe, 2015). On the other hand, the level of SCFAs in stool can be affected by numerous factors, such as the amounts of bacteria that produce SCFAs, the intake of soluble fiber in diet, the transit time, and/or the drug intake. There were other studies reporting that the fecal SCFAs and ammonia concentrations were elevated in children with ASD (Wang et al., 2012). The increased butyric acid (BA) levels in stool were associated with deficits in the social behavior of the male offspring of the VPA-exposed mice (de Theije et al., 2014b). The physical condition of mother may also affect the risk of ASD in the offspring (Roberts et al., 2014; Raz et al., 2015). The study by Foley et al. has found that prenatal exposure to PPA significantly impairs the social behaviors of neonatal and adolescent offspring rats, showing the possibility that the gut microbiota of the mother may influence risk of ASD in the offspring (Foley et al., 2014). Furthermore, studies have demonstrated that both intracerebroventricular and peripheral administration (i.e., oral gavage, which simulates passage from the gut to the brain) of PPA to adult rats induced broad behavioral deficits that were remarkably consistent with observations in human subjects with ASD (El-Ansary et al., 2012; MacFabe, 2012). Superabundant PPA can readily enter the bloodstream and cross the BBB. In the brain, it can accumulate within neurons, inducing intracellular acidification, which may alter neurotransmitter release and neural activity (Karuri et al., 1993). PPA and BA administration to rodents also

induced broad alterations in gene expression, including the expression of genes related to neurotransmitter systems, neuronal cell adhesion molecules, inflammation, oxidative stress, lipid metabolism and mitochondrial function, all of which have been implicated in ASD (El-Ansary et al., 2012; El-Ansary and Al-Ayadhi, 2014; Nankova et al., 2014).

A large percentage of ASD patients have a history of extensive antibiotic use. Oral antibiotics disrupt the protective microbiota and cause the proliferation of anaerobic bacteria in the gut. For example, *Clostridia*, *Bacteroidetes* and *Desulfovibrio* are common bacteria that may promote GI symptoms and autistic behaviors in ASD (Bolte, 1998; Finegold, 2011; MacFabe, 2012). In addition to modulating the intestinal immune system, these bacteria can also produce certain metabolites that contribute directly to the pathology of autism. For instance, *Clostridium tetani* is a ubiquitous anaerobic bacillus that produces a potent neurotoxin, the tetanus neurotoxin (TeNT). The vagus nerve is capable of transporting TeNT and provides a route of ascent from the intestinal tract to the brain. TeNT disrupts neurotransmitter release by proteolytic cleavage of synaptobrevin, which results in a wide variety of behavioral deficits that are observed in autism (Bolte, 1998). Additionally, a metabolic product that is specific to the genus *Clostridium*, 3-(3-hydroxy phenyl)-3-hydroxypropionic acid (HPHPA), induces autism symptoms by emptying and depleting catecholamines in the brain. This observation supports the correlation between the etiology of autism and the genus *Clostridium* (Kesli et al., 2014). *Desulfovibrio* is another anaerobic Gram-negative bacillus that does not produce spores and that differs from *Clostridium*. This sulfate-reducing bacterium accounts for much of the abnormality in sulfur metabolism and produces important virulence factors may contribute to the pathophysiology of autism (Finegold, 2011; Finegold et al., 2012). A recent study in Cell has provided direct evidence for the contribution of the gut microbiota to the behavioral abnormalities that are seen in a mouse model of ASD. Adult maternal immune activation (MIA) results in offspring that display features of ASD, dysbiosis in their gut microbiota (alterations in *Clostridia* and *Bacteroidia*) and an altered serum metabolomic profile. Treating naive mice with the metabolite 4-ethylphenylsulfate (4EPS), which is increased by MIA, induces ASD-related behavioral abnormalities, which suggests that gut microbiota effects on the host metabolome impact organismal behavior (Hsiao et al., 2013). These findings support a microbiota–gut–brain connection in a mouse model of ASD.

THE POTENTIAL THERAPEUTICS OF ASD BY TARGETING THE MICROBIOTA–GUT–BRAIN AXIS

Probiotics

Probiotics are a group of nonpathogenic microorganisms that live in the gut, such as the lactic acid-producing bacteria *lactobacilli*, *lactococci*, *bifidobacteria* and *Saccharomycetes*. The effects of probiotics have been demonstrated in the modulation of the gut microbiota composition and the intestinal immune system, thereby promoting food digestion and nutrition absorption and improving the intestinal barrier function (Critchfield et al., 2011). Oral administration of probiotics has been successfully used to treat a variety of GI difficulties, including infectious diarrhea, IBD, and IBS (Guandalini, 2014). Additionally, recent studies have proven that probiotic administration may be an effective therapy for ASD through the modulation of the microbiota–gut–brain axis. During a double-blind, placebo-controlled, crossover design feeding study, oral administration of *Lactobacillus plantarum WCFS1* (a probiotic) significantly increased the number of *lactobacilli*/*enterococci* and reduced the count of *Erec482* (*Clostridium* cluster XIVa) compared to placebo. *L. plantarum WCFS1* treatment also effectively improved stool consistency and decreased the overall behavior scores of autistic subjects (Parracho et al., 2010). Linday also reported that *Saccharomyces boulardii* may be a potential adjunctive treatment for children with autism and diarrhea (Linday, 2001). Although the exact mechanism of the therapeutic effects of probiotics remains unclear, existing studies have suggested that they may target circulating neurotransmitters and neuroimmune responses within the microbiota–gut–brain axis. In a study of 97 subjects, probiotics intake had an obvious influence on the fecal SCFAs of ASD subjects (Adams et al., 2011). Plasma from 85 children demonstrated that probiotics significantly decreased the concentration of myeloperoxidase, a marker for inflammation and oxidation, in autistic individuals (Russo, 2015). Hsaio et al. also provided direct evidence of the beneficial effects of probiotics. In their research, the MIA offspring receiving *Bacteroides fragilis* treatment had significantly reduced autism-related behavioral abnormalities and GI defects (Hsiao et al., 2013). *B. fragilis* treatment improved the integrity of the intestinal barrier and altered 34% of all metabolites in serum. 4EPS, a uremic toxin and a possible urinary biomarker for autism, is the most significant metabolite to have been altered (Gilbert et al., 2013; Persico and Napolioni, 2013). Therefore, probiotics have emerged as a promising therapy for the treatment of ASD.

Trichuris suis ova (TSO)

TSO is the purified egg of *T. suis*, which is a common parasite in the GI tract of pigs. Due to its immunomodulatory properties and beneficial effects on mucosal barrier function, TSO has been widely used in multiple IBD studies. Some researchers have also proposed that TSO may be a possible therapy for ASD (Siniscalco and Antonucci, 2013). In one rare case, clinicians reported that the administration of 2500 ova every two weeks over a period of 10 weeks improved the patient's autistic symptoms. Once the dose of TSO was reduced, the autistic symptoms reappeared and then improved again when the dose was returned to an elevated level (Jouvin and Kinet, 2012). Additionally, Hollander's group conducted a small preliminary TSO study involving 10 ASD subjects with an autoimmune condition. In this 28-week, double blind, randomized, crossover study the group demonstrated the feasibility

and safety of using TSO in autistic adults and have found a potential benefit from this type of treatment in all parameters (Friedrich, 2014).

Diet

It is believed that many environmental factors could affect the microbiota–gut–brain axis, not least of which is the daily food intake. It has been shown that food can influence the composition of the gut microbiota. For example, the counts of *Clostridium difficile* and *Escherichia coli* are significantly lower in the gut microbiota of breast-fed infants than in infants who were formula-fed (Penders et al., 2005). Furthermore, dietary emulsifiers can alter the gut microbiota localization, composition, and pro-inflammatory potential (Chassaing et al., 2015). Diet-induced changes in the microbiota could then influence serum metabolites and modulate the brain activity in the host (Tremaroli and Backhed, 2012). Therefore, certain foods may restore the balance of the micro biota–gut–brain axis and have therapeutic effects on ASD-related deficits. A gluten-free, casein-free (GF/CF) diet was reported to improve the symptoms of ASD children. In a study that contained 387 participants, a strict GF/CF diet resulted in a clear improvement in ASD behaviors, physiological symptoms, and social behaviors (Pennesi and Klein, 2012). However, the conclusions of the GF/CF diet are controversial. One study by Johnson et al., does not support the use of a GF/CF diet in ASD treatment because no improvement in behavioral symptomology was observed (Johnson et al., 2011). In addition to the GF/CF diet, the ketogenic diet (KD), which is a high-fat and low-carbohydrate diet, demonstrated a beneficial effect on the playful behaviors that are observed in VPA rats. As the KD was able to modify complex social behaviors and mitochondrial respiration, it may be another useful treatment option for children with ASD (Ahn et al., 2014).

SUMMARY

In this review, we have briefly summarized the neurobiological role of the microbiota–gut–brain axis in the pathology of autism. The possible mechanisms are illustrated in Fig. 1. Individuals with ASD often suffer from GI symptoms and gut microbiota disorders. Additionally, researchers have provided direct evidence supporting the gut microbiota as a likely contributor to the autistic behavioral abnormalities in a mouse model of ASD. Restoring the balance of the microbiota–gut–brain axis offers promising beneficial therapeutic effects on autistic deficits; however, direct clinical evidence for a role of the microbiota–gut–brain axis in ASD is relatively limited. In the future, more randomized double-blind clinical studies are required to determine the role of the microbiota–gut–brain axis in the etiology of ASD.

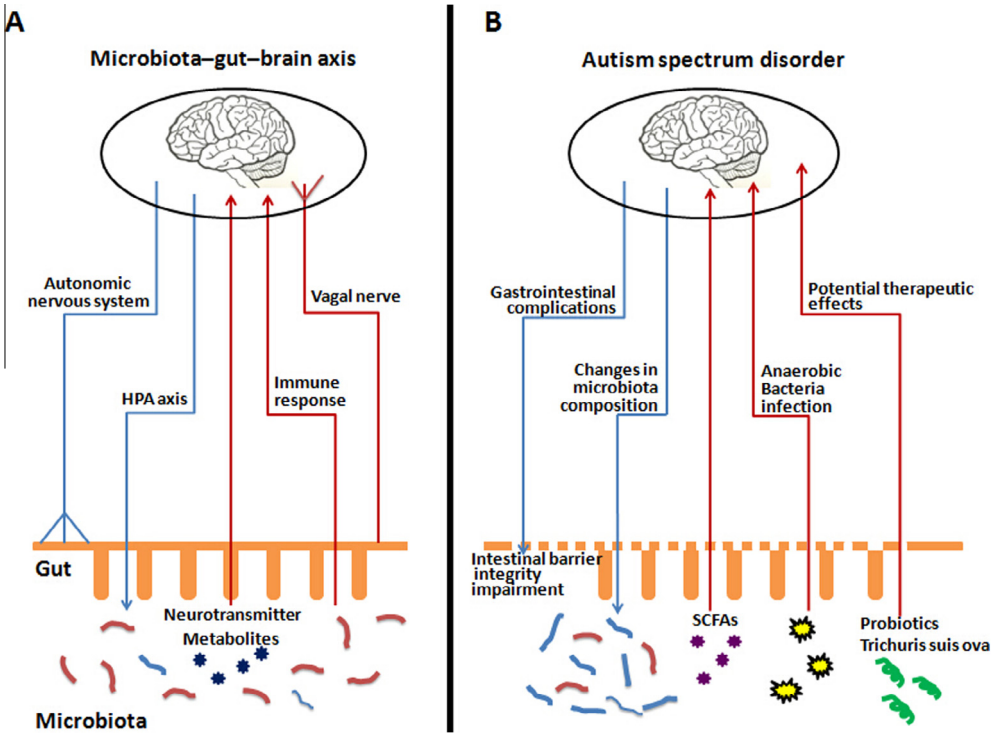

Fig. 1. The microbiota–gut–brain axis and its potential role in autism spectrum disorder (ASD). (A) The bidirectional communication within the microbiota–gut–brain axis occurs mainly through the autonomic nervous system (ANS), HPA axis, neuroendocrine, and neuroimmune pathways. (B) The manifestations of disturbances within microbiota–gut–brain axis in the pathology of ASD. Autistic deficits are associated with gastrointestinal symptoms and compositional changes in gut microbiota. Conversely, the noxious metabolites derived from gut microbiota and the intestinal anaerobic bacteria infection may participate in the development of ASD. Modulators of microbiota–gut–brain axis, such as the probiotics and *Trichuris suis ova* (TSO), have shown potential therapeutic effects in ASD. HPA: hypothalamus–pituitary–adrenal; SCFAs: short-chain fatty acids.

COMPETING INTERESTS

The author states that the present manuscript presents no conflict of interest.

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